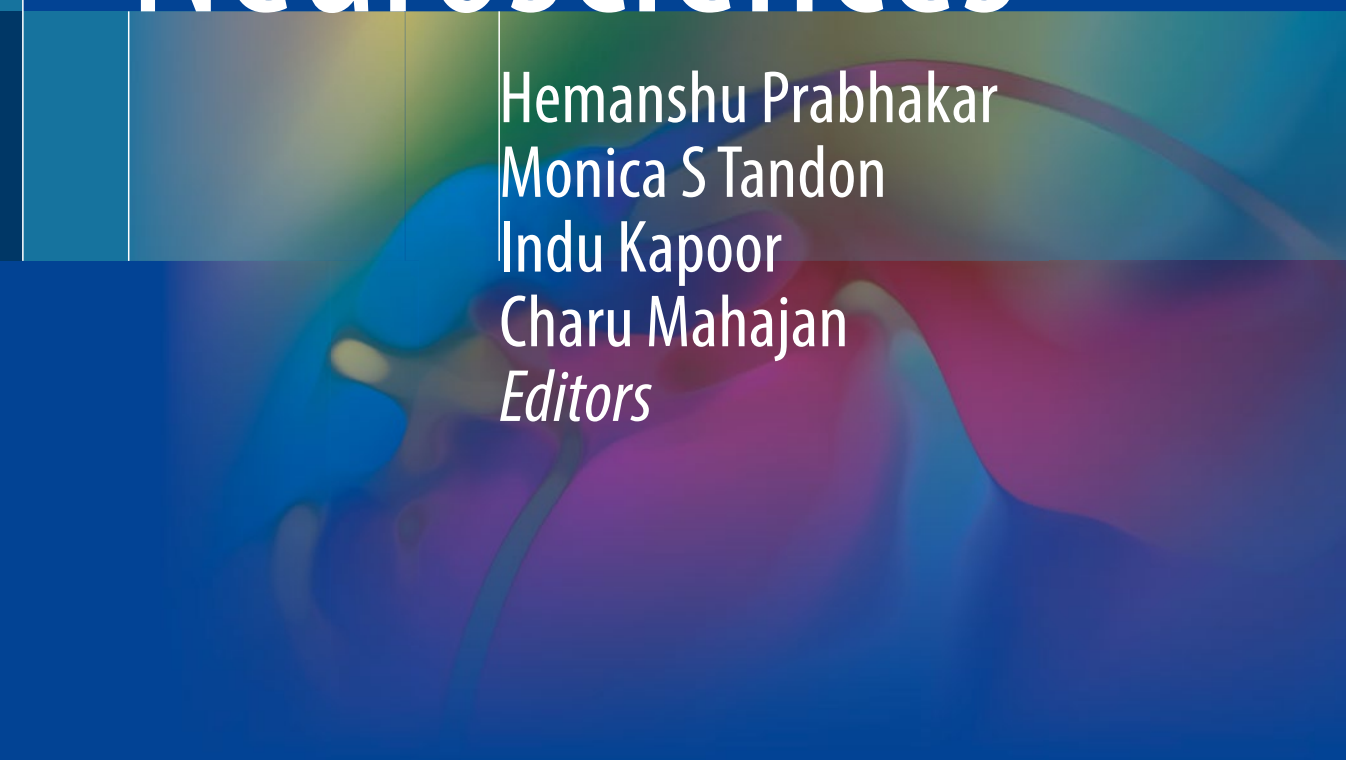
Transfusion Practice in Clinical Neurosciences

Hemanshu Prabhakar
Monica S Tandon
Indu Kapoor
Charu Mahajan
Editors



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Editors
Hemanshu Prabhakar
Neuroanaesthesiology and Critical Care
All India Institute of Medical Sciences
New Delhi, Delhi, India

Indu Kapoor
Neuroanaesthesiology and Critical Care
All India Institute of Medical Sciences
New Delhi, Delhi, India

Monica S Tandon
Anesthesiology and Intensive Care
G B Pant Institute of Medical Education and Research
New Delhi, Delhi, India

Charu Mahajan
Neuroanaesthesiology and Critical Care
All India Institute of Medical Sciences
New Delhi, Delhi, India

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To Ma and Pa.

—Hemanshu Prabhakar

Dear Dad, this one is for you. I am because you were.

—Monica S Tandon

To my little boy Ansh, and my husband Deepak, who make me a better person with each growing day.

—Indu Kapoor

To my parents, who always believe in me.

—Charu Mahajan

Preface

Fluid management is the basis of all anesthetic managements in surgical patients. Its importance in neuroanesthesia is possibly of more relevance because while maintaining hydration of the patient, simultaneously we provide sufficient relaxation to the brain to facilitate surgery. Certain fluid types such as those containing glucose are detrimental to the brain. The use of hyperosmolar therapy is unique to the practice of neuroanesthesia. Likewise, large fluid shifts and blood loss are often observed during neurosurgical procedures.

It is extremely relevant to understand the physiology of blood and blood transfusion. There remains a disagreement over the threshold values of hemoglobin at which blood transfusion should be started. Several aspects of transfusion of blood and blood products are comprehensively covered in this book.

Total parenteral nutrition is another form of fluid administration and requires special consideration. A special section on total parenteral nutrition highlights the important of this clinical aspect of practice of transfusion of fluids.

A book providing detailed information on all the above fluids is topical to present times. This book will be useful for any medical practitioner associated with neuroanesthesia and allied branches such as neurointensive care, neurosurgery, and neurology. It will provide a quick and easy access to understand basics of fluid administration and choice of the right fluid for neurosurgical and neurologic patients. This book will provide an insight into all possible aspects of blood transfusion and total parenteral nutrition in neurologic patients.

New Delhi, Delhi, India — Hemanshu Prabhakar
New Delhi, Delhi, India — Monica S. Tandon
New Delhi, Delhi, India — Indu Kapoor
New Delhi, Delhi, India — Charu Mahajan

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Contents

About the Editors

Hemanshu Prabhakar is a Professor at the Department of Neuroanaesthesiology and Critical Care at All India Institute of Medical Sciences (AIIMS), New Delhi, India. He received his training in neuroanesthesia and completed his PhD at the same institute. He is the first Indian to be awarded the degree of PhD in the country. He is a recipient of the AIIMS Excellence Award for his notable contribution to academia and has published over 250 papers in peer-reviewed national and international journals. Dr Prabhakar is a reviewer for various national and international journals, and is also a review author for the Cochrane Collaboration. He has a special interest in evidence-based practice of neuroanesthesia. Dr Prabhakar is a member of various national and international neuroanesthesia societies and is past secretary of the Indian Society of Neuroanesthesia and Critical Care. He is an invited scholar for various national and international conferences. He is on the editorial board of the *Indian Journal of Palliative Care* and is the past executive editor of the *Journal of Neuroanaesthesiology* and *Critical Care*. He is the first Indian to publish international books in the specialty of neuroanesthesia. He is featured in the *Limca Book of Records* as a prolific writer in the field of neuroanesthesiology. The honorary fellowship by the Society of Neurocritical Care (SNCC) has been conferred upon him.

Monica S Tandon is currently Director Professor in the Department of Anesthesiology and Intensive Care (Neuroanesthesia Division) at G.B. Pant Institute of Postgraduate Medical Education and Research (GIPMER), New Delhi, India. She received her training in neuroanesthesia and neurocritical care at the same institute and has over twenty years of experience in the subject. She has numerous publications in national and international journals, and has written chapters in several books on neuroanesthesia and neurointensive care. She is also a Section Editor for the *Journal of Neuroanesthesiology* and *Critical Care*. Besides being a member of several national scientific societies, she has served on the Executive Committee of the Indian Society of Neuroanesthesiology and Critical Care. She has a keen interest in mentoring students, and has delivered talks on a wide array of neuroanesthesia topics, as an invited faculty at numerous national and international conferences.

Indu Kapoor is an Additional Professor in the Department of Neuroanaesthesiology and Critical Care at All India Institute of Medical Sciences (AIIMS), New Delhi, India. She received her training in neuroanes-

thesia at the same institute. Dr Kapoor has a special interest in evidence-based practice in neuroanesthesia. She has several publications in national and international journals to her credit and has written numerous chapters for various national and international books. She has published over 100 papers in several national and international journals. She is also a reviewer of various scientific journals and a review author for the Cochrane Collaboration. She is a recipient of the prestigious TN Jha Award at both the state and national level for her thesis work. Additionally, she is a member of various scientific societies and has been an invited faculty member at various conferences.

Charu Mahajan is an Additional Professor in the Department of Neuroanaesthesiology and Critical Care at All India Institute of Medical Sciences (AIIMS), New Delhi, India. After completing DM in neuroanesthesia at AIIMS, she joined the institute as a faculty member. She has over a decade of research experience and has received various awards for scientific presentations. She has several publications in various national and international journals, coauthored books, and authored chapters in many books. She is a reviewer for the Cochrane Collaboration. Dr Mahajan is also a member of various scientific societies and is a reviewer for several reputable scientific journals.

Part I

Fluids: Basic Consideration

Body and Brain Fluid and Volume Kinetics

Robert G. Hahn

Abstract

The capillary and cell membranes are important barriers to the distribution of fluid in the body. The former separates the plasma from the interstitial fluid, and the latter separates the extracellular fluid (ECF) from the intracellular fluid (ICF). The volumes of these body fluid spaces are tightly controlled by nervous and hormonal mechanisms.

Infusion fluids can be tailored to distribute on either or both sides of these barriers. In general, iso-oncotic fluid accumulates in the plasma and isotonic fluid in the ECF space. For scientific purposes, translocation of fluid across the capillary and cell membranes can be estimated by means of mass balance calculations, while the disposition of an infusion fluid over time is best studied with volume kinetic analysis.

The capillary walls of the brain control the chemical environment by pumping mechanisms and are not permeable for diffusion of substances other than water ("blood-brain barrier"). However, low osmolality allows more water to enter the brain and quickly increases the hydration of the neurons. The sensitivity of the brain volume to changes in serum osmolality has important implications for the choice of infusion fluid when caring for patients with neurotrauma who are undergoing neurosurgery. The brain lacks lymphatic vessels, so the filtered fluid is returned to the plasma via the cerebrospinal fluid. The cerebral fluid pressure is maintained at approximately 10 mmHg by absorption of fluid into the cerebrospinal fluid system. At high pressures, filtered fluid can also pass directly into venous sinuses.

Keywords

Body water · Physiology · Crystalloid solutions · Pharmacokinetics · Extracellular space · Physiology · Intracellular space Pharmacokinetics · Saline solution Hypertonic

Barriers to Water Distribution

The human body consists of billions of cells bathing in an aqueous solution with a salt concentration similar to that of prehistoric seawater. The water volumes outside and inside the cells are tightly controlled by a combination of semipermeable membranes and pumping functions.

Two main barriers regulate fluid distribution. The first one is the *capillary membrane* that separates the blood from the interstitial fluid. This

R. G. Hahn (✉)
Anaesthesia and Intensive Care, Karolinska Institutet, Stockholm, Sweden

Södertälje Hospital, Södertälje, Sweden
e-mail: r.hahn@telia.com

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membrane is highly permeable to water and electrolytes, while larger elements, like blood cells and plasma proteins, do not pass at all or they pass very slowly. Elements dissolved in body water attract water by virtue of their *osmolality.* The osmotic pressure exerted by these large intravascular molecules maintains the plasma volume and is termed *oncotic* or *colloid osmotic* pressure.

The second barrier for fluid distribution is the *cell membrane* that surrounds all body cells. The distribution of electrolytes across this membrane determines how much water will be located on either side. The distribution of electrolytes, in turn, depends on active pumping mechanisms located in the cell membrane itself.

Translocation of water across the cell membrane can be achieved deliberately by the clinician. Infusing sodium chloride at a concentration higher than 0.9%, which corresponds to the normal body osmolality of 295 mosmol/kg, withdraws water from the cells and shrinks them. Conversely, infusing a solution with a sodium concentration lower than 0.9% increases the volume of the cells.

Not all substances in an infusion fluid remain outside the cells; some enter the cells sooner or later. Therefore, the osmolality of a solution does not always determine the distribution of fluid across the cell membrane. Examples of penetrating substances are ethanol and amino acids. Therefore, one often uses the *tonicity* to describe the ability of an infusion fluid to redistribute water across the cell membrane. An *isotonic* fluid remains in the outside the cells only. Hence, ethanol and amino acids in isoosmotic solutions are considered hypotonic.

Nevertheless, even here the nomenclature can be misleading. One example is when fluids contain glucose. A 5% glucose solution is initially isotonic, but water slowly enters the cells anyway, along with the uptake of glucose. The end products of glucose metabolism are carbon dioxide and water, which have tonicities of zero.

The capillaries of the brain have a much lower permeability than the remainder of the body. Electrolytes and proteins are stopped (by the "blood-brain barrier"), while those that finally enter require pumping mechanisms. By contrast, water passes freely. The brain cells are therefore susceptible to changes in osmolality [1]. Metabolic and physical damages are other factors that cause brain cells to swell—one of the feared complications of neurotrauma. These concerns are important because the brain is encased within a bony structure (the skull) and cannot undergo much expansion before the intracranial pressure increases sharply.

Body Fluid Volumes and Their Control

The body fluid compartments consist of extracellular fluid (ECF) and intracellular fluid (ICF), which make up 20% and 40% of the body weight, respectively, in an adult male. The fractions are higher in children and lower in the elderly. The ECF is, in turn, divided into plasma and interstitial fluid, which are located on either side of the capillary membrane (Fig. 1). The cellular components of the blood (erythrocytes, leukocytes) belong to the ICF space.

The body fluids circulate constantly. The entire blood volume is pumped around the cardiovascular system within 1 min. Plasma is filtered in the capillaries and hydrates the interstitial fluid space, where the exchange of gases and nutrients with the cells takes place. The interstitial fluid is slowly directed to lymphatic vessels and then passes to the lymph nodes, where antibody reactions take place, and is then returned to the plasma. This circuit is accelerated by the infusion of crystalloid fluid.

The osmolality and the volumes of the body fluids are maintained within narrow limits by a multitude of hormonal and neurological mechanisms. *Vasopressin* (AVP) is secreted in small amounts from the neurohypophysis in response to slight hyperosmolality and in large amounts in response to hypotensive hemorrhage. *Atrial natriuretic peptide* (ANP) and *brain natriuretic peptide* (BNP) are secreted from the cardiac atrium and ventricle, respectively, in response to locally elevated fluid pressures. Both hormones increase the capillary filtration of albumin, as well as urinary excretion. The cardiac hormone

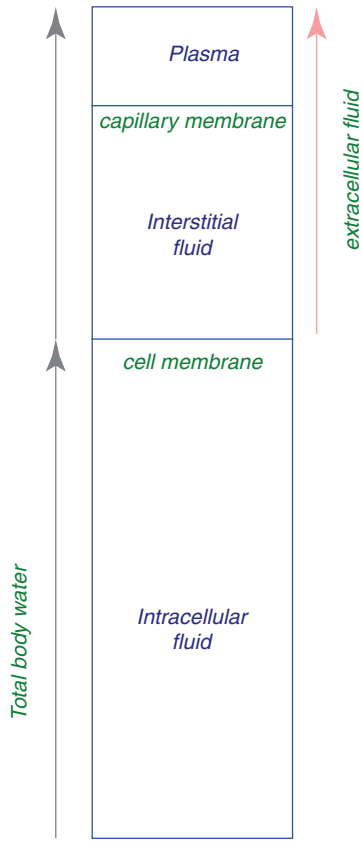

Fig. 1 Schematic drawing of the body fluid spaces

levels may increase in response to vigorous fluid therapy. *Cortisol* and *aldosterone* are steroid hormones that are secreted in greater amounts in response to trauma, and they increase the ECF volume.

Nervous system activity also affects the fluid balance. The vascular tone is governed by the sympathetic nervous system, which maintains the size of the "vascular costume." Specific receptors also have an impact on the fluid balance; for example, β_1-adrenergic stimulation (isoprenaline) retains fluid, and α_1-stimulation (phenylephrine) increases the urinary excretion, even in the anesthetized state [2].

Water Turnover

The minimal recommended intake of water in humans is 1.0 mL/kg/h. The limit is often set 25% higher to obtain a "safety margin" for sweating and unforeseen losses. Children have a greater metabolic activity and therefore require more fluid. Naturally, the fluid requirement also increases greatly in many disease states, like burn injuries and diarrhea. The body also creates approximately 300 mL of water per day from its energy metabolism. The water intake is needed to compensate for evaporation from the skin and lungs (*insensible water losses*), as well as for maintaining a baseline urine flow that is sufficient for the excretion of metabolic end products (such as creatinine).

The need for a fluid volume is markedly increased during anesthesia, for several reasons. One is that anesthesia causes vasodilatation, which increases the "unstressed" blood volume. The plasma volume should then be expanded to maintain adequate venous return to the heart; otherwise, the hemodynamics needs to be supported by administration of a vasoconstrictor. Moreover, the general depression of the autonomous system during anesthesia redirects blood flows between vascular beds, which might induce local disturbances of tissue perfusion. The aim of expansion of the plasma volume at the initiation of anesthesia is combat these disturbances. Moreover, blood loss during the surgery, and the fact that oral fluid intake has been temporarily stopped, also increases the need for fluid. Contrary to common belief, the loss of water by evaporation from surgical wounds is not particularly impressive. As a rule, open abdominal surgery with wide exposure of the intestines doubles the insensible fluid losses.

Derangement of the Body Fluid Volumes

The physiological tolerance to derangement of the body fluid volumes varies greatly. Most delicate is a loss of blood volume (hypovolemia), which initially is compensated by an increased stroke volume and sometimes by an accelerated heart rate. When approximately 1 L has been lost, the arterial pressure falls and the patient exhibits signs of *shock*. This situation is directly life-

threatening within minutes if combined with neurotrauma that has raised the intracranial pressure.

Tolerance is greater for a loss of ECF volume (*volume depletion*), which occurs in diarrhea, ileus, and diabetic ketoacidosis. Here, 3–4 L, or even more, can be lost before shock ensues.

The tolerance for losses of ICF is poorly known, but it is far greater than for volume depletion. Dehydration of the ICF is associated with poor intake of water in the elderly. The chief compensation is to increase the renal water conservation by concentrating the urine. If the capacity of the kidney is not sufficient, the plasma osmolality increases. A value exceeding 300 mosmol/kg is a frequently used criterion for dehydration of the ICF space [3].

The Starling Equation

The forces involved in the distribution of fluid across the capillary membrane are summarized as follows in the classical *Starling equation*:

$$\text{Fluid exchange} = K_f \left[\left(P_c - P_i \right) - \sigma \left(\pi_p - \pi_i \right) \right]$$

where K_f is a proportionality constant; P_c and P_i are the hydrostatic fluid pressures in the capillary and interstitium, respectively; and π_p and π_i are the colloid osmotic pressures in the plasma and interstitial fluid, respectively. The symbol σ is the reflection coefficient, which explains how easily macromolecules pass through the capillary wall. A reflection coefficient of 1.0 means that the membrane is impermeable, while 0 means that the molecule passes without any difficulty. The value of σ varies greatly between vascular beds. In a normal man, P_c is 17–25 mmHg, P_i is −3 mmHg, and π_p is 25 mmHg. In typical tissues, π_i amounts to only 5 mmHg.

The Starling equation summarizes our possibilities for infusing fluid that translocates a volume across the capillary membrane. Infusing a crystalloid fluid increases P_c and dilutes π_p, both of which promote a distribution of volume from the plasma to the interstitial fluid space. Infusing a colloid with a π_p higher than 25 mmHg recruits fluid from the interstitial fluid space to the plasma. Modern microcirculatory research holds that this type of recruitment cannot occur across the capillary wall. However, this is an academic issue, as recruitment does occur either by the lymph or by transcapillary flow.

The sensitivity of the brain to changes in serum osmolality has implications for the choice of infusion fluid in neurotrauma and neurosurgery. Isotonic infusion fluids should be used when providing volume expansion to compensate for anesthesia and/or hemorrhage due to the sensitivity of the brain to changes in osmolality. Hypotonic infusion fluids should be avoided, whereas hypertonic fluid has a place in the clinical handling of cerebral edema.

Cerebral Circulation

The brain has a more delicate system for regulating its fluid content than is found in the rest of the body. The "blood-brain barrier" prevents fluid shifts from the plasma to interstitial fluid by restricting passive diffusion of even small molecules. Therefore, the capillaries of the brain are much less "leaky" than are capillaries elsewhere. However, changes in hydrostatic and oncotic forces in the plasma may still, to some degree, change the water content of the brain, as water is freely diffusible [4].

Filtered water is circulated by means of the cerebrospinal fluid system, as the brain lacks lymphatic vessels. The cerebrospinal fluid volume amounts to approximately 150 mL of the total volume of 1.7 L contained in the brain and spinal cord. The turnover rate is approximately 500 mL per day.

Most tissues have autoregulated blood flow governed by factors such as metabolic rate and the availability of oxygen. Increases in the local blood flow and hydrostatic pressure also stimulate the glycocalyx to release nitric oxide, which causes vasodilatation and makes room for more blood.

The blood flow to the brain, which amounts to 15% of the cardiac output, follows these general principles, but it is also regulated by carbon dioxide and pH. Increases in any of these dilate the cerebral vessels, thereby allowing a more efficient washout of metabolic end products from the brain. This is considered important as neuronal activity strongly depends on both the carbon dioxide pressure and on pH.

Autoregulation protects the brain from being affected by variations in arterial pressure and operates in a mean arterial pressure range between 60 and 140 mmHg. If the pressure becomes excessive, the sympathetic nervous system constricts the cerebral arteries to limit the capillary filtration. The cerebral fluid pressure is maintained at approximately 10 mmHg by absorption of filtered fluid into the cerebrospinal fluid that then circulates around the brain and the spinal cord. The arachnoid villi also have a valve function that allows direct entry of fluid into the venous sinuses in cases where the intracranial pressure exceeds the venous pressure.

Brain edema is most often caused by trauma that damages the blood-brain barrier and causes inflammatory swelling in the injured areas. The edema compresses the blood vessels, thereby decreasing the perfusion. Elevation of the carbon dioxide pressure might not be sufficient to restore the blood flow, and ischemia develops. This is a situation where the clinician must take prompt action to limit cell death and even to save the brain. For this purpose, fluid therapy with hypertonic fluid that reduces the edema is of paramount importance.

Head trauma that is combined with circulatory shock from hemorrhage poses an even more complicated problem. Here, the mean arterial pressure (MAP) must be restored sufficiently to allow perfusion of the brain. The cerebral perfusion pressure is given by the difference between the MAP and the intracranial pressure, which is approximately 10 mmHg. In neurotrauma, where the intracranial pressure is markedly elevated, the MAP may become a crucial parameter for the survival of the brain. High venous pressure might also be a problem, as the filtered fluid enters the venous system directly in cases where the intracranial pressure is high. The cerebral perfusion pressure is then determined as the difference between the MAP and the pressure in the jugular vein.

Fluid Translocation Across the Cell Membrane

The brain is susceptible to changes in osmotic pressure, which governs the fluid distribution between the ECF and ICF.

The equation below shows the equilibrium that always persists between the ECF and ICF. Assuming that the ECF and ICF volumes are 20% and 40% of the body weight, respectively, and that normal body osmolality is 295 mosmol/kg, we obtain the following [5]:

$$\frac{\text{ECF} \cdot 295 + \text{infused osmoles}}{\text{ECF} + \text{fluid exchange} + \text{infused volume}} = \frac{\text{ICF} \cdot 295}{\text{ICF} - \text{fluid exchange}}$$

The idea behind this mass balance equation is that the amount of solutes divided by the fluid volume must remain the same after manipulation of any of involved factors. The reason is that the osmolality is the same in all body fluid compartments. The only unknown factor in this equation is "fluid exchange," which can change in any direction, although positive values denote translocation from the ICF to the ECF.

This equation can be applied to sodium chloride and mannitol solutions. However, glucose is not pertinent because glucose only remains temporarily outside the cells.

A single extracellular solute can also be used for this calculation. The simplest solute to monitor is plasma sodium, which is the electrolyte that is most often manipulated by fluid therapy intended to control the intracranial pressure. The plasma concentrations before the intervention, Na_o, and at any time t after it has occurred, Na_t, are then connected in the following equation [6]:

$$\text{Fluid exchange} = \text{ECF}_o + \text{infused volume} - \left[\left(\text{Na}_o\text{ECF}_o + \text{infused Na}\right) / \text{Na}_t\right]$$

If urinary excretion has occurred, the voided volume should be subtracted from the infused fluid volume. Similarly, the sodium ions excreted in the urine should be subtracted from the infused amount of sodium.

Fluid Kinetics

Tracers

The volumes of the physiological body fluids spaces can be measured with tracers that distribute in one single physiological fluid space only. The *dilution principle* is then employed to estimate the size of the compartment. This principle means that the volume of distribution of a molecule is the dose divided by the plasma concentration after adequate equilibration. Examples of tracers include radioactive albumin and indocyanine green for the plasma volume, iohexol and bromide for the ECF volume, and deuterium for the total body water.

The benefit of using a tracer is that it yields (presumably) precise information about the size of a body fluid space. Downsides include the abundant potential methodological errors and the ability to obtain (usually) only one measurement. Tracer methods require a reasonable steady state during the mixing period; therefore, capturing the distribution phase of a crystalloid fluid, for example, is not possible with these methods.

Mass Balance

Several methods are available to calculate the distribution of infused fluid between the plasma, the interstitial fluid, and the ICF. The most widely applied protocol is to use a set of mass balance equations, where the blood volume at baseline (BV_o) is estimated based on anthropometric equations and the BV changes are estimated from measurements of the blood Hb concentration at time 0 and at a later time t [7].

$$\text{Hbmass}_o = \text{BV}_o\,\text{Hb}_o$$

$$\text{BV}_t = \text{Hbmass}_o - \text{bled volume}\left(\left(\text{Hb}_o + \text{Hb}_t\right)/2\right)$$

$$\Delta BV_{t-0} = \text{BV}_t - \text{BV}_o$$

$$\text{Clinical efficacy} = \Delta BV_{t-0} / \text{Infused volume}$$

$$\text{Interstitial fluid volume} = \text{infused volume} - \text{urine} - \Delta BV_{t-0}$$

The weaknesses of this approach are that the BV is assumed and that the distribution of Hb molecules must be even throughout the blood volume. No simulation can be performed that predicts the outcome of experiments not performed. One should note that the equation reflects the distribution of the infused fluid volume and not of the Hb molecules. The glycocalyx volume is included when crystalloid fluid is infused, as the glycocalyx is hydrated as well. Whether the

glycocalyx volume is included when colloid fluid is studied is not known.

Volume Kinetics

A more complete approach for the description of fluid distribution and elimination is offered by a research method called *volume kinetics*, which has similarities to pharmacokinetics [8]. The studied fluid is administered over 30 min, and the Hb concentration and the urinary excretion are measured repeatedly over 3–4 h. A kinetic model with (usually) two expandable compartments is fitted to these data, thereby allowing the estimation of a number of parameters in the kinetic model using complex mathematics. A second step is to test for the potential influence of various individual-specific covariates on these parameters. These covariates can be factors such as body weight, gender, age, or arterial pressure (Fig. 2). Many studies have demonstrated that the obtained values correspond reasonably well to the known volumes of the major physiological body fluid spaces.

Volume kinetic analysis of crystalloid fluid shows an initial distribution over the plasma volume. Diffusion across the capillary membrane to the interstitial fluid space occurs with a half-life of approximately 8 min. Complete distribution is finally achieved after 30 min (four half-lives). Iso-oncotic colloid fluid does not have a distribution phase, and hyperoncotic solutions recruit fluid from the interstitial fluid space and, to some degree, from the ICF as well.

The distribution phase for crystalloids makes short bolus infusions a risky practice in neu-

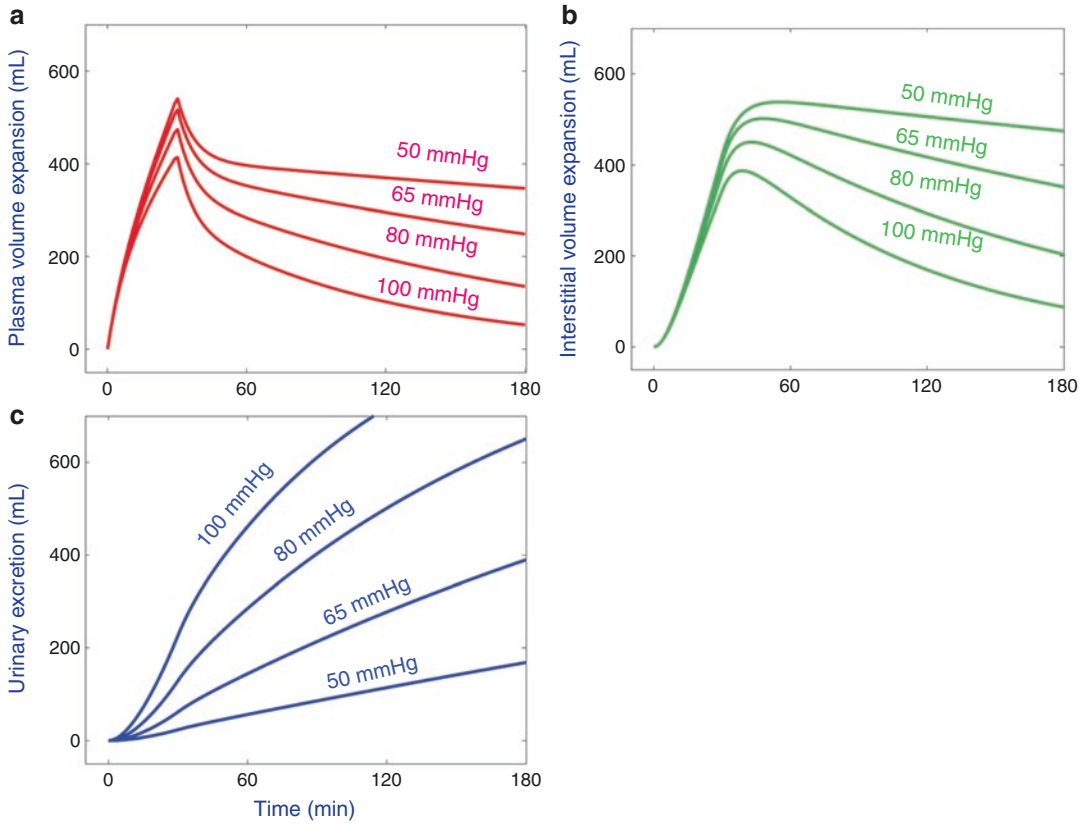

Fig. 2 Volume kinetic plots showing (**a**) plasma volume, (**b**) interstitial volume, and (**c**) urinary excretion, all resulting from covariance between the mean arterial pressure (MAP) and urinary excretion during 78 infusion experiments. Computer simulation of an infusion of 1 L of Ringer's solution over 30 min, based on kinetic data published in *Anesthesia and Analgesia* 2017; 124: 1824–1833

rotrauma patients, as the intravascular hydrostatic pressure might suddenly become very high. By contrast, the rate of infusion does not matter much for colloid infusions. However, colloids expand the plasma volume more than the crystalloid fluids do (iso-oncotic fluids 1:1, 20% albumin 2:1), and the plasma remains expanded for a longer time.

The intravascular persistence of colloid fluid is not greatly dependent on the arterial pressure, but the excretion of crystalloid fluid becomes markedly retarded by a reduction in the arterial pressure, such as occurs during general anesthesia (Fig. 2). In the intensive care setting, this slow excretion can create a similar plasma volume expansion for either colloid or crystalloid fluids from 6–8 h after an infusion and onward.

Urinary Excretion

The diuretic response to infusion fluids may affect their distribution. For example, the urinary sodium concentration in everyday life is approximately 60 mmol/L, and a number of hours are required for the kidneys to increase the excretion to match the concentration of an infused isoosmotic crystalloid fluid. Therefore, serum sodium will remain largely unchanged, and water will be recruited from the cells during the first 1–2 h after initiating an infusion of Ringer's lactate solution, despite the fact that Ringer's has an osmolality of 273 mosmol/kg (plasma has 295 mosmol/kg) [6].

Another example is hypertonic (15%) mannitol, which is marketed as a solution devoid of electrolytes. Mannitol distributes over the entire ECF volume and recruits fluid from the cells by virtue of its hyperosmotic nature (iso-osmotic mannitol is 5%). The induced osmotic diuresis removes the recruited fluid from the body. However, osmotic diuresis brings along extracellular electrolytes and amino acids in an uncontrolled fashion. The loss of electrolytes makes the ECF hypo-osmotic, thereby creating a "rebound" flow of fluid in the opposite direction. This phenomenon would not occur if electrolytes were added to the fluid or supplemented by a separate infusion.

In conclusion, the distribution of an infusion fluid is fairly well predictable from its composition. However, modifications exist due to distribution effects, arterial pressure, and kidney function.

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Basics of Perioperative Fluid Requirements in Neurosurgical Patients

Shilpa Rao and Miriam M. Treggiari

Abstract

Patients scheduled for elective neurosurgical procedures present unique considerations regarding perioperative intravenous fluid management in the context of multiple distinctive factors encountered in this patient population. Commonly used indicators for adequate volume replacement such as urine output may be challenging to interpret due to concurrent use of diuretics, for example, mannitol. In this chapter, we discuss the basics of fluid physiology and blood-brain barrier mechanisms regulating fluid shifts. We also discuss preoperative factors contributing to hypovolemia in neurosurgical patients, assessment of volume status, and considerations for volume replacement.

Keywords

Intravascular volume · Blood-brain barrier
4-2-1 rule

S. Rao (✉)
Department of Anesthesiology, Division of Neuroanesthesia, Yale School of Medicine/Yale University, New Haven, CT, USA
e-mail: shilpa.rao@yale.edu

M. M. Treggiari
Department of Anesthesiology, Yale School of Medicine/Yale University, New Haven, CT, USA

Basics of Fluid Physiology

Water comprises approximately 75% of body mass in infants and about 60% in adults. There is constant movement of water throughout different compartments of the body via multiple active transport mechanisms. Broadly, the total body water is distributed in two main compartments: extracellular fluid and intracellular fluid. In adults, extracellular fluid comprises approximately 20% of total body weight and intracellular fluid comprises approximately 40% of total body weight. Physiologically, water moves across (semipermeable) membranes following the osmotic gradient, with water tending to move from the compartment with lower osmolarity to the side with higher osmolarity to equilibrate the gradient. Osmolarity is defined as the concentration of a solution expressed as the total number of osmotically active solute particles per liter of fluid. Plasma osmolarity is tightly regulated with normal values between 285 and 295 mOsmoles/L. The osmolarity of commonly administered intravenous fluids is in reference to plasma osmolarity.

Basic Physiology of the Blood-Brain Barrier and Pericytes

The blood-brain barrier (BBB) is a partition between the vascular compartment and the brain interstitial fluid regulated via tight junctions and

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highly specialized endothelial cells. It mainly functions as a dynamic barrier for metabolic transport bidirectionally, due to its selective permeability. The BBB is readily permeable to gaseous molecules such as oxygen and carbon dioxide, as well as water, but it is impermeable to ions and other solutes for which active transport is required. Lipid-soluble substances cross the BBB through diffusion. However, larger molecules such as complex proteins have a restricted access through the BBB, mostly via complex receptor-mediated mechanisms.

An intact BBB is essential to maintain the delicate extracellular environment around synapses, axons, and neurons. Multiple pathological conditions can cause disruption of BBB and increase permeability or intracellular water content, thereby leading to fluid shifts across the membranes resulting in vasogenic or cytotoxic cerebral edema. Some of these conditions include but are not limited to tumors, bleeding, trauma, vascular malformations, etc. In the setting of these pathological conditions, progressive utilization of the normal cerebral compensatory mechanisms eventually leads to increased intracranial pressure with the slightest increase in volume.

The neurovascular unit (NVU) is a complex functional and anatomical unit composed of endothelial cells and their BBB, forming tight junctions; a basal lamina covered with pericytes including astrocytes, neurons, and interneurons; and an extracellular matrix. This unit as a whole regulates fluid balance and overall homeostasis of the BBB. Pericytes are vascular mural cells present in the basement membrane of blood microvasculature. Their processes extend along capillaries, precapillary arterioles, and postcapillary venules. Central nervous system pericytes are uniquely positioned in the neurovascular unit between endothelial cells, astrocytes, and neurons. They integrate, coordinate, and process signals from their neighboring cells to generate diverse functional responses that are critical for regulation of the BBB permeability and autoregulation.

Figure 1 shows the basic composition of neurovascular unit.

An important concept in the processes regulating fluid shifts in the brain is the transport mecha-

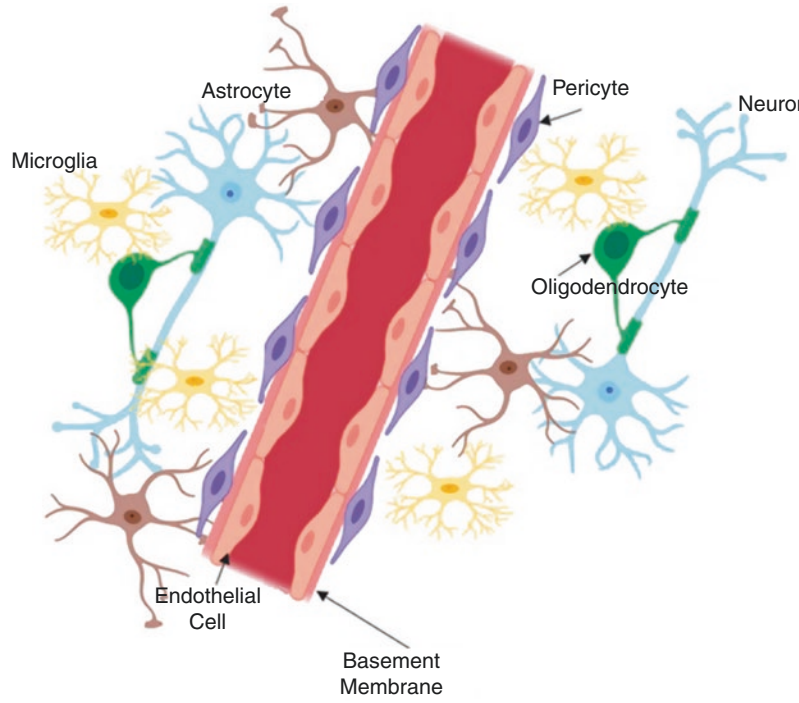

Fig. 1 Structural and cellular composition of the neurovascular unit. (Nzou G, Seeds MC, Wicks RT, Atala AJ. Fundamental neurovascular components for the development of complex and dynamic in vitro brain equivalent models. *J Alzheimers Neurodegenerative Dis*)

nisms related to sodium physiology. Sodium is one of the major electrolytes in the body. Normal sodium levels are 135–145 mmol/L. Among other functions, Na facilitates a normal balance of fluids and plays an important role in nerve conduction and muscle function. Sodium levels are tightly controlled via receptors in the heart, blood vessels, and kidneys through the secretion of natriuretic peptides. The sodium levels in the body affect the blood volume and interstitial fluid. For example, in the presence of hyponatremia (low sodium levels), the kidneys stimulate the adrenal glands to secrete aldosterone, which in turn, cause the kidneys to retain sodium and excrete potassium, thereby increasing blood volume.

In the presence of an intact BBB, since the BBB is impermeable to Na, the intravenous administration of hypertonic sodium causes a rapid increase of plasma osmolality, thereby creating an osmotic gradient between the intracellular compartment of the CNS and the intravascular compartment, leading to a reduction in brain volume with associated reduction of intracranial pressure, thus favoring brain relaxation.

Perioperative Evaluation of Volume Status

During the preoperative phase, performing an adequate history and physical examination in an awake, conscious, neurologically intact, and cooperative patient should alert the anesthesiologist regarding the possibility of hypovolemia (intravascular volume depletion) or dehydration. The patient may complain of postural dizziness, headache, lethargy, and feeling of thirst or hunger. In a pediatric patient, poor weight gain and failure to meet milestones/failure to thrive can point to a poor nutritional status, apart from obtaining feeding history from the primary caregiver.

Basic physical examination techniques include assessment of skin turgor, mucus membranes, etc.

Preoperative vitals may show tachycardia and/or associated hypotension. The heart rate response may not be completely manifest in elderly patients due to poor beta receptor responsiveness. However, there are multiple factors that could contribute to preoperative tachycardia and hypotension, and the anesthesiologist needs to be familiar with their differential diagnosis. Some of the commonly noted caused of tachycardia include preoperative anxiety and pain. Importantly, use of antihypertensives or improper selection of blood pressure cuff during measurement may cause an inappropriately lower blood pressure reading. Hypovolemia is typically unmasked at induction of general anesthesia when cardiovascular depression associated with induction medications, as well as decreased venous return from positive pressure ventilation/PEEP, can lead to hypotension.

During general anesthesia, surrogate identifiers of volume status are typically used. These include increased heart rate (HR) above baseline values and drop in blood pressure (BP) from baseline values or below acceptable mean arterial pressure (MAP < 55–60 mm Hg). However, as in the preoperative patient, there are multiple factors contributing to altered cardiovascular physiology during general anesthesia. Besides the challenges of evaluating volume status based on static hemodynamic indices of HR or mean arterial pressure (MAP), monitoring of urine output to evaluate volume status is also potentially problematic. Typically, a Foley catheter is inserted to monitor urine output intraoperatively. Oliguria, as defined as a low urine output (<0.5 ml/kg/h), may indicate hypovolemia with inadequate volume replacement. However, the concurrent use of diuretics, such as mannitol during neurosurgeries, may make the interpretation of this parameter unreliable as well.

If a central venous catheter is available, trending the central venous pressure (CVP) may be used as a surrogate to assess volume status; however, CVP has been extensively reported to be inaccurate to determine cardiac preload, especially if in the lower range of values, and is a poor predictor of fluid responsiveness [1]. Dynamic indices of cardiovascular function are known to be better predictors of fluid responsiveness particularly during positive pressure ventilation. Respiratory variations in the arterial pressure waveform can be visually observed to assess response to fluid challenges [2]; however, these indices must be used with caution and clinically correlated.

Other more invasive techniques involve the use of Pulse Contour Cardiac Output (PiCCO), transpulmonary thermodilution (pulmonary artery catheter), or transesophageal echocardiography to visualize left ventricular volume and size estimates. Although these techniques are widely used in the ICU setting, they are rarely practiced in neuroanesthesiology.

Calculating Plasma and Blood Volume

In a normal adult, plasma volume is estimated using the following formula: total blood volume × (1 − hematocrit).

In renal failure patients, plasma volume is typically calculated using Kaplan-Hakim formula [3] using data derived by the hematocrit value and the body weight. Calculated plasma volume (cPV) = (1 − hematocrit) × [a + (b × weight in kg)] where adjustment factors were $a = 1530$ in males and 864 in females, and $b = 41$ in males and 47.9 in females [4]. As evident from the formula, the plasma volume is dependent on body weight and hematocrit/blood volume.

Blood volume refers to the total volume circulating within the arteries, capillaries, veins, venules, and chambers of the heart at any given point of time. The components of blood volume include red blood cells (erythrocytes), white blood cells (leukocytes), platelets, and plasma.

The estimated blood volume calculator (see below) utilizes parameters such as patient age, sex, and weight. On an average, neonates and premature neonates have a higher blood volume per kilogram as compared to adults.

Average blood volume = patient weight (kg) * (average blood volume in mL/kg)

The average blood volume per demographic (mL/kg) is listed as follows:

Adult male = 75
Adult female = 65
Infants = 80
Neonates = 85
Premature neonates = 95

This calculator serves as a guide for transfusion requirements and volume replacement in different age groups.

Formerly, restrictive fluid management was practiced for patients with cerebral tumors with the assumption that fluid administration could enhance cerebral edema [4]. However, it is now recognized that hypotension due to hypovolemia can decrease cerebral perfusion pressure and cerebral blood flow with undesirable consequences.

Common Formulas Used to Calculate Fluid Deficit

One of the commonly used formulas in clinical practice is the 4-2-1 rule for intravenous fluid replacement for fasting patients. This is especially useful in pediatric patients and avoids fluid overload. The ideal body weight (IBW) of the patient is used for calculations.

IBW is calculated as:

$$\text{Males}: \text{IBW} = 50\,\text{kg} + 2.3\,\text{kg for each inch over 5 feet}$$

$$\text{Females}: \text{IBW} = 45.5\,\text{kg} + 2.3\,\text{kg for each inch over 5 feet}$$

4-2-1 rule

$$4\,\text{ml/kg/h. for the first } 1-10\,\text{kg} +$$

$$2\,\text{ml/kg/h. for } 11-20\,\text{kg} +$$

$$1\,\text{ml/kg/h. for} > 20\,\text{kg}$$

It must be kept in mind that the 4-2-1 rule is only a guideline for maintenance intravenous fluid replacement during the intraoperative period. It is typically recommended that approximately half of the fluid deficit resulting from preoperative fasting be administered in the first hour of anesthesia, along with maintenance fluids. Any additional losses in the form of bleeding or third space losses must be assessed incrementally and replaced accordingly.

Effects of Fluid Composition on Intravascular Volume Status

Crystalloids have wide variability in osmolarity and can be classified into hypotonic, isotonic, and hypertonic in relation to plasma osmolarity, as listed in Table 1.

The most commonly used fluids for routine intraoperative neurosurgeries not involving major blood loss are isotonic crystalloids. Even if slightly hypotonic, typically, the authors recommend Plasmalyte and/or Ringer's lactate for maintenance infusion at a rate of 2–4 mL/kg/h. Caution must be exercised while administering large volumes of Ringer's lactate since it contains approximately the equivalent of 100 mL of free water per liter, which could potentially cause cerebral edema and increased intracranial pressure over time. While 0.9% normal saline is isotonic, caution must also be exercised while administering large volume of 0.9% normal saline due to high chloride load, as this has been associated with hyperchloremic metabolic acidosis and possible renal dysfunction [5].

Hypotonic fluids, e.g., D5W (5% dextrose in water), must be avoided in neurosurgical patients, since they can exacerbate cerebral edema and lead to undesirable hyperglycemia. Free water can easily cross blood-brain barrier.

Hypertonic crystalloids include increasing concentrations of sodium in the solution (1.5%, 3%, and 23%). Hypertonic crystalloids can be mixed as sodium chloride or sodium acetate. When hyperchloremia becomes an issue, especially for longer-term infusions or if serum chloride is already elevated, sodium acetate solutions

Table 1 Composition of commonly used intravenous fluids: crystalloids

	MOsm/l[a]	mEq/l					g/l	
Intravenous fluids		Na^+	Cl^-	K	Ca	Mg	Lactate	Dextrose (g/l)
5% dextrose in water (D5W)	278							50
5% dextrose in 0.45% NaCl	405	77	77					50
5% dextrose in 0.9% NaCl	561	154	154					50
5% dextrose in Ringer's solution	525	130	109	4	3			50
Ringer's solution	309	147	156	4	4–4.5			
Lactated Ringer's solution	275	130	109	4	3		28	
5% dextrose in Lactated Ringer's solution	525	130	109	4	3		28	50
Plasmalyte[b]	298	140	98	5		3		
0.45% NaCl	154	77	77					
0.9% NaCl	308	154	154					
3.0% saline	1026	513	513					
5.0% saline	1710	855	855					
7.5% saline	2566	1283	1283					
20% mannitol	1098							

Tommasino C, Fluids and the neurosurgical patient. *Anesthesiol Clin North Am* 20(2): 329–46, 2002. Reproduced with permission from Elsevier, Inc.

[a]Osmolarity = calculated value (osm/l = mg÷molecular weight × 10 × valence)

[b]Acetate 27 mEq/L and gluconate 23 mEq/L

are preferable. Assuming the BBB is intact, hyperosmolar solutions exert their effects by osmotically shifting water from the intracellular and interstitial spaces toward the intravascular space. This effect has been demonstrated in brain tissue with normal blood-brain barrier [6].

Mannitol is being used as the mainstay of treatment of raised intracranial pressure (ICP), to a maximum dose of 1.2 g/kg of body weight, by monitoring closely plasma osmolarity not to excel 320 mOsm/L. Mannitol is an osmotic diuretic, and it exerts its effect on lowering ICP by reducing intracranial water content. However, in its biphasic mechanism of action prior to its diuretic effect, it first increases plasma volume and decreases viscosity, via its dose-dependent osmotic effects. This osmotic effect traps water and solutes in the tubular fluid, thus increasing sodium, potassium, chloride, and bicarbonate excretion via the kidneys.

Since there is no large body cavity exposed during craniotomies, there is typical minimal third space losses. Likewise, in the absence of unexpected complication, hypovolemia from blood losses is relatively uncommon during cerebral surgery. When evaluating volume replacement, it is also necessary to account for the obligatory fluid volume administered in concomitance with medication infusions during neurosurgical procedures. One common consequence of large volume fluid infusion is a reduction in hemoglobin/hematocrit. This hemodilution is typically accompanied by an increase in the cerebral blood flow due to improved rheological conditions including reduction in blood viscosity [7]. In the normal brain, the increase in CBF produced by hemodilution is an active compensatory response to a decrease in arterial oxygen content, and this response is essentially comparable to that seen with hypoxia [8, 9]. In the face of brain injury, the normal CBF responses to hypoxia and to hemodilution are attenuated, and loss of either response may contribute to secondary brain injury [10]. A hematocrit level of 30–33% is considered to yield the optimal combination of viscosity and O_2 carrying capacity, and may be associated with improved neurologic outcomes [11].

Risk Factors for Perioperative Hypovolemia

Dehydration in surgical patients occurs from inadequate oral intake (causes listed below) from multiple factors. In the perioperative setting, since most of the neurosurgeries are performed under general anesthesia, patients presenting for elective neurosurgeries are typically fasting (nil per oral (NPO)) overnight, for a duration of about 10 h, per preoperative fasting guidelines [12].

Adequate monitoring, repletion, and maintenance of intravascular volume status is important during the perioperative period, and fluid management is a primary responsibility for the anesthesiologist. Inadequate volume replacement can lead to hemodynamic instability, tachycardia, hypotension, decreased ability to cope with surgical stress, as well as exaggerated response to anesthetic medications. All of these factors can lead to inadequate cerebral perfusion.

Causes of perioperative decrease in volume status include the following:

Preoperative factors

1. Preoperative fasting
2. Preexisting bowel obstruction and/or mechanical bowel preparation
3. Emergency surgeries with associated preexisting bleeding or third space volume losses
4. Nausea, vomiting, and/or associated poor oral intake due to large brain tumors
5. Preoperative diabetes insipidus
6. Preoperative cerebral salt wasting syndrome

Intraoperative factors

1. Vasodilation associated with anesthetic medications
2. Patient positioning. e.g., reverse Trendelenburg position which decreases venous return from lower extremities
3. Positive pressure ventilation with higher levels of positive end-expiratory pressure and Valsalva maneuvers

4. Surgical site bleeding with inadequate replacement
5. Special medications used during neurosurgical procedures to improve brain compliance such as mannitol, or other diuretics such as furosemide
6. Intraoperative diabetes insipidus in certain pituitary surgeries or severe traumatic brain injury

Postoperative factors

1. Ongoing bleeding from surgical site
2. Inability to transition to oral fluids with inadequate intravenous replacement
3. Nausea and vomiting in the postoperative period with inadequate replacement
4. Continued use of mannitol and/or diuretics
5. Postoperative diabetes insipidus

A combination of above factors may be encountered by the anesthesiologist in various settings—e.g., in the operating room, in the post-anesthesia care unit (PACU), or in the intensive care unit (ICU). It is important to conduct an early and adequate assessment of volume status and replace fluids accordingly.

Conclusion

In conclusion, there are multiple factors regulating total body water, plasma volume, and blood volume. They exert direct and indirect effects on cerebral homeostasis, and have influences on intracranial pressure and volume. Patients undergoing neurosurgery have altered cerebral autoregulation, and have multiple perioperative factors contributing to dehydration and/or hypovolemia. The practicing neuroanesthesiologist is required to have an understanding of basics of neurophysiology and of fluid requirement, in order to recognize and treat fluid deficits and shifts during the perioperative period.

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Part II

Fluids: Types of Fluids

Crystalloids

Shraya Banerjee

Abstract

Clinical utility of intravenous crystalloids in restoring the hydration, resuscitation, and perioperative maintenance is often undermined amidst the plethora of other clinical skills. Intravenous crystalloids are the most commonly prescribed agents in the emergency departments, intensive care unit, operation theatres, and hospital wards. Historically, pioneering work on cholera patient's rehydration marked the advent of intravenous crystalloid therapy. Development of Hartmann's solution for treating children was another milestone achieved. Current day clinical practice witnesses a basket of choice of intravenous crystalloids which are isotonic, hypotonic, or hypertonic to plasma. Traumatic brain, spine injury patients and other neurosurgical patients pose a challenge for the intensivist and anesthesiologist in formulating their fluid therapy because of ongoing cerebral edema and fear of worsening neurological outcome. The chapter highlights the important crystalloids and their composition and uses in neuroscience practice.

Keywords

Crystalloid · Fluid therapy · Isotonic fluid
Hypotonic fluid · Hypertonic fluid
Neuroscience · Balanced-buffered crystalloids

Background

Intravenous fluids containing electrolytes of small molecular weight (less than 30,000 daltons) which can cross any semipermeable membrane are designated as crystalloids. Discovery of crystalloids dates back to 1861 when Sir Graham essentially classified fluids into crystalloids and colloids based on their property to diffuse through parchment membrane. Annually, approximately 30 million patients receive intravenous fluid in the healthcare setting for one of the many indications [1, 2]. Intravenous crystalloids are cornerstone for treatment of severely dehydrated patients, also used in resuscitation of blood volume in trauma patients, as a maintenance fluid perioperatively or as a carry fluid for medications [3, 4]. Intraoperative use of crystalloids was initiated in the nineteenth century [5]. Normal saline and lactated ringer are the most commonly used crystalloid worldwide in clinical practice [6].

This chapter gives an overview of commonly used crystalloids and their composition, indication, side effects, and interaction, which are used in routine neuroscience practice.

S. Banerjee (✉)
Neuroanaesthesia & Critical Care, Indraprastha Apollo Hospital, New Delhi, India

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Properties of Ideal Crystalloid

There exists a vast choice of intravenous fluid in the clinician's armamentarium to treat dehydration and blood or fluid loss for maintenance perioperatively. With so many pharmacological companies and commercial preparation in the market, the treating doctor finds himself in a state of clinical dilemma while choosing the right fluid. "One fluid fits all patients" concept is rudimentary as the patient's pathology and clinical state guides the fluid prescription tailoring. Ideal crystalloid is hard to find which suffices all the requirements in an ailing patient. The general properties of an ideal fluid are listed:

Colorless, odorless, nonallergenic, nonreactive, P^H similar to plasma, maximum retention in the intravascular compartment, composition same as the plasma, no harmful by-products, stability at room temperature, long shelf life, no effect on coagulation, ready availability, no religious obligation, inexpensive [7].

Classification of Crystalloids

Traditionally, intravenous crystalloids are classified as [8]:

Isotonic crystalloids: These fluids have solute concentration similar to that of plasma. When administered, it remains in the extracellular compartment and contributes to the intravascular volume, e.g., 0.9% NaCl, Ringer's lactate, and Plasmalyte A 148.

Hypotonic crystalloids: These fluids have solute concentration lower than that of plasma. Intravenous administration causes cellular swelling, for example, 0.45% NaCl and 5% dextrose.

Hypertonic crystalloids: These fluids have solute concentration higher than plasma. The osmotic pressure gradient generated by its intravenous infusion draws water out of the cells and increases the intravascular volume, for example, 3% NaCl and 20% mannitol.

Another classification system is based on their clinical use.

Crystalloids for maintenance: This fluid group is used to replace the bodily insensible losses. 5% dextrose and 0.45% NS with dextrose are classical examples.

Crystalloids for replacement: This fluid group is used to replace fluid deficit due to vomiting, diarrhea, trauma, burns, and intraoperative loss, for example, 0.9% NaCl and Ringer's lactate.

Special crystalloids: This group of fluid is used for miscellaneous purpose like 20% mannitol to decrease intracranial pressure by virtue of osmotic diuresis, injection sodium bicarbonate to correct acid-base abnormality, injection KCl to correct hypokalemia, etc.

What Is Balanced-Buffered Salt Solution?

Evolution of balanced salt solution [9] is linked to the observation that metabolic acidosis is often associated with administration of high volumes of normal saline [10].

Earlier, 0.9% NaCl was considered the ideal crystalloid for intraoperative fluid therapy. However, this concept became increasingly doubtful when metabolic acidosis was noted in patients who were administered large volume of normal saline (>20 ml/kg/h). The reason being high chlorine content of normal saline (154 meq/L versus 103 meq/L) compared to human plasma [11]. The concern was more evident in patients with compensated renal function [12].

Stewart proposed the theory of strong ion difference to explain the metabolic acidosis caused by chloride excess. Under normal physiological conditions, the balance of cations and anions is maintained in any solution following the principle of electroneutrality. The strong ion difference of plasma can be calculated as:

$$SID = [(Na^{+2}) + (k^{+2}) + (Mg^{+2}) + (Ca^{+2}) - (Cl^{-2}) + (lactate)].$$

Fluctuation in the strong ion difference directly alters the plasma P^H. Large volume of intravenous 0.9% normal saline reduces the plasma strong ion difference because of its high chloride content. This reduction in strong ion difference will increase dissociation of water to H^+ and OH^- leading to fall in P^H and hyperchloremic metabolic acidosis [13].

Evidence from preclinical models [14, 15] and studies involving human adults [16] strongly suggest that chloride-rich intravenous fluid can attribute toward acute reduction of kidney blood flow and function. Animal studies show that excess chloride ions decrease the glomerular filtration rate by direct vasoconstriction and reduction in renal cortical perfusion. Similar effect was observed in healthy adults who were administered high-volume chloride-rich fluids. These observations led to the way for invention of balanced salt solutions.

Balanced salt solutions are crystalloid solutions having P^H similar to plasma (7.44), by the virtue of added buffer and it contains equal number of dissociated anions and cations [17]. Balanced crystalloids or balanced-buffered crystalloids have sodium, potassium, and chloride content near to that of extracellular fluid. They exert minimal influence on the physiological acid-base balance.

Classical example is Hartmann's or Ringer's lactate in which lactate acts as a buffer. Over the years, other balanced-buffered salt solutions were marketed including Normosol (Abbott Labs), Isolyte (B. Braun Medical), Plasmalyte A 148 (Baxter Healthcare), etc.

However, based on a recent Cochrane review [18], it seems that current evidence is insufficient to conclude if perioperative administration of buffered compared to non-buffered crystalloid fluids can have a substantial impact on mortality and organ system function in adult patients following surgery. Some benefits of buffered fluid were measurable in biochemical outcomes, particularly a significant reduction in postoperative hyperchloremia and metabolic acidosis. More research is needed on relevant clinical outcomes.

Salient Features of Commonly Used Crystalloids in Neuroscience Practice

There are wide range of crystalloids available for clinical use. The chemical composition of the most commonly used crystalloids and their advantages and disadvantages are summarized in Tables 1 and 2.

Normal Saline

Hartog Hamburger, a Dutch physiologist in 1896, invented normal saline while conducting in vitro studies on erythrocyte lysis. Normal saline (0.9% NaCl) is the most commonly used crystalloid in the current day neuroanesthesia practice perioperatively. Tonicity and sodium content of normal saline lie within 10% of the physiological limits of plasma; however, the unphysiological levels of chloride ions in normal saline are responsible for the metabolic acidosis seen following large volume administration. The property of normal saline which makes it the intravenous fluid of choice in the neurosurgical patient is its osmolar-

Table 1 Chemical composition of crystalloids of clinical use

Crystalloid	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	Glucose	Acetate	Malate	Gluconate	Lactate	Osmolarity	P^H
Normal saline	154				154						308	4.5–7
Ringer's lactate	130	4	2.7		109					28	273	6–7.5
Ringer's acetate	145	4	2.5	1	127		24	5			309	6–8
Plasmalyte A 148	140	5		3	98		27		23		294	7.3–7.4
Isolyte	141	5		3	98		27		23		295	6.3–7.3
Sterofundin ISO	140	10	2.5	1	127		24	5			309	5.1–5.9
D5W						50					278	3.5–5.5
DNS	154				154	50					585	3.2–6.5

Electrolytes are expressed in mmol/L, glucose in g/L, and osmolarity in mOsml/L

Table 2 Advantages and disadvantages of crystalloids

Crystalloids	Advantages	Disadvantages
Normal saline	• Cheap, easy availability, minimal interaction with other administered drugs • Minimal effect on coagulation pathway, hypertonic to plasma • Choice of fluid for reducing cerebral edema	• Composition is unphysiological compared to human plasma • Hyperchloremic metabolic acidosis • Unfavorable for chronic kidney disease patients, patients on ketogenic diet with metabolic acidosis • Doesn't provide calorie replacement
Ringer's lactate	• Balanced ionic composition, near physiological to plasma • Hyperchloremic acidosis not seen	• Hypotonic to plasma: can worsen cerebral edema, lactic acidosis in liver failure patients • Doesn't provide calories • Interferes with blood transfusion and medications
Plasmalyte A 148	• Balanced-buffered crystalloid composition similar to human plasma • Isotonic property causes no net movement of water across compartments • Gaining popularity as replacement fluid in neurosurgical patients • Decreases requirement of magnesium in ICU patients • Calcium-free: no interaction with blood transfusion • Better preservation of acid-base balance • Adverse renal events are lesser compared to normal saline in critically ill patients	• Cost of procurement is higher than normal saline • Does not meet energy requirements in ICU patients • Absence of cerebral edema reducing property • False-positive galactomannan test in healthy patients • Safety evaluation for pediatric population and carcinogenic potential is still under trial • Classified as Category C for pregnant patients
Isolyte	• Balanced-buffered crystalloid of newer composition simulating human plasma • Various subtypes are present targeting specific clinical condition • Maintenance fluid in pediatric patients as dextrose is an active formulation	• Incompatibility with phenytoin and diclofenac is reported with Isolyte • Not used in neurosurgical patients because of dextrose in formulation • Safety in geriatric and pregnancy is still under trials
Sterofundin	• Balanced-buffered fluid gaining popularity as a maintenance and replacement fluid in abdominal and thoracic surgeries • Isotonic in nature: no worsening of cerebral edema • Hyperchloremic acidosis is not seen with its use in traumatic brain injury patients • Better preservation of acid-base balance	• Costlier than normal saline • Presence of calcium interferes with blood transfusion • Safety profile in pediatric and pregnant patients under experiment
Dextrose-containing fluid	• Pediatric maintenance fluid with Ringer's lactate, normal saline • Provides calories to critically ill patients • Treatment of symptomatic hypoglycemia • Can provide free water for treating hypernatremic state • Adjuvant for other medications, e.g., inotropes • ERAS protocol—dextrose-rich formulation	• Hypotonic fluid causes water retention in the brain. Increases intracranial pressure • Glucose-containing solution is associated with worse neurological outcomes

ity being marginally higher than human plasma (308 versus 290 mOsmo/L). It prevents development of cerebral edema by decreasing the total brain water in patients who have raised intracranial pressure.

Current day neuroscience practice witnesses a wide range of applicability of normal saline. It is primarily used in acute brain, spinal cord trauma for volume resuscitation in patients of hypovolemic shock. Normal saline is used in day-to-day periop-

erative management of neurosurgical patients, in the neuro-intensive care unit, and for correction of mild levels of asymptomatic hyponatremia. Normal saline also finds its use in daily preparation of multiple anesthetic drugs as a diluent, carrier fluid for other drugs. Heparinized saline is used for flushing the arterial line to maintain its patency. Normal saline can be safely administered in the same blood tubings in patients receiving blood transfusion. It is employed as a wash solution for RBCs in cell saver machines for autologous blood transfusion. It finds its use in hemodilution as a part of "triple H therapy" in subarachnoid bleeding patients experiencing vasospasm.

Calculation of Osmolarity of 0.9% Normal Saline

$$\text{Molarity} = \text{weight} / \text{molecular weight}$$

$$\text{Molar value of NaCl} = 9\,\text{g} / \text{L} / 58.43 / \text{mol} = 0.154\,\text{mol} / \text{L of normal saline}$$

$$\text{One molecule of NaCl breaks into } Na^{+} \text{ and } Cl^{-} \text{ ions}$$

$$\text{Osmolarity} = \text{two times the molar value} = 308\,\text{mOsm} / \text{L}$$

Volume Effects of Normal Saline

In human body, sodium is the most abundant solute in the extracellular fluid (ECF). Nearly 75–80% of ECF is present in the interstitium. When sodium is administered intravenously, it gets distributed in the various fluid compartments in the same manner. The main effect is expansion of the interstitial volume (75%). Plasma volume resuscitation occurs but in a lesser magnitude (25%).

One liter of isotonic normal saline will add 275 ml volume to the plasma and 750 ml to the interstitial fluid compartment.

Adverse Effects

In 1998, Kellum and colleagues first quantified the effect of saline on acid-base balance. Hyperchloremic metabolic acidosis is seen in large volume intravenous administration of normal saline (>20 ml/kg bodyweight). This is seen in prolonged surgeries which require large volume of crystalloid. As a direct effect of metabolic acidosis, cardiovascular side effects noted are transient hypotension, inflammation, increased requirement of vasopressors, and decrease in microcirculation. In animal models, macrophage activation and increased expression of nuclear factor kappa-B (inflammatory markers) were seen in cell culture of hyperchloremic fluid [2]. In patients with renal compromise, these effects are magnified and are of great concern [19].

Hypertonic Saline

Various strengths of hypertonic saline are available commercially (3%, 7.5%, 20%, 30%) with different osmolarities. Clinically, among all the available strengths, 3% hypertonic saline with an osmolarity of 1026 mOsmol/L is most used to reduce raised ICP. Intravenous administration of hypertonic saline generates an osmotic gradient between the neuronal cells and the extracellular space and draws water from the cells into the intravascular compartment. This is the primary action of hypertonic saline which decreases the edema in the brain cells. Secondary actions are plasma volume expansion, increased cardiac output, and decreased peripheral vascular resistance which effectively improve the cerebral circulation and perfusion.

Hypertonic saline decreases intracranial pressure (ICP) by the virtue of its ability to create an osmotic gradient and resultant cellular dehydra-

tion. Its action of decreasing the ICP is considered superior compared to mannitol, though neurological outcome in patients is comparable. Hypotension seen with mannitol administration is not a concern with hypertonic saline. It is used as a standard of care therapy for cases of raised ICP refractory to mannitol treatment. It is also used to correct symptomatic hyponatremia seen in cerebral salt wasting syndrome [20]. Benefits are easy availability, easy storage, cheap, less chances of infection, and minimal interference with coagulation.

Points for Clinical Use of Hypertonic Saline

- Cerebral dehydration and central pontine myelinolysis can occur due to rapid correction of serum sodium.
- Iatrogenic hypernatremia, hyperchloremia, and hypokalemia can develop if serum sodium levels are not monitored. Recommendation is to maintain serum sodium levels <160 mEq/L.
- Rise in plasma osmolarity (>350 mOsm/L) can occur if unregulated volume of hypertonic saline is administered.
- Iatrogenic reversal of the osmotic gradient can occur causing the blood-brain barrier to open, leading to extravasation of hypertonic saline into the brain tissue. This is seen in the backdrop of extremely high load of intravenous hypertonic saline.
- It should always be administered in central veins as it can cause necrosis of peripheral veins.
- Epileptic patients who are on ketogenic diet should be monitored for worsening of metabolic acidosis if large volume normal saline is infused. It is suggested to administer a balanced salt solution in these patients to counter the acidosis.

Ringer's Solution

British physician Sydney Ringer in 1880 introduced an electrolyte solution which was used as a diluent in his experiment on isolated frog myocytes [21]. This solution contained calcium, potassium, and sodium and was intended to initiate muscular contraction experimentally. This solution gradually paved its way into the clinical practice as an intravenous fluid [22]. In 1930, Alexis Hartmann, an American pediatrician, modified the solution by addition of sodium lactate as a buffering agent. The new lactated Ringer's solution also popularly known as Hartmann's solution became one of the most widely used fluids for routine intravenous use.

The modern-day Ringer's lactate is composed of Na^{+} = 130, k^{+} = 4, Ca^{2+} = 3, Cl^{-} = 110, and lactate = 28 in meq/L of solution. The P^{H} is 6.4 and an osmolarity of 273 mOsm/L which is slightly hypotonic to human plasma. Because of its hypotonic nature, it is not used in neurosurgical, traumatic brain, and spine injury patients who are prone to develop cerebral edema.

The chloride content of Ringer's lactate is approximately equal to human plasma, and this explains the reduced risk of high chlorine-driven metabolic acidosis seen with large volume normal saline administration. The addition of lactate as a buffer made it possible to lessen the chloride concentration significantly and to retain electroneutrality of the resultant solution [23].

Points in Clinical Use of Ringer's Lactate

- Large volume intravenous administration of hypotonic Ringer's lactate can decrease the plasma osmolality and increase the brain water content and lead to rise in intracranial pressure. Its use as an intraoperative fluid in neurosurgical patients is not advised for the same reason.
- Calcium in Ringer's lactate can bind with the citrate present as an anticoagulant in stored RBC bags for transfusion. This interferes with the anticoagulation effect and facilitates clot formation.
- Specific drugs such as amphotericin, ampicillin, aminocaproic acid, and thiopentone interact with the calcium present in the Ringer's lactate and hamper its efficiency. It is not a recommended diluent for drug preparation.

- Major concern with Ringer's lactate is high load of lactate 28 meq/L causing hyperlactatemia. However, in healthy subjects with normal metabolism of lactate in the liver, lactic acidosis is rare. In patients with impaired lactate metabolism seen in advanced stages of hepatic failure and patients with circulatory shock, high volume of Ringer's lactate administration is worrisome [11]. It has been observed experimentally that 1 liter of Ringer's lactate infused in average blood volume of 5 liters raises serum lactate by 4.6 mmol/L. Out of this, only 25% is expected to stay in the vascular compartment. In patients with zero lactate clearance, this much load of lactate is metabolized effectively.

Ringer's acetate: To overcome the side effect of lactic acidosis, an alternate buffer acetate was used instead of sodium lactate. This modified fluid came to be known as Ringer's acetate. The osmolarity of this solution is 276 mOsm/L and P^H of 6–8. In Ringer's acetate, concentration of sodium, potassium, calcium, and chlorine is similar to Ringer's lactate. The only difference is presence of magnesium ion (1 mmol/L) and acetate buffer (27 mmol/L). Acetate is metabolized into carbon dioxide and water via citric acid cycle [24].

Plasmalyte A 148

Plasmalyte A 148 is a newer congener of the balanced-buffered crystalloid family. It has been developed from the basic Ringer's lactate. It is marketed by the Baxter Healthcare group by the name Plasmalyte A 148 [25]. The numeric "148" denotes the total sum of cations present in total.

The composition of the fluid is very similar to the human plasma comprising of Na = 140, K = 4, Mg = 1.5, Cl = 98, acetate = 27, and gluconate = 23 in mmol/L. The dual buffer-containing fluid has a P^H same as that of plasma (7.4) and osmolarity of 295 mOsm/L [26].

Acetate is metabolized into carbon dioxide and water, whereas gluconate is excreted unchanged in the urine. It is available in 1 liter and half liter transparent collapsible intravenous fluid bags.

It is gradually gaining use as an intraoperative replacement and maintenance fluid for neurosurgical patients. The isotonic nature of the fluid results is no net movement of water across the fluid compartments in the body; hence, cerebral swelling is not found with its use. Absence of calcium in its formulation allows blood transfusion simultaneously. Due to its alkalinizing effect, renal elimination of acidic drugs such as aspirin, barbiturates, and lithium increases [26]. Gluconate present in its preparation is responsible for galactomannan antigenicity testing falsely positive in healthy adults. Galactomannan antigen is used a biomarker for pulmonary aspergillosis [26]. However, cost of procurement of Plasmalyte is higher than normal saline [27].

Various randomized control trials have been conducted to compare normal saline and Ringer's lactate with that of Plasmalyte as an intraoperative fluid of choice for neurosurgery patients. In the ICU setting in traumatic brain injury patients, Plasmalyte has shown significant promise. SPLIT [28] and SALT [29] are the two cluster randomized trials which compared 0.9% normal saline with Plasmalyte A 148 and Ringer's lactate with 0.9% normal saline in ICU patients, respectively. The 30-day in-hospital mortality was found to be lower in the patient groups receiving Plasmalyte. The results of these two studies were further supported by future trials named SMART and SALT-ED [30, 31].

Isolyte

Isolyte is a balanced crystalloid solution made commercially available by B. Braun Healthcare group (B. Braun, Melsungen AG, Germany). The Isolyte family consists of a range of subtypes which include Isolyte solution—S, P, E, G, M, and E. These subtypes are designed by careful modification of various electrolyte compositions to be used in different age groups and different types of fluid loss in acutely ill patients.

The composition of Isolyte S is same as that of Plasmalyte A with p^H of 6.3–7.3 and osmolarity

of 295 mOsm/L. Other Isolyte solution subtypes are prepared keeping this composition as a basic mold with electrolyte concentration in various permutations and combinations.

Isolyte P is marketed for pediatric patients. Its osmolarity is 368 mOsm/L and comprises 50 grams dextrose, Na = 25, K = 20, Cl = 22, acetate = 23, citrate = 3, and HPO_4 = 3 in mmol/L. Isolyte P is used as a maintenance fluid for children. It is not used for resuscitation in hypovolemic state due to risk of hyponatremia. Isolyte E has an osmolarity of 595 mOsm/L and is the only Isolyte fluid subtype containing magnesium. The composition of the fluid is 50 g dextrose, Na = 140, K = 10, Cl = 103, Ca = 5, Mg = 3, acetate = 47, and citrate = 8 in mmol/L. Isolyte G comprises 50 g dextrose, Na = 63, K = 17, Cl = 150, and NH_4Cl = 70 in mmol/L. Osmolarity is 508 mOsm/L. It is used for correction of alkalosis. Isolyte M is composed of 50 g dextrose, Na = 40, K = 35, Cl = 40, and HPO_4 = 15 in mmol/L. Osmolarity is 410 mOsm/L. Though the Isolyte fluid family is gradually finding prominence in pediatric medicine, because of the presence of dextrose in its formulation, it is not suitable for the neurosurgical patients.

Sterofundin ISO

Sterofundin is another intravenous fluid of the balanced-buffered crystalloid group. It is marketed by the name of Sterofundin ISO by B. Braun, Melsungen AG, Germany. The solution has an osmolarity of 309 mOsm/L and composition is Na = 140, K = 10, Cl = 127, Ca = 2.5, Mg = 1, malate = 5, and acetate = 24 in mmol/L. The presence of malate buffer differentiates it from Plasmalyte A 148 and Isolyte, the other two balanced-buffered crystalloids of clinical use. The P^H of the fluid is 5.1–5.9. It is infused intravenously to replace the extracellular fluid loss. Sterofundin can be infused through a peripheral vein. The ionic composition of chloride, acetate, and malate is present in a balanced manner to maintain electroneutrality and to prevent metabolic acidosis. Sodium and chloride get distributed in the extracellular space, whereas magnesium, potassium, and calcium go intracellularly following their natural homeostatic distribution. In various preclinical and animal studies, acetate metabolites, e.g., nitrates, have been found to be associated with myocardial depression and hemodynamic instability. This is predominantly observed in patients receiving hemodialysis receiving large volume acetate-containing fluid. However, acetate metabolism doesn't alter the glucose and insulin level in the body unlike lactate.

Currently the use of Sterofundin intraoperatively is gaining popularity in various abdominal, cardiothoracic surgeries. But in patients undergoing neurosurgical procedures, the intraoperative usage is limited.

Few trials have been conducted where 0.9% normal saline is compared with Sterofundin and Ringer's lactate [32, 33]. Results from the study deduced better preservation of electrolyte and acid-base balance with Sterofundin compared to Ringer's lactate. Risk of hyperchloremic metabolic acidosis is also lesser with Sterofundin.

Dextrose-Containing Fluid

The term dextrose refers to the dextrorotatory isomer of glucose. This form is metabolizable and is the only form used in intravenous fluids. One gram of dextrose provides 3.4 kilocalories. When fully metabolized, a 5% dextrose solution will provide 170 kilocalories per liter, which prevents the breakdown of endogenous protein in the highly catabolic state of critically ill patients. Historically, it was very popular as an intravenous fluid for calorie replacement before enteral and parenteral nutritional regimens evolved [34].

Addition of 50 g of dextrose to any intravenous fluid increases the osmolarity to 278 mOsm/L. The osmolarity of D_5-normal saline is 560 mOsm/L and D_5W (dextrose in water solution) is 252 mOsm/L. Currently, glucose-saline combinations come in different concentrations commercially; examples are half normal saline-dextrose (0.45% NS and 5% dextrose), 0.9% NS-5% dextrose solution, lactated

Ringer's solution-5% dextrose solution, etc. Indications for its use include treatment of symptomatic hypoglycemia, maintenance fluid for premature neonates for non-neurosurgeries, neonates of diabetic mother, pediatric patients with mitochondrial disease, etc. [34]. This hypotonic fluid is clinically used to correct hyperosmolar-hyperglycemic state and cellular dehydration in diabetic ketoacidosis. D5W is also used to provide free water to correct hypernatremia in patients with diabetes insipidus. Twenty percent dextrose in water is a hypertonic fluid compared to plasma and is an osmotic diuretic. Dextrose-rich oral liquid preparations are fed to patients for day-care surgeries and have been advocated in enhanced recovery after surgery (ERAS protocol) [35].

The predominant effect of dextrose-containing solution is cellular swelling as this solution is hypotonic in nature. It is ineffective in raising the plasma volume as merely 10% of the infused fluid is retained in the intravascular compartment. Once administered intravenously, glucose is rapidly metabolized and leaving behind free water which crosses the cellular membrane and causes increase in brain water content. The use of glucose-containing fluid in patients with raised intracranial pressure such as acute traumatic brain injury is not favorable. This is predominantly because of the cerebral swelling caused due to free water compromising the raised intracranial pressure further. Moreover, hyperglycemia is detrimental in neurosurgical patients as it is associated with worse neurological outcome in traumatic brain or spinal injury patients and in patients presenting with ischemic stroke and subarachnoid hemorrhage. Though the mechanism of hyperglycemia and worse neurological outcome is still not clear, one theory is widely accepted: it states that excess glucose present in the brain tissues is shunted into lactic acid production in ischemic period. Increase in lactate in the neuronal cells is responsible for the neurotoxic effect in the event of preexisting high glucose in response to stress of trauma. Release of excitatory amino acid such as glutamate in response to ischemic stress is also postulated for unfavorable neurological outcome in conjunction with increased lactate. In summary, dextrose-containing fluid should be avoided is neurosurgical patients except for treating hypoglycemic episodes.

NICE-Sugar trial is a large multicentric trial where 6104 ICU patients were enrolled to see the effect of intensive and conventional glucose control on neurological outcome. The results suggest a target glucose level <180 mg/dL is optimum for management in neurosurgical patients.

Points in Clinical Use of Dextrose-Containing Solution

- Excessive use of electrolyte-free dextrose solution can cause dilutional hypokalemia.
- Risk of volume overload in patients with congestive heart failure and renal impairment.
- RBC hemolysis if dextrose-containing solution is run through the same IV set.
- May cause phlebitis and thrombosis at the injection site.
- High concentration dextrose solution, e.g., 50% dextrose to be preferably administered via central line.
- Monitor blood glucose levels carefully specially in patients with diabetes mellitus and electrolyte disbalance.

Special Crystalloids of Clinical Importance

Mannitol

Ubiquitous in neuroscience practice, mannitol is a naturally occurring six-carbon sugar alcohol [36].

It is an isomer of sorbitol occurring naturally in marine algae, mushroom extracts, and tree exudates. It is classified as a hypertonic crystalloid and is the key to osmotherapeutic reduction of raised intracranial blood pressure in neurosurgical patients. Various strengths of mannitol solution are available commercially: crystalline white, granular powder form soluble in water, and pre-constituted form. For clinical use, it is available in sterile bags in strength of 10% and 20% weight/volume. The osmolarity of 20% mannitol is 1100 mOsm/L and a P^H of 6.3.

Mannitol is an osmotic diuretic, freely filtered through the renal tubules because of low molecular weight (182). It is not absorbed orally. It is not reabsorbed from the renal tubules and it continues to exert its osmotic diuretic action in the tubules. Other actions are release of vasodilatory prostaglandins in the renal vasculature causing increase in tubular ultrafiltrate flow and substantial free radical scavenging property.

Mannitol is used in food processing industries as well apart from its medical use. However, FDA-approved uses of mannitol are few. Indications are treatment of raised intracranial pressure, treatment of raised intraocular pressure when other medications are refractory, and as a diuretic in acute renal failure to prevent oliguria and irreversible renal damage and to flush out toxic metabolites and drugs.

The Brain Trauma Foundation and European Head Injury Consortium identify level II and level III evidence for supporting mannitol in treating raised ICP in traumatic brain injury patients [37]. It is the most commonly used agent in the emergency departments to reduce cerebral edema of any etiology. The action is exerted at two levels: one immediate action is increase in the plasma volume and delayed action is the osmotically mediated one. Plasma volume expansion leads to decrease in blood viscosity and improves regional cerebral microcirculation and oxygenation in turn. Rise in the cardiac output secondary to plasma expansion also contributes to the increased cerebral blood flow indirectly. As a compensatory mechanism, cerebral vasculature constricts in the region of intact autoregulation, thus reducing intracranial pressure. Mannitol cannot cross the blood-brain barrier. When administered intravenously, the osmolarity of the plasma increases, and an osmotic gradient is created between the cerebral neurons and brain vasculature. Gradually, the brain water is drawn out of the cerebral extracellular space into the intravascular compartment. The excess water along with mannitol reaches the renal tubules as is excreted in the form of dilute urine. This is the fundamental basis of mannitol's cerebral edema treating action. Intact blood-brain barrier is a prerequisite for the effective cerebral edema lowering action. However, the ICP lowering action is dose and duration dependent. The guideline for dosage of mannitol to decrease cerebral edema is 0.25–1 g/Kg bodyweight to be infused intravenously over a period of 20–30 min. The peak effect comes at 30–45 min and lasts up to 6 h. Intraoperatively, the peak action of mannitol must coincide with the time of dural opening for supratentorial brain tumor surgery and should be planned in accordance with the ongoing surgery. Extremely high plasma osmolarity has been observed with multiple repeated dose of mannitol. It is recommended to monitor serum osmolarity, and it is not favorable to use mannitol if plasma osmolarity is more than 320 mOsm/L as it can precipitate acute tubular necrosis. The urine output should also be monitored before mannitol therapy.

Mannitol is an effective drug in lowering the ICP in acute phase following trauma, but current evidence is inconclusive for its use in ICU for traumatic brain injury patients after the acute phase is over. The Brain Trauma Foundation advocates the use of ICP monitoring in these patients in ICU as long as mannitol effectively lowers ICP and plasma osmolarity is maintained.

Mannitol also causes various side effects: hypernatremia, hypovolemia, hypotension, metabolic acidosis, pulmonary congestion, heart failure, local site necrosis if extravasation occurs, thrombophlebitis, allergic reactions, and anaphylaxis. Rebound increase in ICP is encountered when mannitol enters the blood-brain barrier leading to accumulation of fluid in the brain parenchyma and worsening the vasogenic cerebral edema. It is most likely because of presence of mannitol in the circulation for a prolonged period or after repeated ongoing slow intravenous infusion which fails to establish the required osmotic gradient. In various animal studies, the "volume regulatory response" of the astroglial cells has been examined in the presence of hypertonic saline and mannitol. Astroglial cells resist

osmotic cell shrinkage by activating ionic cotransporters present at the cell membranes in response to hyperosmotic agents [38]. It is basic homeostatic mechanism to retain the cell volume. Data from these studies concluded exposure to mannitol can interfere with this homeostatic mechanism and can cause paradoxical cell swelling. Moreover, there is compensatory accumulation of idiogenic osmoles inside the brain parenchyma which attributes to the osmotic gradient causing rebound fluid movement in the brain parenchyma. This follows the withdrawal or renal clearance of hyperosmotic agents such as mannitol.

Points in Clinical Use of Mannitol

- Contraindicated in hypovolemic state.
- Not to be used if serum osmolarity is more than 320 mOsm/L.
- Monitor electrolyte and urine output during ongoing mannitol therapy.
- After stopping mannitol abruptly, chances of rebound cerebral edema present: addition of furosemide with mannitol in the treatment chart can counteract it to some extent.

Details of hyperosmotic therapy are described elsewhere in the book. Other crystalloids of miscellaneous use such as sodium bicarbonate, potassium chloride, etc. are mainly used to correct electrolyte imbalances and will be discussed elsewhere.

Summary and Key Points

- Crystalloids are intravenous fluid containing electrolyte with low molecular weight and can cross semipermeable membrane.
- There are three broad groups of crystalloids classified based on tonicity: isotonic, hypertonic, and hypotonic crystalloids.
- Balanced-buffered salt solutions are family of intravenous fluids which contain electrolytes near to the composition of human plasma. The acid-base neutrality is maintained by addition of different buffering agents.
- Osmotic gradients determine the direction of water movement between brain extracellular space and vasculature.
- Clinically, in the event of cerebral edema following traumatic injury, tumor, and intracranial bleeding, osmotic gradient is created by the administration of hypertonic fluid, for example, hypertonic saline and mannitol, to reduce edema.
- Oncotic pressure has no impact on neuronal cell edema.
- Normal saline is most commonly used as replacement fluid perioperatively in the management of neurosurgical patients owing to its hypertonicity.
- Dextrose-containing fluids are avoided as they are linked to cerebral edema formation due to free water excess and are associated with worse neurological outcome.
- No single intravenous fluid is best for all neurosurgical conditions, but the current evidence dictates the use of isotonic balanced crystalloids for better preservation of electrolyte balance and favorable outcomes.

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Colloids

M. V. S. Satya Prakash and Kirthiha Govindaraj

Abstract

Crystalloid solutions are commonly used for fluid administration during many situations to maintain an euvolaemic state. But we, the anaesthesiologists, face many situations where we need to achieve an euvolaemic state with small amount of fluid, which cannot be achieved with crystalloids due to their lower volume effect and shorter intravascular persistence. In these situations, colloids are more useful than crystalloids. But, at the same time, colloids have other complications like problems in coagulation system, anaphylactic/anaphylactoid reactions, etc. To achieve an optimal euvolemic state, we need to use crystalloids and colloids in a planned manner individualised to the patient in a scientific approach. This chapter deals with the pharmacology of colloids useful for the anaesthesiologist and intensivist in guiding the transfusion of colloids.

Keywords

Colloids · Protein and non-protein colloids · Colloid oncotic pressure

M. V. S. Satya Prakash (✉) · K. Govindaraj
JIPMER, Puducherry, India

Colloids are the liquids which contain osmotically active substances that increase the oncotic pressure of the intravascular compartment, leading to the alteration in volume status of the patient.

Classification

Many classifications exist:

1. *Natural colloids*: fresh frozen plasma and albumin
   Artificial colloids: dextran, gelatin and hydroxyethyl starch
2. *Protein colloids*: fresh frozen plasma, albumin and gelatin
   Non-protein/synthetic colloids: dextran and hydroxyethyl starch
3. *Natural colloids*: fresh frozen plasma and albumin
   Semisynthetic colloids: dextran, gelatin and hydroxyethyl starch

Recently, few mixture of fluids were developed to increase the plasma volume expanding effect of colloid, by combination of hypertonic crystalloids with colloids such as HyperHAES (7.2% NaCl +6% HES 200) and RescueFlow (7.5% NaCl +6% dextran 70) [1, 2]. Hypertonic fluids and fresh frozen plasma are discussed in the following chapters (Table 1).

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Table 1 Different characteristics of different colloids

	Mean Mw (kDa)	Initial volume effect	Duration of plasma expansion (h)	Maximum daily dose	Water binding capacity (ml/g of colloid)	Survival in the body (days)	Oncotic pressure (mmHg)
4% albumin	69	90–130	1–3	No limit	18	21	20–29
20% albumin	69	120–160		No limit	18	21	100–120
6% dextran 70	70	100	5	1.5 g/kg	29	28–42	56–68
10% dextran 40	40	130–200	3–4	1.5 g/kg	37	6	168–191
3.5% urea-linked gelatins	35	80	1–3	No limit	41.7	7	25–29
5.5% cross-linked gelatins	30	80	1–3	No limit			25–29
4% succinylated gelatins	30	80	1–3	No limit	42.8	7	25–29
HES 670/0.765	670	100	5–6	20 ml/kg	20	2–65	25–30
HES 200/0.62	200	145	5–6	20 ml/kg			25–30
HES 200/0.5	200	100	3–4	33 ml for 6% solution and 20 ml/kg for 10% solution	30	7	30–37 for 6% solution and 59–82 for 10% solution
HES 130/0.4	130	100	3–4	50 ml/kg			36
HES 70/0.5	70	100	1–2	20 ml/kg	30	7	

Physical Properties

The behaviour of the colloids in the intravascular space depends on certain physical properties of the substance. They are discussed below:

1. *Molecular Weight*: There are two types of molecular weight for colloids. They are weight average molecular weight (Mw) and number average molecular weight (Mn).
   (a) Weight average molecular weight (Mw): This determines the viscosity [4] and Mw is influenced more by the large molecules in the intravascular system, and thus gives the larger value. Hence, molecular weight measurement depends on the contributions of molecules according to their mass, which gives weight average molecular weight. It is the sum of each molecule‘s weight divided by the total mixture’s weight times the weight of the molecule [3].
   (b) Number average molecular weight (Mn): This is the better indicator of intravascular persistence, i.e. this determines the oncotic pressure that is generated by the fluid in the intravascular compartment [4]. It is total weight of all the polymer molecules in a sample divided by the total number of polymer molecules in a sample. In simple terms, this can be taken as simple numerical average of the individual weights [5].
2. *Dispersity*: If all the molecules in the fluid contain same molecular weight/mass and shape, then it is called as “monodisperse”; and if the fluid contain molecules of a different range of molecular weight and shape, then they are called as “polydisperse”. Albumin is a monodisperse fluid, whereas other colloids are polydisperse fluids. The ratio of weight average molecular weight (Mw) to number average molecular weight (Mn) is an index measure of degree of polydispersity [6]. If the

ratio is 1, then it is a monodisperse fluid and higher the number, the fluid has more dispersity. When this polydisperse colloid is infused, smaller molecules below the renal threshold are rapidly excreted by the kidney, while the larger molecules are retained for more time in the vascular space. Depending upon the degradability, these molecules undergo degradation to smaller osmologically active substances. As there is continuous supply of osmologically active smaller molecules, the osmotic effectiveness of the colloid is maintained for a longer time frame than that of a crystalloid. Colloids like gelatin have the shortest duration of volume expansion [7].

3. *Concentration*: Concentration mainly influences the initial volume expansion effect of colloid [6]. But the concentration of the colloid fluid depends on the amount and concentration of carrier solution that is used to dissolve the colloid molecule. The carrier solution commonly used is normal saline. But few colloids with balanced salt solution as carrier are also available. The colloids, which are supplied in balanced salt solution, have less chance of developing hyperchloremic acidosis than with normal saline [6, 8, 9].
4. *Plasma Half-Life*: The plasma half-life depends on three properties: molecular weight, elimination route, and the organ function. If the elimination pathway is affected, then there is proportional increase in plasma half-life of colloids. Majority of the colloids are found to be excreted through the kidney. So, if the renal system is affected, then the plasma half-life gets prolonged.
5. *Electrolyte Content*: Electrolyte content of the fluid depends on the type of carrier solution that is used to make the colloid fluid. Salt-poor albumin contains less amount of sodium. Urea-linked gelatins contain calcium and also small amounts of potassium, whereas succinylated gelatins contain low chloride and potassium.
6. *Osmolality/Osmolarity*: Almost all colloid solutions that are available are found to have near normal plasma osmolality.
7. *Colloid Oncotic Pressure and Volume Expansion*: Colloid solutions are either hypo-, iso-, or hyper-oncotic. Four per cent albumin is slightly hypo-oncotic, 5% albumin is iso-oncotic and 20% and 25% albumin are hyper-oncotic. Six per cent HES is iso-oncotic and 10% HES is hyper-oncotic. Dextran solutions are supplied as hyper-oncotic and gelatins are supplied as iso-oncotic solutions. Oncocity of the solution influences the initial volume expansion. The higher the oncocity, the greater the initial volume expansion. Among the available solutions, dextran 40 generates the highest colloid oncotic pressure of about 168–191 mmHg.
8. *Acid-Base Composition*: Albumin and gelatin solutions are available in physiological pH, while other solutions available as mildly acidic pH.

Characteristics of an Ideal Colloid

1. Easy to manufacture.
2. Able to transport easily without constrains of temperature control.
3. Inexpensive with long shelf life.
4. It should get distributed only in the intravascular compartment, without leaking to any other compartments.
5. No specific storage or infusion requirements.
6. No upper limit of volume for transfusion.
7. It should be iso-oncotic as well as isotonic to the plasma with low viscosity.
8. It should get metabolised completely without getting accumulated in the body.
9. Should not depend on any organ for its metabolism and excretion.
10. Half-life should be at least 6–12 h.
11. There should not be any effect on organ function with repeated administration.
12. Should not have any adverse effects.
13. Should not transmit any diseases.
14. Non-pyrogenic, non-allergic, non-immunogenic and non-antigenic.

Presently, there is no ideal colloid available in the market. Five per cent albumin and 6% HES 130/0.4 solutions satisfy the maximum criteria compared to the other colloids.

Individual Colloids

Albumin

Albumin is the only natural colloid that is available in the market. It is available in the formulations 5%, 20% and 25%. Five per cent albumin is iso-oncotic, whereas others are hyper-oncotic fluids.

History: The first case series on albumin use in clinical practice was reported on soldiers, who were injured in Pearl Harbor attack in World War II [10]. The first use of albumin as a single case report was addressed few months before in a case of bilateral fracture of tibia and fibula with five rib fractures. Albumin was used as a resuscitation fluid, and this showed the colloid effects of albumin along with its anti-inflammatory properties.

Physiochemical Properties: Albumin is a protein with single polypeptide chain, having 585 amino acids with high amount of lysine and aspartic acid, and few methionine or tryptophan residues and no carbohydrate or prosthetic groups with molecular weight of 69,000 Daltons [11]. It forms 50–60% of the total plasma protein content, and it contributes to about 80% of the oncotic pressure of intravascular compartment [12].

Albumin structure has three main sites. They are as follows:

(a) Cysteine residues: Cysteine, at position 34, has a thiol (-SH) group useful for binding nitric oxide, other oxidants and nitroso groups, useful for neutralising reductive substances (harmful for cell life) that are generated during the cell metabolism. This occurs by nitrosylation and thiosylation processes, and helps in scavenging of oxidative free radicals.

(b) Domain I and II: These domains are responsible for binding or transporting the endogenous and exogenous molecules. Hypoalbuminaemia causes reduced binding of these substances, thereby increasing the availability of active substances either leading to increased effect or producing adverse effect of the drugs.

(c) Imidazole residues: Albumin has 16 imidazole residues, responsible for buffering action of acid-base status of the intravascular compartment [10].

Metabolism: Albumin is produced in the liver around 10–12 g/day, and enters completely into the intravascular compartment. In the intravascular space, about 7 g/h of albumin passes into the interstitial space at different degrees and rates depending on the anatomical location, by a process called "transcapillary filtration" [13]. Thus, transcapillary filtration occurs passively in the areas where the endothelium has large gaps, and occurs actively with the help of a receptor albondin in the areas, where there are tight endothelium bindings with no or small gaps [14, 15]. The movement of albumin between intravascular and interstitial space is continuous, and the amount that is lost from intravascular space to interstitial space is circulated back to intravascular space through lymphatic channels. During this process, albumin gets metabolised to about 10 to 12 g/day. This indicates that there is a balance in the total amount of production to the total amount lost daily. But the liver has the capacity to maximise its daily production of about 200–300% [16]. However, certain conditions like inflammation, trauma, stress, infection and critical illness decrease the capacity of liver production of albumin. The rate-limiting step in albumin production is the lack of amino acids such as leucine, arginine, isoleucine and valine.

Properties and Its Functions

1. *Oncotic Property*: Albumin increases the colloid oncotic pressure by three mechanisms.
   (a) The negative charge that is present in the albumin molecule attracts the sodium molecules, thus holding the water.
   (b) Donnan effect due to its negative charge.
   (c) Albumin binds to interstitial matrix and sub-endothelium, thereby reducing the permeability of these layers through its scavenging actions.

Five per cent albumin causes 80% initial volume expansion, whereas 25% albumin causes

200 to 400% initial volume expansion which lasts for about 16–24 h.

2. *Ligand Binding*: Albumin has affinity to bind to many substances such as fatty acids, pharmaceuticals, metal ions, etc. that contributes to transport, detoxification, drug delivery and antioxidant properties. Domain I site has affinity to large heterocyclic compounds, dicarboxylic acid compounds and bulky endogenous substances like bilirubin, porphyrin, etc. Domain II site is a small area, and its binding is more stereo specific. There are other binding sites in these domains for some drugs and compounds. Cysteine 34 residue has affinity to bind to many drugs such as cisplatin, D-penicillamine and N-acetylcysteine. This residue is also accounted for the nitrosylation and thiosylation processes leading to antioxidant properties of albumin [17]. N-terminal portion of albumin can bind to Co, Ni and Cu ions, and Cys-34 residue can bind to Au, Ag and Hg ions. Albumin can also bind to haem, leading to the formation of haemopexin molecule which has antioxidant properties. Drugs that compete for the same site for binding on albumin can displace with one another depending on their strength of affinity towards albumin and change the amount of active metabolite for their actions.
3. *Free Radical Scavenging or Antioxidant Property*: This property of albumin is due to the thiol group present in the albumin. Once the albumin is infused to the patient in sepsis, its concentration is found to be at a higher level for about 4 to 6 hrs. But its thiol activity is found to be present for more than 18 hrs. This indicates that the redox potential of infused albumin lasts for more time than the albumin level.
4. *Pro-inflammatory and Anti-inflammatory Property*: Thiol group that is present in albumin aid in the anti-inflammatory action. Albumin is found to decrease the binding of activated polymorphonuclear leucocytes to aortic endothelial cells in vitro [18]. Albumin is shown to decrease the respiratory burst of neutrophils in response to cytokines, such as tumour necrosis factor.
5. *Capillary Permeability*: Albumin can directly or indirectly change the capillary permeability by its action on the vascular endothelium. Albumin can directly bind to the interstitial matrix and sub-endothelium, and it can change the capillary permeability. Albumin can indirectly influence the capillary permeability by binding to the arachidonic acid or forming peroxynitrate albumin, thereby protecting the tissues from ischaemic reperfusion injury.
6. *Coagulation Effects*: Albumin has an antithrombotic and anticoagulant effect, because of its capacity to bind nitric oxide (NO) to form S-nitrosothiols, thereby inhibiting the rapid inactivation of NO and allowing prolongation of its antiaggregatory effects on platelets [19].
7. *Microcirculation*: Albumin reduces microcirculatory fluid leakage from the capillary ending, thereby improving the flow at the microcirculation. This increases the oxygen delivery at the tissue level.

Indications

FDA-Approved Indications

1. Hypovolaemia with or without shock: This is a second-line therapy, if the response is inadequate from infusion of crystalloids. Dose is 500 ml of 5% albumin that can be repeated every 30 min.
2. In cirrhotic patients: To prevent central volume depletion after paracentesis. Dose is one dose of albumin 25% i.e. 5–10 g/l of ascitic fluid drained for more than 5 L of ascites drained [20]. If less than 5 L of ascites is drained, it is recommended to use other colloids rather than albumin by the International Ascites Club [21].
3. Cardiopulmonary bypass: Albumin can be used as a priming solution in cardiopulmonary bypass circuit, as it was found to reduce the postoperative mediastinal haemorrhage by preservation of platelet count and also

maintains the colloid osmotic pressure during bypass period.
4. Haemolytic disease of newborn: Albumin can be used as an adjunct therapy during exchange transfusion for hyperbilirubinaemia, due to its ability to bind to unconjugated bilirubin. Dose is 1 g/kg of 25% albumin during exchange transfusion.
5. Twenty-five per cent albumin can be used for treating ovarian hyperstimulation syndrome for volume expansion in conjunction with crystalloids (Grade C recommendation) in the dose of 15–20 ml/h for 4 h [22].
6. Loop diuretic along with 100 ml of 25% albumin for 7–10 days can be used to reduce the oedema in patients with acute nephrosis and nephrotic syndrome, which is refractory to cyclophosphamide and corticosteroid treatment [23].
7. Hypoalbuminaemia in critically ill patients can be benefitted with the albumin infusion [24]. However, albumin infusion for malnourished patients to treat hypoalbuminaemia is not recommended.
8. Albumin can also be used to decrease the volume of fluid to be infused during the first 24 h after burns.
9. Twenty-five grams of albumin with frusemide thrice a day for 3 days has shown improvement in oxygenation and haemodynamic status in cases with acute respiratory distress syndrome [25].
10. 5% albumin can be used as a second-line therapy, in patients (with hypoalbuminaemia) on haemodialysis who are resistant to crystalloids while treating hypotension.

Non-FDA-Approved Indications

1. Spontaneous bacterial peritonitis (SBP): Albumin infusion along with antibiotics has shown decrease in renal impairment in SBP patients [26]. Dose is 5%albumin, 1.5 g/kg for the first 6 h and 1 g/kg on day 3 [27].
2. Albumin is used in Molecular Adsorbent Recirculating System (MARS) in the treatment of acute liver failure, as an extracorporeal liver replacement option as a bridge to liver transplantation [28, 29].
3. After liver transplantation, as the patient might be in hypoproteinaemic state. Dosage recommended is 100–400 ml of 25% albumin daily in adults and 1.5 ml/kg/day in children.

Contraindications

1. Hypersensitivity to the manufactured albumin.
2. Hypervolemic states such as severe anaemia, congestive heart failure, etc.
3. Different manufacturers produce albumin with different capacities to bind to metal ions and its level of oxidation. Vanadium contamination causes nephrotoxicity.
4. Albumin should not be used for parenteral nutrition purposes.

Adverse Effects

1. Anaphylactic/anaphylactoid reactions can occur. These can appear as nausea, vomiting, pruritus, urticaria, chills, hypotension, etc. Slowing or stopping the infusion can relieve the symptoms.
2. If large amount of albumin is transfused, it can lead to metabolic burden on the patient due to splitting of albumin into amino acids.

Advantages: It is a natural colloid, so it has less adverse or side effects.

Disadvantages: It is costly. So, in many situations, cost-benefit analysis may not favour its administration.

Precautions to be followed during administration of albumin:

1. If the albumin is cloudy or contains deposits, it should not be used.
2. Once the container is opened, it must be used fully or the remaining amount should be discarded. It should not be stored and reused.
3. Albumin should not be diluted in water for injection, as this may cause haemolysis in recipients.
4. Serum electrolyte concentration should be monitored and replaced if necessary, as 20%

and 25% albumin are relatively low in electrolytes.
5. If large volume of albumin is transfused in a short period of time, care must be taken about the haematocrit and the coagulation parameters, as albumin can cause dilutional problems.

Dextran

Dextran is a polymer of glucose molecules of various sizes, produced by the action of the bacteria *Leuconostoc mesenteroides* (B512 strain) on sucrose molecules of contaminated sugar beets with the help of the enzyme sucrase.

Physicochemical Properties: Dextran is available as 10% dextran 40 (molecular weight of 40 kDa) and 6% dextran 70 (molecular weight of 70 kDa). Colloid oncotic pressure of dextran 70 is highest among the available colloids (168–191 mmHg). The retaining power of water of 1 g of dextran 40 is 30 ml, and that of dextran 70 is 20–25 ml [30]. Plasma volume expansion capacity of dextran 40 is 175%, and that of dextran 70 is 100% [31]. Intravascular half-life of dextran 40 is 5 h, and that of dextran 70 is 6–8 h [1].

Metabolism: After intravascular administration, 70% of dextran is excreted by the kidney unchanged. Remaining dextran is broken down to glucose molecules, by the enzyme dextronase [32]. Older dextrans cause rouleaux formation and interfere with cross-matching of blood, but newer dextrans are devoid of this adverse effect.

Properties/Functions of Dextran

1. It causes volume expansion effect by attracting the water molecules.
2. It decreases the blood viscosity, thereby improving the microcirculation at the tissue level more than the other colloids [30]. Dextran also reduces the interaction between leucocytes and intravascular endothelium, thereby having a positive effect on reperfusion injury at the level of ischaemic areas.

Indications

1. It increases microcirculation, and at the same time has the properties to reduce thromboembolic events. Dextran 40 can be used in surgeries, where vascular anastomosis is done and in microsurgical reimplantations.
2. As a volume expander secondary to crystalloids.

Dose: It is recommended not to use dextran more than 1.5 g/kg to prevent its side effects. Regimen for prevention of thromboembolism for microsurgical reimplantations is 500–1000 ml over 4–6 h on day 1, and followed by 500 ml over 4 to 6 h on alternate days for up to 20 days. In these cases, only dextran 40 can be used, but not dextran 70.

Adverse Effects

1. Anticoagulation effects: Dextrans are found to cause dose-dependent, acquired von Willebrand syndrome. It causes decrease in the von Willebrand factor along with decreased activated factor VIII: c level and promotes fibrinolysis, leading to increased bleeding tendency. Dextrans are found to cause decreased A10 on ROTEM and prolong PT and APTT [33].
2. Anaphylactic/anaphylactoid reactions: Dextrans cause the worst anaphylactic/anaphylactoid reactions due to formation of dextran reactive antibodies of IgG class [30, 32]. They cause type III anaphylactic reactions. Incidence and severity of these reactions can be reduced by pretreatment with 20 ml of monovalent dextran hapten (dextran 1).
3. Renal dysfunction: Due to the production of hyperviscous urine, dextrans are found to cause swelling and vacuolisation of tubular cells in the renal tubule, thereby causing obstruction to the renal tubules. This may lead to decreased urine output and renal dysfunction. To prevent renal dysfunction, it is recommended to infuse equal amount of crystalloids along with dextran. Renal dysfunction is more pronounced, when renal perfusion is reduced or there is a pre-existing renal disease.

4. Older dextrans cause rouleaux formation and interfere with cross-matching of blood, but newer dextrans are devoid of this effect.

Contraindications

1. Hypersensitivity to dextrans
2. Pre-existing renal impairment
3. Patients with diagnosed coagulation disorders

Gelatins

Gelatins are produced from collagen. Gelatins were first introduced during World War I for the treatment of shock [5]. Early products of gelatin had high molecular weight of around 100,000 Da, thereby generating high oncotic pressure and more volume expansion effect. These forms had high chances of solidifying into gel, because of high viscosity when stored at low temperature. This leads to manufacturing of gelatins with low molecular weight by the method of chemical degradation.

Physicochemical Properties

Three forms of gelatins are available now.

1. Urea-linked gelatin: It is manufactured by the action of alkali, followed by thermal degradation on the collagen from cattle bones. Its weight average molecular weight (Mw) is around 35,000 Da, and number average molecular weight (Mn) is around 24,500 Da. It is sold under the trade name Polygeline and 3.5% Haemaccel. Its osmolarity is 301 mOsm/L. It contains Na^+ 145 mmol/L, K^+ 5.1 mmol/L, Ca^{++} 6.25 mmol/L and Cl^- 145 mmol/L. As it contains good amount of calcium and potassium, it may increase calcium concentration during a large volume resuscitation and might be useful in patients with hypokalaemia.
2. Succinylated gelatin: It is manufactured by thermal degradation and by adding succinic acid anhydride to calf skin collagen. It is available under the trade name 4% Gelofusine. Its molecular weight is 23 kDa and osmolarity is 274 mOsm/L. It contains Na^+ 154 mmol/L, K^+ 0.4 mmol/L, Ca^{++} 0.4 mmol/L, and Cl^- 120 mmol/L. As it contains low amount of potassium and chloride, it is helpful in patients with hyperchloremic metabolic acidosis. As it contains less calcium, it is compatible with blood transfusion when compared to other gelatins.
3. Cross-linked or oxypolygelatins: Its weight average molecular weight is around 30 kDa. It is available as 5.5% Gelofundiol with an osmolarity of 296 mOsm/L.

Gelatins exert volume expansion capacity for about 1–3 h [30]. Among the colloids, gelatins have least duration of volume expansion effect with lesser plasma half-life, as they are excreted rapidly by the kidney due to their smaller molecular weight. They exert volume expansion to around 70–80% of volume infused. As all gelatins are pyrogen-free and preservative-free, they can be stored for up to 3 years at 30 °C.

Metabolism: Once gelatins are infused, they are rapidly distributed into the extravascular space (16%), and at the same time, they are excreted by the kidney (17%) due to their smaller size. Larger molecules are metabolised by reticuloendothelial system by the enzyme proteases (3%) within 2 to 4 h.

Indications

1. Hypovolaemia along with crystalloids to have volume expansion effect
2. Acute normovolaemic haemodilution during allogeneic blood transfusion
3. As a preloading solution during regional (neuraxial) anaesthesia

Adverse Effects

1. Gelatins can cause anaphylactoid reactions mediated by histamine release.
2. Gelofusine, found to increase the time to reach maximum clot strength, reduces the rate of fibrin formation and impairment of platelet aggregation [4].
3. Gelatins were found to increase renin and aldosterone activity during paracentesis.

Advantages

1. It is cheaper and cost-effective.
2. There is no upper limit for transfusion of gelatins. So, repeated infusions in shorter time interval can be given.
3. As gelatins are smaller-sized molecules and they are excreted freely by the kidney, they do not cause renal dysfunction.
4. Longer shelf life and easy to store.
5. No risk of infection and transmission of pyrogens.
6. Gelatins can be used as a carrier solution for intravenous infusion of other substances, as there are no known compatibility problems.

Contraindications: Hypersensitivity to gelatins

Hydroxyethyl Starch (HES)

HES are derivatives of a glycogen resembled polysaccharide amylopectin. Amylopectin is hydrolysed by circulating enzyme amylase [30]. Amylopectin has a half-life of 20 min in the humans. The anhydrous hydroxyl residues of amylopectin molecule are replaced with hydroxyethyl residues to produce hydroxyethyl starch. Hydroxyethylation makes the molecule resistant to hydrolysis by amylase, thereby increasing its half-life. Depending on the level of hydroxyethylation, many products are developed. They are hetastarch, hexastarch, pentastarch and tetrastarch. The higher the molar substitution ratio, the more the resistance to degradation by amylase [32]. Earlier it was believed that the higher the substitution, the more the plasma half-life; thus, it gives more duration of volume expansion [34]. But this was found to have more adverse effects of the product. Hence, it was found that the hydroxyethylation should not be more or less, but it should be optimum. Among the HES solutions that are available, recently developed tetra-starches have less side effects with maximum possible desirable effects. HES products are described by three numbers, e.g., 6%HES (130/0.4). The first number indicates the concentration of the solution, the second number indicates the mean molecular weight of the product and the third number indicates molar substitution ratio.

Physicochemical Properties

1. Concentration: This depends on the carrier that is used to make the solution. HES are available in either 6% or 10% solutions. This influences the initial volume expansion effect. Six per cent gives 100% volume expansion, as they are iso-oncotic and 10% gives 145% volume expansion as they are hyper-oncotic [6].
2. Molecular weight (Mw): Depending on the Mw (weight average molecular weight), HES solutions are classified into low molecular weight (<70,000 Da), medium molecular weight (130,000–260,000 Da) and high molecular weight (>450,000 Da). The higher the molecular weight, the slower the degradation; and the more the plasma half-life, the more the accumulation of substances in the body.
3. Molar substitution (MS): It is the average number of hydroxyethyl residues per glucose residue. If MS is 0.5, it indicates that there are five hydroxyethyl residues per ten glucose molecules. The higher the MS, the more the resistance to degradation; and the more the plasma half-life, the more the accumulation in the body occurs. If MS is 0.7, it is called as hetastarch, 0.6 hexastarch, 0.5 pentastarch and 0.4 tetrastarch.
4. C2/C6 ratio: Substitution of hydroxyethyl residues occurs at C2 (common) or C6 or occasionally at C3 glucose molecules. The higher the C2/C6 ratio, the more resistant to the action of amylase for degradation; and the more the plasma half-life, the more the accumulation in the body.

Pharmacokinetics: HES of lower molecular weight produces the oncotic effect, whereas the higher molecular weight gives the duration of the effects. But it was found that the duration of the oncotic effect does not increase after reduction of molar substitution below 0.4. This indicates that the oncotic effect of the smaller molecules peaks at MS of 0.4. After the infusion of HES, mole-

cules with lower molecular weight are excreted by the kidney, and the molecules with higher molecular weight are continuously degraded by the α-amylase enzyme to smaller molecules. The molecules which do not get degraded are engulfed by the reticuloendothelial system for further degradation and found to stay in the body for more than 42 days [35, 36]. Medium-sized molecules are excreted through bile and faeces. These molecules get deposited at tissues like the liver, skin and histiocytes, at higher doses in keratinocytes, sweat gland epithelia, endothelial cells, and perineural, endoneural and Swann cells in cutaneous nerves. The main clinical manifestation is pruritus resistant to antihistaminics, neuroleptics, glucocorticoids, etc. [37]. Plasma clearance is faster with tetra-starches than the higher molecules. It was found that tetra-starches are 23 times faster cleared from plasma when compared to hetastarches [34]. The duration of volume expansion is highest with hetastarches with 5 to 6 h, lowest with 70/0.5 HES (1–2 h) and medium with 130/0.4 HES (3–4 h) [31]. The volume expansion effect with various HES solutions is 100%. The water binding capacity of HES is 20 to 30 ml/g [1, 2].

Indications

1. To restore the haemodynamics in a hypovolemic patient.
2. Due to the property of improvement in microcirculation, it was found to be beneficial to give HES in shock patients to a limited amount in place of crystalloids.

Contraindications

1. Hypersensitivity to the starch solutions.
2. HES causes increase in amylase levels. This may cause difficulty in interpretation of amylase levels in pancreatitis patients.

Dosage: Maximum daily recommended doses are as follows:

20 ml/kg/day for the fluids 6%HES670/0.75, 6%HES600/0.7, 6%HES450/0.7, 6%HES200/0.62, 10%HES200/0.5 and 6%HES70/0.5

33 ml/kg/day for the fluids 6%HES200/0.5, 10%HES130/0.42 and 10%HES130/0.4

50 ml/kg/day for the fluids 6%HES130/0.42 and 6%HES130/0.4

Advantages: Third-generation HES are comparable to the albumin in their uses and side effect profiles. But it is cheaper than albumin.

Adverse Effects

1. Higher molecular weight HES molecules interact with platelets and plasma coagulation factors, such as factor VIIIc and von Willebrand factor, and reduce their level. Platelet activity is also reduced due to blockade of platelet fibrinogen receptor glycoprotein IIb-IIIa. This causes increase in activated partial thromboplastin time leading to altered coagulation status and more bleeding [6]. But these effects were found to be minimal and comparable to that of albumin with tetra-starches such as HES130/0.4.
2. Tissue storage: Higher molecular weight HES molecules accumulate in the reticuloendothelial system of various parts of the body and can cause drug-resistant pruritus. This is minimal with tetra-starches.
3. Renal function: High molecular weight and high molar substituted HES molecules can cause osmotic nephrosis like lesions in the proximal and distal renal tubules leading to impairment in renal function. But tetra-starches are comparable to gelatin in terms of chances of renal dysfunction due to their low molecular weight and low MS.
4. It was found that patients developed mild to moderate hyperbilirubinaemia after transfusion of certain HES fluids. This might be due to impaired excretion of bile secondary to increased formation of bilirubin, due to more fragmentation of erythrocytes. Potato-derived 6%HES130/0.42 is contraindicated in liver failure patients [6].
5. HES molecules can cause anaphylactoid reactions leading to pruritus, etc.

Favourable Effects of Tetra-starches

1. Microcirculation: During hypovolaemia, several counter-mechanisms get stimulated leading to decrease in microcirculation. It was found that tetra-starches improve the micro-

circulation, over and above the effects due to correction of hypovolaemia compared to crystalloids. This is hypothesised due to lower whole blood viscosity due to correction of hypovolaemia with tetra-starches than with crystalloids [38]. The lower viscosity facilitated improved microcirculation leads to better flow dynamics.
2. Inflammation: Tetra-starches are found to decrease the release of IL-6 and IL-8 due to tissue trauma by interfering with endothelial cell activation (by reducing the release of mediators) and inhibiting neutrophil adhesion to the endothelial cells of the tissues.
3. Special groups: Waxy-maize-derived 6%HES130/0.4 is the only HES variety that was studied in all the special groups such as in elderly and in paediatric patients. It was found to be safe and comparable to the albumin in its action and adverse effects.

Tetra-starches: These are manufactured from either waxy-maize or potato. These two have some differences in their characteristics and effects, even though both are tetra-starches (Table 2).

Because of these differences, it is widely speculated that these two forms are not bioequivalent. But as few studies are available with potato-derived HES and a wide range of studies are available with waxy-maize-derived HES, no conclusive evidence had accumulated on this issue [39].

Miscellaneous

Few manufacturers are marketing the solutions that contain the mixture of hypertonic solutions and colloids. They are HyperHAES (7.2% NaCl +6% HES 200) and RescueFlow (7.5% NaCl +6% dextran 70). Even though they had shown promising results in studies, they are not widely used in general practice as they are thought to have higher incidence of complications.

HyperHAES

This is a mixture of 7.2% NaCl with 6% hydroxyethyl starch 200/0.5. It is a hypertonic and isooncotic solution. 100 ml solution contains 6 g of hydroxyethyl starch and 7.2 g of NaCl. Its osmolarity is 2464 mOsm/L with a pH of 3.5 to 6, Na^+ 1232 m.mol/L and Cl^- 1232 m.mol/L. Due to its high osmolarity, it mobilises the fluid from inter-

Table 2 Summary of the differences between waxy-maize HES and potato-derived HES

Character	Waxy-maize-derived HES	Potato-derived HES
Available form	130/0.4	130/0.42–130/0.45
Structure	98% of amylopectin is branched	75% of amylopectin is branched and remaining amylopectin is linear chained
	Highly branched amylopectin	20 to 30% (by weight) is linear branched and available as amylose rather than as amylopectin. So, the available HES contains both hydroxyethylated amylopectin and hydroxyethylated amylose, which can be excreted easily
C2/C6 ratio	9:1	6:1
	Has lower intrinsic viscosity than the potato-derived product	Has higher intrinsic viscosity than waxy-maize product due to degree of difference in branching
Free phosphate	–	34–84 ppm
Total phosphate	15 ppm	205–290 ppm
Degree of esterification with phosphoric acid	Low	High
Molar substitution	0.41	0.45
Degree of substitution	0.34	0.4

stitial space to the intravascular compartment. Its volume expansion effect is 200 to 300. Weight average Mw is 200 kDa. Number average Mw is 60 kDa [1].

Metabolism: NaCl is distributed into the extracellular space in 30 min, and finally eliminated by the kidney. HES is metabolised like that of 6%HES200/0.5 as described above. Plasma half-life is around 4 hrs.

Indications: Acute hypovolaemia and shock. Infusion of HyperHAES should be followed by infusion of standard volume therapy containing electrolytes and fluids. For HES infusion, if included in the standard volume therapy, the maximum dose should include the volume that was given in HyperHAES.

Contraindications: Known hypersensitivity to hydroxyethyl starches, circulatory overload, decompensated congestive heart failure, severe liver insufficiency, coagulation disorders, renal failure with anuria, pregnancy, hyperosmolarity, dehydration, severe hypernatraemia or hyponatraemia and severe hyperchloraemia or hypochloraemia

Special precautions during administration: Serum electrolytes and serum osmolarity should be monitored regularly (especially in diabetics).

Adverse Effects: Increase in coagulation parameters, anaphylactoid reactions (skin rash, bronchospasm, etc.), central pontine myelinolysis, increase in serum amylase levels, local reactions like thrombophlebitis, hypernatremia and hyperchloraemia

Dose: Maximum recommended dose is 4 ml/kg, not more than 250 ml as a single dose. It can be administered through peripheral route, even though its osmolality is higher. Repeated infusions are not recommended.

RescueFlow

It is a mixture of 7.5% of hypertonic saline with 6% dextran70. Its volume expansion effect is 200–300. Its weight average Mw is 70 kDa. Number average Mw is 39 kDa. Its osmolarity is 2568 mOsm/L with Na^+ is 1283 mmol/L and Cl^- is 1283 mmol/L. Once infused, it rapidly mobilises the fluid from intracellular and interstitial space into the intravascular space, thereby decreasing tissue oedema. So, it may be useful in patients with tissue oedema such as burns and traumatic brain injury. The dextran, which is present in solution, sustains the volume expansion effect for more time after the hypertonic saline is redistributed to the extracellular space in 30 min.

Functions: It increases the intravascular volume, tissue perfusion, microcirculation and decreased inflammatory response [40].

Dose: 4 ml/kg to the maximum of 500 ml as a single dose only [41]

Adverse Effects: Anaphylactoid reactions, worsening of coagulopathy, hypernatraemia, hyperchloraemia and renal dysfunction

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Hyperosmolar Fluids

Cristiane Tavares,
Ana Laura Lindner Latorre de Alcântara,
Kazuco Nakai Murata, and Seigi Sasaki

Abstract

Intravenous hyperosmolar fluids have been used for the clinical management of intracranial hypertension. The most suitable agent depends on the patient's age, comorbidities, and clinical status. Since hypertonic saline causes an intravascular volume expansion, it can be advantageous for hypovolemic patients. Still, it should be used with caution in patients with cardiac heart failure, in whom it may precipitate acute pulmonary edema. In contrast, mannitol induces a strong diuretic response that can lead to a severe blood volume depletion that should be promptly treated to avoid complications. Other concerns related to its use are the rebound phenomenon and a potential risk of hematoma expansion in patients with intracranial hemorrhages. The main concern in patients receiving hypertonic saline is hypernatremia. It poses a theoretical risk of osmotic demyelination when serum sodium levels rise quickly, especially in hyponatremic patients. Both agents can cause renal injuries but through distinct mechanisms. Whereas high serum mannitol concentrations can lead to osmotic nephrosis, renal function impairment associated with hypertonic saline infusion seems to be mediated by hypernatremia and hyperchloremia. Further research is warranted to determine the optimal agent and their best means of administration (boluses vs. continuous infusions) for each neurocritical condition. More extensive clinical trials are needed to address long-term outcomes, adverse events, and quality of life with both agents.

Keywords

Hypertonic solutions · Mannitol · Hypertonic solution · Saline · Intracranial hypertension · Traumatic brain injuries · Brain edema · Anesthesia · Neurosurgery

C. Tavares (✉)
Department of Anesthesiology, Surgical Sciences and Perioperative Medicine, Hospital das Clinicas, University of Sao Paulo Medical School, Sao Paulo, Brazil
e-mail: cristiane.tavares@hc.fm.usp.br

A. L. L. Latorre de Alcântara
State Institute of Brain Paulo Niemeyer, Rio de Janeiro, Brazil

K. N. Murata
Department of Functional Neurosurgery, Hospital das Clinicas, University of Sao Paulo Medical School, Sao Paulo, Brazil
e-mail: kazuco.murata@hc.fm.usp.br

S. Sasaki
Portuguese Beneficence Hospital, Sao Paulo, Brazil
e-mail: seigi@ig.com.br

Hyperosmolar Fluids

As early as 1919, Weed and McKibben observed noticeable changes in the brain volume after the infusion of hypertonic or hypotonic solutions, disrupting the long-held dogma that the volume

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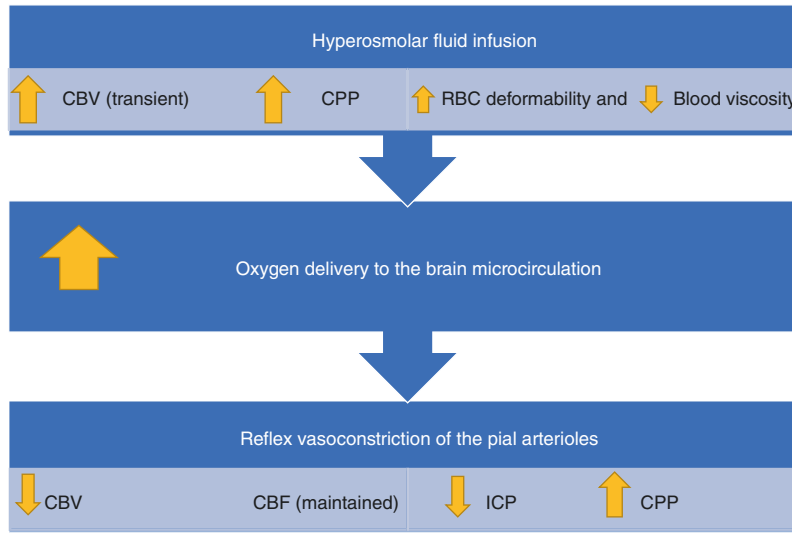

Fig. 1 Hyperosmolar fluid mechanism of action (based in Freeman and Welbourne [4]). (CBV, cerebral blood volume; CPP, cerebral perfusion pressure; RBC, red blood cell; CBF, cerebral blood flow; ICP, intracranial pressure)

of the brain was constant [1]. The first case series in which hypertonic fluids (initially in the form of urea) were used to treat elevated intracranial pressure were described in the 1950s [2]. Over time, many other hypertonic infusions such as bicarbonate 8.4%, sodium lactate, mannitol, and hypertonic saline have been used.

For decades, mannitol has been considered the gold standard even without consistent evidence of benefit [3]. However, more recently, there has been a controversy (the so-called sugar or salt debate) regarding the potential superiority of hypertonic saline over mannitol in several clinical settings. Still, further research is warranted to find out the optimal agent, their best means of administration (boluses vs. continuous infusion), and their precise mechanism of action [4].

In Fig. 1, we illustrate the primary mechanism of action proposed for the hyperosmolar solutions.

Mannitol

Mannitol ($C_6H_{14}O_6$) is an isomer of sorbitol found in many fruits and vegetables and has been industrially manufactured from the hydrogenation of fructose and glucose [4].

Due to its small molecular weight (182 Daltons), it is readily filtered by the glomerulus. It doesn't undergo biotransformation and is almost entirely excreted in the urine after 24 h, with only 7% being reabsorbed [4, 5].

In animal models, it inhibits the renin-angiotensin system and acts as a free radical scavenger, reducing ischemia-reperfusion lesions [5]. Therefore, it is used in distinct clinical settings, such as cardiopulmonary bypass, aortic cross-clamping, renal transplantation, rhabdomyolysis, and obstructive jaundice [5]. Whereas low mannitol doses have a renal vasodilator effect, improving glomerular filtration rate, higher doses can cause the opposite effect [6].

Mannitol 20% (means that it provides 200 g/L) has approximately the same osmolarity as hypertonic saline 3.2% (1098 mOsm/L). After an intravenous bolus administration, it is distributed primarily in the extracellular compartments. It has an onset of action after 15 min, reaching its maximal effect in 45 min and lasting up to 6 h, with a half-life of 70–100 min [5].

Mechanisms of Action

Three mechanisms have been suggested to explain how mannitol can decrease ICP [5].

First, it transiently increases cerebral blood volume and improves cerebral perfusion pressure. Due to its rheological properties, increasing red blood cell deformability, and decreasing blood viscosity, it enhances oxygen delivery and microvascular flow to the cerebral tissues [7].

Second, reflex vasoconstriction of cerebral arterioles occurs in response to this increment in the microvascular oxygen delivery. Attention should be caught since it may not happen when the blood-brain barrier is not intact, or the cerebral autoregulation is not preserved [8].

Third, a decrease in cerebral blood volume and osmotic dehydration of the brain takes place, alleviating cerebral edema and ameliorating intracranial compliance [5].

In addition to that, Orešković et al. studied the cerebral spinal fluid (CSF) pressures in animal models and proposed a new mechanism for mannitol action based on CSF pressure variation. They suggested that an osmotic retrieval of water from the CSF into the blood circulation occurs predominantly in the spinal part of the system and increases the CSF circulation, leading to a drop in CSF pressure that begins very fast and lasts up to 40 min [9].

Mannitol and the Cardiovascular System

The hemodynamic response to an intravenous bolus of mannitol is typically triphasic [5].

Firstly, after 15 min, due to a sharp elevation in serum osmolarity, there is a rapid increase in intravascular volume. Consequently, there is a significant increment in cardiac output and pulmonary capillary wedge pressure [5].

Secondly, after 45 min approximately, there is a drop in the intravascular volume below the baseline values. It occurs due to vasodilation that takes place primarily in skeletal muscles and can cause severe hypotension with increased lactate levels. Osmotic diuresis can worsen this phenomenon due to depletion of blood volume and should be carefully monitored. It is crucial to avoid arterial hypotension since it can decrease cerebral perfusion pressure [4].

Thirdly, these hemodynamic variables return to the baseline levels [5].

Mannitol and the Kidneys

As mannitol passes into the nephron, an impairment in water reabsorption occurs in both the proximal convolute tubule and the descending limb of the loop of Henle due to its increased osmotic pressure. Next, there is a progressive reduction in sodium reabsorption in the ascending limb of the loop of Henle and the collecting tube. Hence, there is a dilution of tubular sodium concentration, preventing water from being reabsorbed back into the circulation and resulting in increased diluted urine output [4, 5].

Mannitol also activates the endogenous natriuretic peptide and suppresses the antidiuretic hormone release. Augmenting medullary blood flow dissipates medullary hypertonicity, inhibits tubular reabsorption of salt and water, and results in osmotic diuresis [5].

Around 6–12% of the patients can develop acute renal injury [10, 11]. It usually occurs in patients receiving daily or cumulative doses of mannitol higher than 200 g and 1100 g, respectively, and after 12 h and 7 days (typically within the first 48 h) when serum osmolarity exceeds 320 mOsm/L. Therefore, a high serum concentration of mannitol may be related to it [5].

Since mannitol dosage is not readily available, the osmolal gap can be used instead [12]. This surrogate measure is especially needed for elderly patients with poor neurologic status, with diabetes, in use of diuretics, and with arterial hypotension or sepsis, which are independent predisposing factors for mannitol nephrotoxicity [5]. In case of reaching an osmolal gap higher than 55 mOsm/kg, which corresponds to a mannitol concentration higher than 1000 g/dL, it is advisable to discontinue its infusion and perform hemodialysis, if necessary [5].

The mechanisms of renal injury are not entirely understood. One hypothesis is that excessive doses of mannitol lead to pronounced hypotension and peripheral vasodilation, which in turn causes renal vasoconstriction and osmotic nephrosis in patients with predisposing factors [5]. Renal vasoconstriction is particularly harmful in diabetic patients since their renal blood flow is unevenly distributed, increasing medullary susceptibility to ischemic injuries. The concomitant use of loop diuretics inhibits the compensatory mechanism of increasing sodium reabsorption in response to intravascular volume depletion, leading to a strong diuretic effect. Patients with preexisting renal disease can have a

prolonged mannitol half-like (from 70 to 100 min to more than 36 h). Therefore, it is advisable to closely monitor the intravascular volume and arterial pressure of these patients [5].

Osmotic nephrosis refers to an intracellular vacuolization caused by mannitol pinocytosis in the tubular cells of the kidney. These vacuoles eventually fuse with lysosomes and reduce the proximal tubule's lumen diameter, leading to unpredictable sequelae [5].

Hydroelectrolyte and Acid-Base Changes

Mannitol infusion typically induces a hypokalemic and hypochloremic alkalosis with volume contraction caused by excessive diuresis [13], but dilutional metabolic acidosis can also occur due to a solvent drag mechanism [5].

It is expected that for each increase in 100 g/dL in the mannitol serum concentration, the plasmatic sodium falls between 1.6 and 2.6 mEq/L and that for each increase of 182 mg/L in mannitol serum concentration, serum osmolarity increases by 10 mOsm/L. Thus, its repeated administration can cause hypertonic hyponatremia. Hence, it is not recommended to replace sodium to correct this hyponatremia because it would further increase the serum osmolarity. Hyponatremia usually is self-corrected within 3 h after an infusion of up to 1.4 g/kg of mannitol in a patient with normal renal function due to diuresis. If it doesn't occur and osmolarity reaches 310 mOsm/L or more, it is advisable to immediately stop mannitol infusion and proceed to hemodialysis if necessary [5].

Mannitol facilitates renal excretion of magnesium, potassium, phosphate, and bicarbonate ions. Whereas moderate doses (1 g/kg) of mannitol infusion usually result in mild hypokalemia, higher doses (2 g/kg) can cause hyperkalemia, especially when administrated concomitantly with blood [5]. It can occur due to hemolysis, dilutional acidosis, and a shift of potassium ions from the intracellular into the extracellular space [5].

Diabetic patients or those receiving glucocorticoids may develop a hyperglycemic hyperosmolar state related to mannitol infusion. It can manifest as an unexplained seizure, a new neurological deficit, or confusion [14].

Rebound Phenomenon and Other Concerns

For decades there has been controversy regarding the possibility that a rebound increase in ICP could occur in patients who received mannitol. The rationality for it is that mannitol can cross the blood-brain barrier and accumulate in the brain since its reflection coefficient (that describes the relative impermeability to an intact blood-brain barrier) for mannitol is 0.9. Therefore, it may accumulate in injured brain regions after prolonged infusions, leading to a reverse osmotic shift and rebound ICP elevation [4]. However, this phenomenon has only been demonstrated in rats, and its relevance in humans is still unknown [15].

In addition to that, patients receiving prolonged hyperosmolar infusions can produce and accumulate cerebral idiogenic osmoles that also simulate a rebound phenomenon. The astrocytes provide them in an attempt to equilibrate the osmotic gradient generated. It can possibly explain the need for higher dosages of hyperosmotic infusions to reach the same effect when the treatment lasts several days. Therefore, it is also a concern in patients receiving hypertonic saline solutions [5, 16].

Mannitol use should be carefully monitored or even contraindicated when there is a possibility that the blood-brain barrier is disrupted, such as in patients with severe traumatic brain injuries, intracerebral hemorrhage, or vasogenic edema [5]. When cerebral autoregulation is not preserved, the transient increase in cerebral blood flow that occurs right after mannitol infusion may not be followed by cerebral vasoconstriction, leading to undesirable cerebral hyperemia [5].

Finally, there is also a concern that, since the therapeutic reduction in water content occurs predominantly in undamaged regions of the brain, hyperosmolar treatment could potentially exacerbate pressure gradients within the skull and lead to herniations. Accordingly, modern image techniques can detect slight displacements in brain structures, but they seem to have little clinical relevance [14].

Mannitol Dosages

Oddo M et al. acknowledged in their meta-analysis that mannitol bolus was associated with a reduction in the ICP of approximately 10.9 mmHg (95%CI = 8.2–13.5 mmHg, $p < 0.001$). Heterogeneity was high, but sensitivity analysis using a high correlation between before and after measurements corroborated this finding. By meta-regression, the extent of ICP reduction had no correlation to mannitol dosage. However, after adjusting for initial ICP, they found that for every 100 mg/kg of mannitol administration, there was a decrease of 0.78 mmHg in ICP ($p < 0.003$) [17].

A reasonable dosage of mannitol would be from 0.25 to 1 g/kg [18]. Other authors claim that it is safe to administer mannitol boluses from 0.15–0.2 g/kg up to 2 g/kg over 30–60 min [5]. However, it is crucial to avoid its prolonged administration, as mentioned before in this chapter, due to the formation of cerebral idiogenic osmoles and potential nephrotoxicity. As serum mannitol dosage is not readily available, when reaching an osmolar gap higher than 55 mOsm/kg or a serum osmolarity higher than 320 mOsm/L, mannitol infusion should be immediately discontinued. It is also recommended to avoid the administration of more than 200 g of mannitol per day or cumulative doses higher than 1100 g [5].

Hypertonic Saline

Even though mannitol has been considered the gold standard hyperosmolar agent for decades, hypertonic saline has recently gained popularity. One of its main advantages is not crossing the blood-brain barrier (its reflection coefficient is 1), which means that it doesn't accumulate in the brain tissue [18]. It seems to be as much or even more advantageous than mannitol in several clinical settings. Apart from it, patients who do not respond to mannitol may benefit from repeated boluses of hypertonic saline [19].

Hypertonic saline is the hyperosmolar solution of normal saline. It is usually available at 3 (or 3.2)%, 5%, 7.5%, and 23% concentrations. As a hypertonic solution, it can ameliorate cerebral perfusion and diminish cerebral edema, decreasing ICP. Different from mannitol, it doesn't cause a strong diuretic response. Thus, it generates a prolonged expansion of the intravascular volume, which may be highly desirable in hypovolemic patients. However, it may be hazardous for cardiac heart failure patients since it can precipitate acute pulmonary edema [4].

It doesn't cross the blood-brain barrier; therefore, it doesn't penetrate the brain tissue, remaining in the intravascular compartment [4, 5]. When used in concentrations higher than 3% through a peripheral cannula, it can lead to extravasation injuries, such as thrombophlebitis and subcutaneous infiltration [4].

Mechanisms of Action

As a hyperosmolar agent, its classical mechanism of action has been attributed to reducing brain water content due to its osmotic properties. Thus, it shares the favorable rheologic and osmolar gradient effects involved in ICP reduction with mannitol [20]. However, a sustained decrease in ICP appears to occur even after serum sodium values return to levels that its osmotic effect is no longer expected to be active. Thus, other mechanisms seem to be involved [21].

Several theories have been proposed. Hypertonic saline seems to restore Na/glutamate release, which has an undesirable toxic excitatory effect in the injured brain [22]. It also appears to normalize cellular resting membrane potential and cell volume [16, 23], stimulate arterial natriuretic peptide [24], inhibit neuroinflammation [25], and reduce CSF production [21].

Another postulated mechanism of its action for ameliorating cerebral edema is the down-regulation of aquaporin-4 expression in the astrocytes [26].

HTS and Cardiovascular System

Aiming to observe the cardiovascular effects of HTS, healthy volunteers with average vascular permeability had their cardiovascular parameters studied. After an infusion of 4 ml/kg of hypertonic saline 7.5% as a single dose over 30 min, an increase of plasma volume was noticeable, equiv-

alent to almost twice the infused volume. There was also an increase in the cardiac index, mean arterial pressure, and heart rate. However, stroke volume didn't seem to change significantly. A significant increase in the extracellular and intravascular volumes from the baseline was reported and suggested to be partially achieved due to the shift of water from the intracellular into the extracellular compartment. The researchers also acknowledged that interstitial water initially decreased during the infusion of HTS and then began to increase, reaching higher levels than the baseline at the end of the procedure [22].

Hypertonic saline infusion rapidly increases intravascular volume. Thus, it should be used cautiously in patients with cardiac heart failure or any other condition that a volume overload is potentially harmful. Concomitant use of furosemide can mitigate this risk [14].

HTS and the Kidneys

Acute kidney injury has been reported in up to 16% of patients who received NaCl 3% continuous infusion in neurocritical care settings. It is associated with prolonged ICU stay and higher inhospital mortality [27]. Even though bolus administration seems to be less harmful, there is not enough evidence to support one dosing strategy over the other [28].

Whereas mannitol may cause renal injury mainly because of hypovolemia due to excessive diuresis, hypertonic saline appears to be nephrotoxic through a different mechanism, mediated by hypernatremia and hyperchloremia. Raised sodium and chloride concentrations can cause renal vasoconstriction and, thereby, impair renal perfusion [29].

Hydroelectrolyte and Acid-Base Changes

The impact of HTS on acid-base balance is not entirely understood. It can cause mild acidosis, which may stimulate respiratory drive. It can also be associated with hyperchloremia and other hydroelectrolyte disturbances [4, 14].

Therefore, it is highly recommended to monitor renal function and electrolytes in patients receiving hypertonic saline infusions [30]. Hyperchloremia (Cl > 110 mEq/L), hyperosmolarity, and severe hypernatremia (Na > 155 mEq/L) are apparently related to acute renal injury [28].

Hypernatremia is a critical concern since it poses a theoretical risk of osmotic demyelination (formerly called central pontine myelinolysis) when serum sodium levels rise very quickly, especially in hyponatremic patients [31]. It is noticeable that elevated ICP conditions are commonly associated with SIAD (syndrome of inappropriate antidiuretic hormone secretion) and cerebral waste syndrome. Hence, close monitoring of serum sodium levels, sometimes every 4 or 2 h, is advisable [31].

HTS Dosages

In their meta-analysis, Oddo et al. reported that hypertonic saline infusion was associated with an average ICP reduction of 8.8 mmHg (95%CI = 6.5–11.1 mmHg, $p < 0.001$). The dose was not a predictor of ICP reduction. However, the inclusion of the initial ICP together with the dose in a multivariate meta-regression approach generated statistically significant slopes [17].

There is not enough evidence in the literature regarding the benefit of targeting a specific serum sodium concentration when administering hypertonic saline. Instead, it is advisable to constantly monitor neurological symptoms, ICP (when possible), and sodium changes to adjust the treatment accordingly [28].

Half-Molar Sodium Lactate (SL-Totilac™ Innogene Kalbiotech, Singapore, Malaysia) or Hypertonic Lactate (HL)

An alternative to hypertonic saline or mannitol to treat elevated ICP, hypertonic lactate, also called half-molar sodium lactate (SL-Totilac™ Innogene Kalbiotech, Singapore, Malaysia), has been recently studied. Apart from being a hyperosmolar solution, its effects cannot be only attributed to the classical osmotic mechanism of action since lactate also seems to be involved [32].

Lactate is one major oxidative substrate produced by injured brain cells. It has a unique role in

Table 1 Hypertonic solutions

	Mannitol 20%	Hypertonic saline
Cardiovascular system	Phase 1 (after 15 min): rapid increase in intravascular volume Phase 2 (after 45 min): drop in intravascular volume below the baseline values due to vasodilation and osmotic diuresis	Prolonged and rapid expansion of the intravascular volume—caution should be taken in patients with cardiac heart failure or conditions in which a volume overload could be deleterious
Acute kidney injury	6–12%; associated with high serum concentration of mannitol (surrogate measure: osmolal gap higher than 55 mOsm/kg	Up to 16%; mechanism mediated by hypernatremia and hyperchloremia
Hydroelectrolyte and acid-base changes	Hypokalemic and hypochloremic alkalosis with volume contraction Hypertonic hyponatremia (usually self-corrected) Risk of hyperglycemic hyperosmolar state	Hypernatremia (risk of osmotic demyelination) Hyperchloremia, mild acidosis
Concerns	It shouldn't be used in patients with any suspicious of rupture of the blood-brain barrier and loss of cerebral autoregulation	Pediatrics patients- sustained (>72 h) serum sodium greater than 160 mEq/L may be associated with thrombocytopenia, anemia, and deep vein thrombosis
	Rebound phenomenon Accumulation of cerebral idiogenic osmoles in prolonged infusions	It doesn't seem to cross the blood-brain barrier but also can induce cerebral idiogenic osmole formation in prolonged infusions

inducing cerebral vasodilation when oxygen delivery is diminished. The brain can use lactate as an alternative energy source when there is insufficient glucose availability [33]. Furthermore, it also appears to play a role in the metabolic interaction between astrocytes and neurons [34].

Many studies have already shown the efficacy of HL in treating elevated ICP [35, 36]. One of them is a randomized controlled trial with 60 patients with severe traumatic brain injury, in which it was found that those who received 0.5 ml/kg/h of SL within the first 12 h post-trauma had fewer episodes of increased ICP compared to a control group that received normal saline [36]. The authors speculate that sodium accumulates in the extracellular space since lactate is rapidly metabolized in the brain cells. It generates an electric gradient that promotes chloride efflux from the cells. Then, there is an efflux of water from the cells to maintain the osmotic equilibrium, ameliorating the brain cellular edema [35]. Other proposed mechanisms of action for HL are improvement of cerebral hemodynamics [17, 37] and attenuation of energetic metabolic crisis [38, 39].

Despite all these evidences, ESICM (European Society of Intensive Care Medicine) consensus in 2018 didn't provide any recommendation regarding the use of HL as a first-line osmotic solution [17].

In Table 1, we summarize the main differences between mannitol and hypertonic saline.

Clinical Settings

Neuroanesthesia

Considering that a bulging of the brain can significantly lead to difficult surgical access, brain relaxation maneuvers can facilitate surgery since less retraction pressure may be required to expose and manipulate brain structures. Therefore, one of the main goals of neuroanesthesia is to provide adequate brain relaxation [18]. This refers to the content-space relationship of the intracranial cavity after opening the dura. Intracranial hypertension results in an increased volume of the brain that surpasses the capacity of the intracranial space, clearly evident

after the dura opening. Thus, a subjective evaluation by the neurosurgeons of the brain firmness after opening the dura is commonly used to assess brain relaxation status [40].

One of the standard brain relaxation maneuvers is the infusion of hyperosmolar solutions. Within minutes, there is a drop in ICP and a visible reduction of the brain volume during craniotomy. Hyperosmolar therapy effects are comparable to acute forced ventilation, with the advantage of being more consistent and longer-lasting [14].

A systematic review found an improvement in cardiac performance with both hyperosmolar agents. However, this improvement was more evident after the HTS infusion. Mannitol had a more prominent diuretic effect and induced transient hyponatremia [41].

A recent trial compared equimolar 5 ml/kg infusions of 3% HTS and 20% mannitol regarding their effects on blood coagulation. No differences were found between the two groups, as evidenced by ROTEM and standard coagulation tests. It was acknowledged an increase of CFT EXTEM, hematocrit, platelet count, and fibrinogen and a decrease of CT INTEM compared to baseline levels with both agents, but still within the normal range [42].

Intracranial Tumors

Some brain tumors cause a significant brain swelling that may occur pre-, intra-, or postoperatively. Hyperosmolar agents can improve brain elastance pre- or intraoperatively and can also be used to control ICP and cerebral edema after surgery [18].

A systematic review in 2014 suggested that HTS significantly reduces the risk of tense/swollen brain compared to mannitol during elective craniotomies, mainly for tumor resections. However, this data was derived from a limited number of studies. They pointed out the need for high-quality data concerning long-term mortality and outcomes, adverse events monitoring, and quality of life evaluation after both treatments [18].

A more recent meta-analysis also found HTS to provide a higher rate of adequate brain relaxation during craniotomies in comparison to mannitol [43].

Hyperosmotic solutions also can be used for a new approach to the treatment of brain tumors. This strategy is called blood-brain barrier disruption, and it seems to increase the delivery of antineoplastic agents to the central nervous system [44].

Neurointensive Care

Hyperosmolar agents are used to treat cerebral edema in a variety of clinical settings in neurocritical patients [12].

According to the ESICM (European Society of Intense Care Medicine) consensus, osmotherapeutic agents can be used to reduce increased ICP in neurocritical care patients. They recommend a predefined trigger based on clinical and neuromonitoring variables.

They suggest the combination of neurological worsening (defined as a decrease of two points of the GSC motor score, or loss of pupillary reactivity or asymmetry, or deterioration of head CT findings) and ICP >25. They also accept ICP > 25 without other variables but strongly recommend against the use of ICP > 15 independently of other variables as a trigger.

It is advisable to monitor ICP response and measure serum osmolarity and electrolytes, as well as fluid balance and arterial blood pressure to limit side effects of the hyperosmolar therapy. They don't recommend using HTS as a resuscitation fluid in patients with low blood pressure and report insufficient evidence to support hypertonic lactate [17].

Another guideline recently published recommended the use of hyperosmolar therapy to treat ICP elevations or cerebral edema. However, they acknowledged no compelling evidence of an improvement in neurological outcomes [12].

It is proved that the control of elevated ICP has a beneficial effect on survival. Hyperosmolar agents can be used to control intracranial hyper-

tension. However, their beneficial role on survival can only be assumed since there are no trials omitting hyperosmolar therapy from the standard treatment [14]. Outcomes may be affected by unknown or uncontrolled variables, such as comorbidities, associated injuries or complications, and rehabilitation availability [30].

Traumatic Brain Injury (TBI)

The Committee of the Brain Trauma Foundation in 2016 endorsed the use of hyperosmolar agents in the care of patients with severe TBI. Due to limited data, they didn't formally recommend one specific agent over the other. They also removed the recommendation of mannitol use for patients with signs of transtentorial herniation or progressive neurological deterioration [4].

In the setting of TBI, hypertonic saline use has more advantages than mannitol. It provides plasma volume expansion, brain cell immune modulation, and extracellular glutamate reduction and improves cerebral blood flow [5].

A recent Cochrane review compared the effect of hypertonic saline and mannitol in patients with TBI. Even though both treatments proved to be effective, there was a trend favoring HTS because it seemed to have more benefits. There was insufficient data to evaluate long-term outcomes and adverse events, such as rebound phenomenon, pulmonary edema, and acute renal failure [32].

An ongoing multicenter randomized trial (COBI—Continuous Hyperosmolar Therapy in Traumatic Brain-Injured Patients) compares the functional outcome after 6 months of patients receiving hypertonic saline 20% as an add-on to standard care versus a control group receiving only standard care. Hopefully, it will provide some new evidence regarding the long-term benefits of hypertonic saline treatment in patients with TBI [37].

Intracranial Hemorrhage

The impact of ICP lowering on neurological outcomes of patients with intracranial hemorrhages is still unknown. The main challenge is avoiding perihematomal edema expansion since it is correlated with worse neurological outcomes [12, 45, 46]. Some studies have shown a potential risk of hematoma expansion with mannitol use [12, 45, 46], but Misra and colleagues reported no significant change in horizontal or vertical shift documented by magnetic resonance imaging after mannitol administration in these patients [3, 47].

Mannitol shouldn't be used when there is a disruption of the blood-brain barrier since it can penetrate and accumulate in the brain, blunting the osmotic effects and sometimes even aggravating the cerebral edema [5].

Fortunately, some studies have shown a potential benefit of hypertonic saline in this clinical setting [12].

Acute Ischemic Stroke

The current guideline of the American Stroke Association concluded that there is not enough data to support the prophylactic use of hyperosmolar agents based only on early CT swelling without clinical evidence of elevated ICP. Indeed, the preemptive use of mannitol in this situation may even be harmful [12].

For patients with cerebral edema and clinical deterioration, osmotic therapy is reasonable. However, more data is needed to evaluate the effect of each agent depending on the clinical situation [12, 48].

In a small trial, patients with a large hemispheric infarction and a midline shift of >10 mm who received 1.5 g/kg of mannitol were evaluated. It was noticed a slight decrease in the cerebral blood flow restricted to the non-infarcted hemisphere. Thus, the midline shift tended to worsen since the shrinkage occurred mainly in the non-infarcted hemisphere [49].

Hypertonic saline appears to have a more robust and long-lasting effect than mannitol in acute ischemic stroke patients. It also seems to have a faster onset of action. Moreover, patients who didn't respond to mannitol still can have an adequate response to hypertonic saline [48].

Subarachnoid Hemorrhage

Cook and colleagues recommended using hypertonic saline in patients with subarachnoid hemorrhage due to its ability to improve brain tissue oxygenation. They suggested a symptom-based dosage and didn't identify any compelling evi-

dence to support targeting a specific serum sodium concentration while treating these patients. However, they pointed out that the overall quality of the data was low and insufficient to assess the clinical outcomes related to this treatment [12]. There is also a concern related to acute kidney injury in these patients [50].

Even though mannitol at doses varying from 0.25 to 1 g/kg can provide brain relaxation in patients undergoing craniotomies for aneurysm clipping, its effects in this setting are still controversial and need further investigation [5].

Hepatic Encephalopathy

Hyperosmolar therapy can be used as an add-on treatment for patients with fulminant liver failure and encephalopathy. Further research is warranted to investigate the influence of ammonia lowering therapy and define the optimal strategies for treating intracranial hypertension and cerebral edema in these patients [12, 51].

Neuropediatrics

There is a lack of high-quality research explicitly addressed to this population. Therefore, most practical guidelines are based on mixed disease population studies, with both children and adults.

A consortium of pediatric societies developed a comprehensive guideline for TBI pediatric patients based on the recommendations of the Brain Trauma Foundation [52]. They considered as level II recommendation (based on a moderate-quality body of evidence) the administration of boluses of hypertonic saline 3% of 2–5 ml/kg over 10–20 min for the ICP control of these patients. Continuous infusions on a sliding scale or boluses of 23.4% HTS for refractory intracranial hypertension were considered level III evidence (based on a low-quality body of evidence). Regarding safety issues, they recommended avoiding sustained (>72 h) serum sodium concentrations greater than 160 mEq/L since it was associated with complications such as thrombocytopenia, anemia, and deep vein thrombosis. They pointed out that even though mannitol is commonly used to control elevated ICP in neuropediatric patients, there is insufficient evidence to endorse it. They also reported there was not enough data to evaluate the potential beneficial effect of hyperosmotic therapy on the neurological outcomes of this population [52].

In Table 2, we summarize the main findings in the literature concerning the use of mannitol in comparison to hypertonic saline in different clinical settings.

Clinical Case

A 12-year-old female suffered a severe TBI after a car accident. When the rescue team arrived, she was awake, with normal breathing, Glasgow Coma Scale of 8, isodiametric pupils, blood pressure 160 × 80, and HR 120 bpm.

She had no comorbidities besides being overweight (55 kg). She was transferred to the hospital with spinal immobilization, and further investigation showed no medullary injuries. After 2 h of the accident, she developed a conscience level impairment, with a Glasgow Coma Scale of 5. Thus, she was sedated, intubated, and mechanically ventilated. CT scan showed large regions of frontal brain contusion with surrounding edema and no hematomas. An external ventricular drain and ICP monitoring device were placed. The initial ICP was 30 mmHg but dropped to 26 mmHg after CSF drainage. Serum sodium was 139 mmol/L, creatinine was 0.9 mg/dL, and hematocrit was 31% after initial volume stabilization.

Questions

1. Would you recommend a hyperosmolar treatment for this patient? If so, which agent would you prefer?
2. How would you prescribe it?

Discussion—based on [3, 14, 31, 52, 53]

The deteriorating neurological clinical state of this patient points out the risk of further and fatal elevations of intracranial pressure. Since there is no formal indication for neurosurgical treatment, hyperosmolar therapy is an appropriate clinical approach.

As we discussed before in this chapter, there is not enough evidence to support the use of man-

Table 2 Clinical settings: sugar or salt?

	Evidence for ICP lowering benefit	Sugar or salt	Precautions	Long-term outcome benefit	References
Neuroanesthesia	For brain relaxation	Trend toward HTS	Dehydration and HE disturbances with mannitol use	No evidence	[18, 40, 42, 43]
Intracranial tumors	Some kinds of tumors	Trend toward HTS	Rebound phenomenon with mannitol	No evidence	[18, 43, 44]
TBI	Yes, and a potential benefit of HL	Trend toward HTS	AKI and HE disturbances	No evidence yet (COBI)	[4, 5, 12, 32, 37]
Intracranial hemorrhage	Little evidence	HTS	Hematoma expansion and rebound (mannitol) AKI and HE disturbances (HTS)	No evidence	[12, 45, 46]
Acute ischemic stroke	Yes, but preemptive use is not recommended	Trend toward HTS	Decrease in CBF in the non-infarcted hemisphere	No evidence	[12, 48, 49]
Subarachnoid hemorrhage	Low evidence	HTS	AKI and HE disturbances	No evidence	[5, 12, 50]
Hepatic encephalopathy	As an add-on treatment	Both	AKI, HE disturbances (HTS), rebound (mannitol)	No evidence	[12, 51]
Neuropediatrics	Moderate evidence, mainly in TBI	HTS	Anemia, thrombocytopenia, DVT and AKI (HTS)	No evidence	[52]

HTS: hypertonic saline, TBI: traumatic Brain Injury, HL: hypertonic lactate (half-molar sodium lactate), AKI: acute kidney injury, HE: hydroelectrolyte, DVT: deep vein thrombosis, COBI: Continuous Hyperosmolar Therapy in Traumatic Brain-Injured Patients (trial)

nitol in pediatric neurocritical patients. Therefore, hypertonic saline should be more appropriate.

Hypertonic saline is usually administrated in boluses of 150 ml of the 3% solution (513 mmol/L), 75 ml of a 7.5% solution (1283 mmol/L), or 30 ml of 23.4% solution (4008 mmol/L). In pediatric patients, caution should be taken to avoid serum sodium concentrations higher than 160 mEq/L. It may be associated with deep vein thrombosis, anemia, and thrombocytopenia in concentrations higher than 170 mEq/L [52].

Calculating the amount of HTS to reach an initial target sodium concentration of approximately 150 mmol/L, the sodium requirement would be:

Na requirement = (lean body weight, in kg) × (% of the water in the bodyweight) × (desired sodium – current sodium).

Note: the percentage of water in the bodyweight is approximately 0.5 for females and 0.6 for males; since the patient was 12 years old and weighed 55 kg, we considered the value of 0.5:

Na requirement = 55 × 0.5 × (150 – 139).

Na requirement = 302 mmol.

It corresponds to 589 ml of 3% saline or 75 ml of 23% saline.

Therefore, the initial prescription could be 5 ml/kg (275 ml) of hypertonic saline 3% in 10 min, which could be repeated twice to reach an ICP of 20 mmHg. It is highly recommended to monitor serum sodium levels carefully to avoid rapid changes. Renal function, electrolytes, and gasometry should be measured at regular intervals. Moreover, subsequent boluses or continuous infusions could be administered, aiming to improve her neurological status. Extreme hyperosmolarity, as reflected by serum sodium levels higher than 160 mmol/L, is unlikely to have further beneficial effects and may even generate undesirable effects.

Take-Home Messages

- Hyperosmolar solutions can be used to treat cerebral edema in various clinical settings in neurocritical care and neuroanesthesia.
- Caution should be taken in patients with loss of cerebral autoregulation or disruption of the brain-blood barrier.
- Prolonged infusions of both hypertonic solutions can lead to the accumulation of cerebral idiogenic osmoles that can simulate a rebound phenomenon.
- The main concerns associated with mannitol use are dehydration due to osmotic diuresis, acute kidney injury due to high serum concentration of mannitol, and rebound phenomenon.
- The main concerns associated with the use of hypertonic saline are volume overload, acute kidney injury associated with hyperchloremia, and hypernatremia. Extravasation injuries can occur when administered in peripheral cannulas.

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Balanced Fluids

Srilata Moningi and Shibani Padhy

Abstract

Fluid management in the brain-injured neurological patient revolves around the primary aim of maintenance of adequate cerebral blood flow and prevention of intracranial hypertension. The type and tonicity of the maintenance fluid have a tremendous impact on the development of secondary brain injuries and hence outcome in these patients. Historically, 0.9% sodium chloride has been the most frequently administered intravenous fluid in neurosurgical practice. However with a growing body of evidence raising fundamental concerns regarding the hyperchloremia caused by 0.9% saline, novel balanced intravenous solutions have emerged as an attractive alternative in clinical neurosurgery. These "balanced" solutions derive their denomination from being buffered with precursors of bicarbonate and hence more closely mimic plasma electrolyte composition, particularly with regard to their chloride content. With desirable features of preservation of acid-base and electrolyte balance and preservation of renal function, balanced solutions are now seen to have potential to be an ideal or at least a better fluid choice than 0.9% saline in neurosurgery.

This chapter offers a comprehensive and updated review on balanced intravenous solutions, firstly, by providing a physiological background of balanced solutions; secondly, by summarizing their potential pathophysiologic effects; and lastly, by presenting the clinical evidence available at the present time to support or refute their use in specific neurosurgical scenarios.

Keywords

Balanced solutions · Neurosurgery · Crystalloids · Hyperchloremia · Fluid therapy Acid-base equilibrium

Practice Points/Clinical Pearls

1. Fluid management in both routine neurosurgery and neurocritical care should be targeted at euvolemia using isotonic fluids.
2. Balanced fluid prevents hyperchloremia and better preserves acid-base milieu, electrolyte balance, and renal function as compared to saline solutions, with preservation of intracranial pressure.
3. Larger studies are required to investigate the effects of balanced solutions on brain swelling and neurological recovery in specific neuropathological disorders.

S. Moningi (✉) · S. Padhy
Department of Anaesthesiology and Intensive Care,
Nizam's Institute of Medical Sciences,
Hyderabad, India

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Introduction

Fluid management in brain-injured patients has several distinct requisites not seen with other non-neurological patients:

1. Tonicity of the transfused intravenous fluid has a significant impact on the cerebral dynamics.
2. Fluid-induced/fluid-aggravated cerebral edema produces an antagonistic volume-pressure intracranial relationship, resulting in impairment of both cerebral blood flow and oxygenation.
3. Cerebral perfusion pressure goal-directed fluid therapy is intrinsically challenging due to the need for sophisticated CBF and cerebral oxygenation monitoring.

However, the above goal of maintenance of cerebral oxygenation and adequate CPP is met by unique challenges for anesthesiologists and intensivists involved in fluid management of the neurosurgical patient [1]. While on one hand brain-injured patients are often on diuretics for prevention or treatment of cerebral edema and/or intracranial hypertension, they may also require infusion of large quantities of intravenous fluids to correct preoperative dehydration and/or to maintain perioperative hemodynamics as mandated for the management of vasospasm or intraoperative blood loss [1]. The above concerns make appropriate type and composition of the perioperative intravenous fluid an important determinant in the outcome.

While searching for the "ideal" intravenous solution for the brain injured, and with increasing evidence that the commonly used crystalloid solution, 0.9% NaCl, may be harmful [2], novel crystalloid solutions are finding a foothold in neurosurgical practice, namely, intravenous "balanced solutions" [2, 3]. At the present time, no conclusive human data exists, concerning the impact of different compositions of intravenous fluids and balanced solutions in particular, on the injured brain to make firm recommendations.

This chapter will address some of the physical determinants of water movement between the intravascular space and the central nervous system (CNS) and the current evidence surrounding balanced salt solutions in detail. These factors would help make some reasonable recommendations regarding balanced fluid therapy in the neurological patient.

Water Movement Across the Blood-Brain Barrier: Determinants and Physiopathology

The three properties of the blood that are amenable to manipulation with intravenous fluids include [2, 3]:

1. Osmotic pressure (determined by concentrations of small and large molecules)
2. Colloid oncotic pressure (COP; determined by large molecules alone)
3. Hematocrit

1. *Osmotic pressure*: This is the hydrostatic force that equalizes the concentration of water on both sides of an impermeable membrane. Osmolarity describes the molar number of osmotically active particles per liter of solution. In practice, the osmolarity of a solution can be "calculated" by adding up the mEq concentrations of the various ions in the intravenous fluid. Osmolality describes the molar number of osmotically active particles per kilogram of solvent. This value is directly "measured" by determining either the freezing point or the vapor pressure of the solution. For most dilute salt solutions, osmolality is equal to or slightly less than osmolarity.
2. *Colloid oncotic pressure*: COP is the osmotic pressure generated by large molecules (e.g., albumin, hetastarch).
3. *Hematocrit*: Fluid infusion is often accompanied by a reduction in hematocrit. In the normal brain, this hemodilution and decreased arterial oxygen content is often compensated by an increase in cerebral blood flow (CBF) [4–7]. However, it is important to realize that in the backdrop of brain injury, the normal

CBF responses to hemodilution and hypoxia are attenuated, and both changes may contribute to secondary tissue damage [4–7]. A hematocrit level of 30–33% provides the ideal combination of viscosity and O2 carrying capacity, and may improve neurological outcome [1, 4]. However, marked hemodilution (HCT < 30%) exacerbates neurologic injury [6].

The fluid movement across the BBB is determined by the "total" osmotic gradient, generated both by large molecules and small ions (Fig. 1). Since there are very few protein (large) molecules, their effect on serum osmolality is minimal. Also this has an attenuated effect on the alterations in colloid oncotic pressure. These differences explain the peripheral edema due to dilutional reduction of COP and not cerebral edema with the administration of large volumes of isotonic crystalloids [2, 8, 9]. When plasma osmolality decreases, the osmotic gradient drives water into the brain tissue. Even small changes in plasma osmolality (<5%) increase brain water content and ICP [2, 10, 11]. The above scenario describes the situation in conditions of normal BBB (Fig. 1). After a brain lesion, according to the severity of the damage (head trauma, tumor, seizure, abscess, or other damage), there can be varying degrees of loss of BBB integrity, which can respond differently to the osmotic/oncotic changes. With complete breakdown of the BBB, no osmotic gradient can be established [1, 15, 16]. It is possible that with a less severe injury to the BBB, the barrier may function similarly to the peripheral tissue [11]. Finally, there is usually

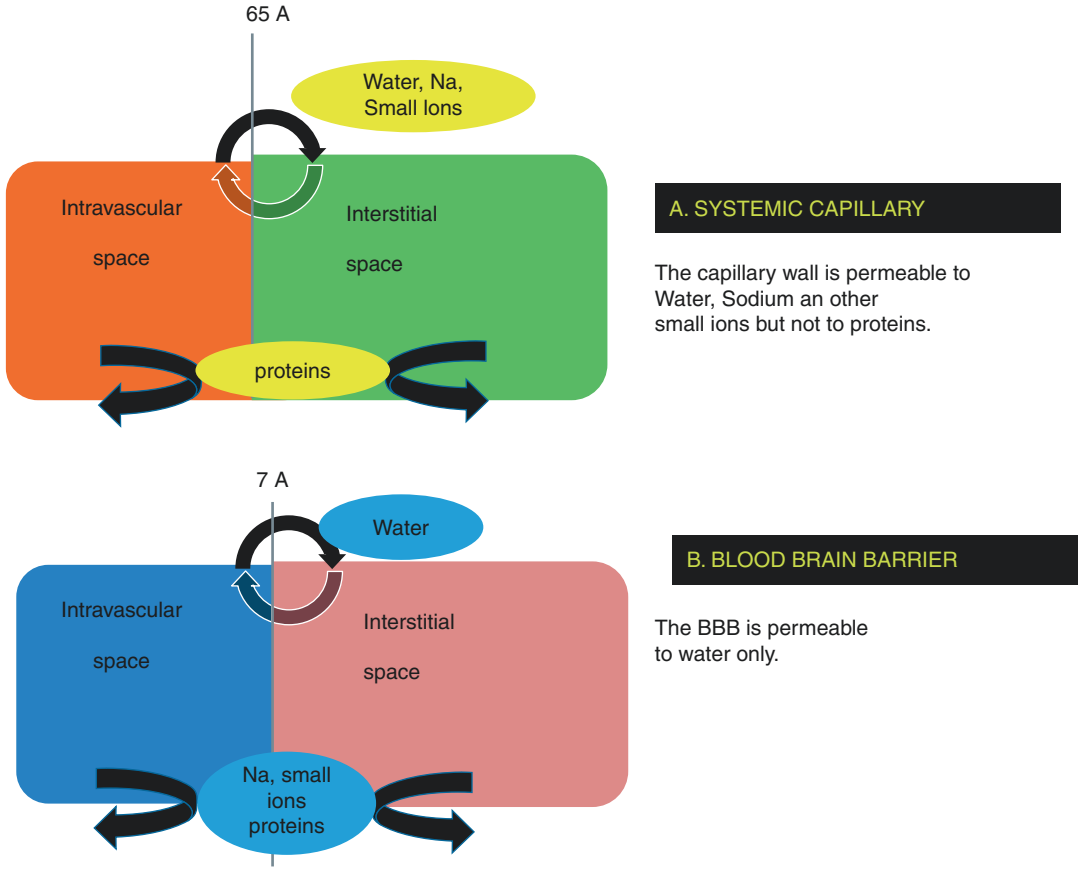

Fig. 1 Schematic representation of fluid and molecular movement across (**a**) systemic capillary membrane and (**b**) blood-brain barrier [2, 3, 8–12]

a significant portion of the brain where the BBB is normal. The presence of a functionally intact BBB is essential if osmotherapy is to be successful [10–12].

Implications in Designing an Intravenous Fluid for Neurosurgical Population

- First is the requisite for osmolarity (hence, the need for electrolytes present in the solution) to be as close as possible to plasma osmolarity. There is definite evidence of increased cerebral edema and intracranial hypertension, consequent to infusion of hypoosmotic solutions in the already injured brain.
- Second is the need, in specific clinical scenarios, for the presence of oncotic pressure in the intravenous fluid. This is imperative to contain or restrict the infused volume within the intravascular compartment.

Intravenous "Balanced" Solutions

Definition

The term "balanced fluids" encompasses intravenous solutions having an electrolyte composition equal to or closest to the plasma composition and also displaying electrical neutrality (total free cations = total free anions) [11–15]. These concepts have further been expanded to the manufacture of "balanced colloid solutions" in which the colloid molecules are incorporated into "balanced" solvents.

Historically, 0.9% sodium chloride has been the most frequently administered intravenous fluid in neurosurgical practice. However, the perioperative use of these saline solutions is seen to be associated with hyperchloremia with its attendant ill effects. With the aim to avoid these deleterious effects of supraphysiological concentrations of chloride as in 0.9% NaCl, more recently, researchers have broadened the term "balanced" solution to also indicate intravenous solutions with low chloride content as compared to plasma [11].

Balanced Fluids and Acid-Base Balance

Bearing the above assumptions in mind, there are two important aspects which need to be considered while designing an ideal "balanced fluid."

Firstly, most of the available intravenous solutions (excepting 0.9% NaCl and pure dextrose-containing solutions) have organic anions added to them (e.g., acetate, lactate, malate, gluconate, etc.), as precursors of HCO3 in order to balance the total cations (Table 1) [11, 12]. This is necessary as the process of including HCO3 directly to the intravenous fluid is complex and often unrealistic.

Secondly, to meet the goals of maintaining electrical neutrality and to avoid both hypotonicity and a high strong ion difference (SID, hence maintaining the Na+-Cl– difference between 24 and 30 mEq L^{-1}), balanced salt solutions have been developed with a relatively high concentration of chloride (Table 1).

Conversely, with the mounting evidence of the deleterious renal effects of supraphysiologic Cl–-containing solutions, balanced fluids have been expected to have lower chloride content as compared to plasma.

Composition of Balanced Fluids: Qualitative and Quantitative

It would be easy to understand from the previous section that two classifications of intravenous "balanced" solutions are available:

(1) Balanced solutions with minimal effect on acid-base equilibrium, with a SID value close to 24–29 mEq L^{-1}, e.g., lactated Ringer's, acetated Ringer's, Sterofundin ISO, Hartmann's solution, Tetraspan, and Hextend

Table 1 Composition of common balanced intravenous fluids

Crystalloids	Na^+	K^+	Ca^+	Mg^+	Cl^-	Lactate	Acetate	Malate	Gluconate	Dextrose	Galatin	HES	SID	Osmolarity
Lactated ringer's	130	4	3	–	109	28	–	–	–	–	–	–	28	278
Acetated Ringer's	132	4	3	–	110	–	29	–	–	–	–	–	29	277
Hartmann's solution	131	5	4	–	111	29	–	–	–	–	–	–	29	279
Plasmalyte	140	5	–	3	28	–	27	–	23	–	–	–	50	294
Sterofundin ISO	145	4	5	2	127	–	24	5	–	–	–	–	29	309
lonolyta	137	4	–	3	110	–	34	–	–	–	–	–	34	286
Gelatins														
Isoplex	145	4	–	1.8	105	25	–	–	–	–	40	–	46	284
Gelaspan	151	4	2	2	103	–	24	–	–	–	40	–	56	284
Starches														
Hextend	143	3	5	0.9	124	28	–	–	–	–	–	60	28	307
Tetraspan	140	4	5	2	118	–	24	5	–	–	–	60	29	297
Volulyte	137	4	–	3	110	–	34	–	–	–	–	60	34	287

(2) Balanced solutions with a Cl– content equal or lower than 110 mEq L^{-1}, e.g., lactated Ringer's, acetated Ringer's, Hartmann's solution, Plasma-Lyte, Elo-Mel Isoton, Isoplex, and Gelaspan (Table 1).

Thus, it is apparent that an "ideal" balanced solution meeting all these three goals of acid-base neutrality, iso-osmolarity, and physiological chloride concentrations cannot be realized in a single intravenous formulation or rather has not been designed so far. All the available balanced solutions fit into just one of the categories described above (i.e., have an effect on acid-base equilibrium with normal chloride content or vice versa) or when fitting into both present with obvious limitations of hypotonicity, as in Hartmann's solution, acetated Ringer's, and lactated Ringer's [12, 15].

Electrolyte Content of Balanced Solutions and the Neurological Patient

Apart from Na + and Cl-, the other important aspect related to "balanced" solutions and bearing relevance in the neurosurgical patient concerns the content of specific electrolytes, in particular of magnesium, calcium, and potassium.

Magnesium and Cerebral Vasospasm

Magnesium, one of the most ubiquitous cations in the body, has been shown to cross the blood-brain barrier in humans and animals [16–19]. In the context of cerebral vasospasm, its role as a physiologic calcium antagonist and hence a potent vasodilator has been the subject of most interest, although some neuroprotective effects have also been documented [16, 17]. One extensively studied therapy in vasospasm is magnesium (Mg) both as a competitive antagonist of calcium at the *N*-methyl-D-aspartate (NMDA) receptor and a noncompetitive antagonist of both IP_3 and voltage-gated calcium channels, leading to smooth muscle relaxation.

Hypomagnesemia, with plasma levels less than 1.5 mg dL^{-1}, is a relatively common finding in critically ill neurological patients admitted to ICU. Though the evidence is sparse, low magnesium levels are associated with poor neurological outcome in patients with TBI, seizures, stroke, and cerebral vasospasm [17–19].

Hence, when dealing with fluid replacement, it may be prudent to employ intravenous fluids containing magnesium, in order to prevent hypomagnesemia. With this rationale, the newer generation of "balanced" fluids (Plasma-Lyte, Sterofundin ISO) has been developed with the inclusion of magnesium, as compared to the older generation (lactated Ringer's, or Hartmann's solution) (see Table 1). Though there are no studies investigating the effects of balanced solutions on the incidence of hypomagnesemia, it would be reasonable to favor the use of these novel balanced solutions, in neurological situations warranting large volume replacements.

Calcium and Neurological Outcome

Hypocalcemia is the commonest electrolyte abnormality observed in acutely ill patients [24] with well-documented deleterious consequences like alterations in muscle contractility, peripheral and central nervous system function, and cardiac dysrhythmias. Hypocalcemia has been implicated as a prognostic factor in mortality and morbidity in patients with stroke and in moderate and severe traumatic brain injury [24].

Though it seems an attractive option to include Ca2+ in an ideal "balanced" solution, especially in the face of large volume replacements, it is offset by the risk of precipitation as Ca2+-citrate or Ca2+-carbonate when infused through a common vascular access. This limitation underlies the rationale for development of Ca2+-free intravenous balanced solutions (Table 1).

Potassium Content

Hypokalemia is a life-threatening electrolyte abnormality often observed in the critically ill and emergent neurosurgical patient [23]. All the available intravenous balanced fluids present a concentration of K+ within normal ranges. This feature however should not be erroneously considered a reason for preferring the use of 0.9% NaCl as the only intravenous solution potentially applicable in the case of the neurological patients with acute or chronic renal failure.

Balanced Solutions Versus 0.9% Normal Saline in the Neurological Patient-Clinical Evidence

Although owing to its osmotic benefits, 0.9% sodium chloride (saline) has been the most popular intravenous fluid in neurological practice [20, 21, 25, 26], there is perpetuating evidence of the supraphysiological chloride content in normal saline to cause hyperchloremia [22, 23], acidosis [26, 27], renal vasoconstriction [28], acute renal injury [29, 36], hypotension [30], inflammation, and death [29–31].

Chloride-mediated renal vasoconstriction [29, 30] and decreased renal perfusion have been implicated to be mechanisms behind the renal dysfunction caused by 0.9% sodium chloride with higher rates of acute kidney injury [29], renal replacement therapy [35], and death [33–35] with saline than with balanced crystalloids, although results have been inconsistent [35]. Recently, several human studies reported that metabolic acidosis, vasoconstriction, and AKI are less pronounced when using a balanced salt solution, which has a physiologic level of chloride and a neutral pH, compared to 0.9% saline [34, 35] in the critically ill patient. However, BC also have potential side effects such as hyperlactacidemia [14] and may exacerbate alkalosis. This is because all BC are relatively alkaline compared to NS [37]. A recent meta-analysis of fluid resuscitation with high versus low chloride content solutions in the perioperative or critical care settings observed fewer days on mechanical ventilation with the use of balanced crystalloids [32].

On the question of neurological effects of normal saline versus balanced crystalloid, such as lactated Ringer's solution or Plasma-Lyte A, there are still no high-quality data in neurocritically ill patients. Albeit few, all the prospective randomized trials that have been conducted in the neurosurgical population have indicated that balanced intravenous fluids provide significantly better control over acid-base balance, sodium, and chloride levels, without increasing intracranial pressure when used as intraoperative fluid maintenance and replacement during elective neurosurgery and in the brain-injured patient [38–41]. In these balanced solutions, the use of malate and acetate allows for the reduction of chloride concentration while ensuring isotonicity. Though the isotonic balanced solutions have a lower osmolarity than normal saline, they have no adverse effects on intracranial pressure due to their lower chloremia-induced neuronal chloride ion efflux, thus limiting brain swelling despite decreased osmolarity compared with 0.9%.

One study has shown that combination of a balanced crystalloid with colloid results in lower serum chloride concentrations and maintenance of acid-base balance compared to unbalanced crystalloid in combination with an unbalanced colloid [38].

At the present time, balanced fluids can at best be said to have the potential to be a better alternative to 0.9% normal saline in the neurosurgical patient, but barring high-quality evidence, firm recommendations cannot be made.

Balanced Fluids in Specific Neurological Scenarios

Traumatic Brain Injury

In TBI, a blunt or penetrating injury incites mechanical and autodigestive destruction of the normally tightly intact endothelium of the blood-brain barrier. This allows uncontrolled movement

of fluid and serum proteins into the brain parenchyma, eventually leading to vasogenic cerebral edema and increased ICP. Intracranial hypertension (ICH) is the primary cause of secondary brain insult and death after brain injury [39]. These patients are prone to ion homeostasis disruption, plausibly due to hormonal dysfunction such as diabetes insipidus and cerebral salt wasting syndrome or through alterations of chloride-dependent channels such as the NKCC1 transporter [39, 41, 42].

Thus, administration of hypo-osmolar solutions should be avoided in brain-injured patients [39, 43]. Hyposmolarity and hyperchloremia with its attendant acidosis are touted to be the two major modifiable implicates of cerebral edema after brain injury.

Chloride channels regulate cell edema [39, 42], and dyschloremia contributes to brain swelling. With the recognition that chloride-rich fluids are the primary cause of hyperchloremic acidosis in critically ill neurological patients [2], a general chloride-restrictive strategy can be recommended for decreased incidence of renal failure and improved neuronal homeostasis.

Balanced solutions have been inconclusively proven to decrease the incidence of hyperchloremic acidosis, in patients with severe brain injury as compared with saline solutions. This feature along with the isotonicity of the balanced solutions may authorize their utilization in the neuro-ICU, but few data are available to make firm recommendations. The Neuro-Intensive Care and Emergency Medicine (NICEM) Section of the European Society of Intensive Care Medicine consensus document stated that HES is not recommended in the context of brain injury [44]. The effect of albumin or artificial colloids in isotonic fluids on outcome in traumatic brain injury has not been investigated.

Subarachnoid Hemorrhage (SAH)

Secondary brain injuries related to cerebral vasospasm and consecutive ischemic brain injury and intracerebral edema are the main contributors to mortality and morbidity in these patients. Hyponatremia and hypovolemia secondary to cerebral salt wasting have been identified as the two most important culprits for these cerebral events.

Traditionally, patients with SAH have been managed with normal saline for baseline and substitution requirements. If hyponatremia is more severe or significant cerebral edema exists, the use of mild hypertonic fluids (1.25 or 1.5% saline) and strict avoidance of free water administration are usually successful in reversing the hyponatremia.

The guidelines of the American Heart Association [45] recommend that volume contraction be treated with isotonic fluids (Class IIa, Level of Evidence B) and that "administration of large volumes of hypotonic fluids should generally be avoided after SAH (Class I, Level of Evidence B)." Similarly, guidelines of the Neurocritical Care Society for the management of patients with SAH recommend maintaining euvolemia and avoiding both prophylactic hypervolemia therapy and fluid restriction to treat hyponatremia [46] (high-quality evidence; strong recommendation). Neither set of guidelines addresses the composition of baseline fluid administration in patients without oral intake.

In SAH, standard fluid management with saline may have alternatives with more balanced solutions resulting in more stable electrolytes, less fluid intake, and less activation of the pituitary axis stress hormones (cortisol, TSH) [40].

A randomized, double-blind trial demonstrates a greater incidence of hyperchloremia, hyperosmolality, and positive fluid balance with 0.9% saline in early SAH, with balanced solutions not causing frequent hyponatremia or hypoosmolality [40]. Awaiting the results of few ongoing studies [47] and need for larger studies, no appropriate conclusions can be drawn on the beneficial effects of balanced crystalloids in SAH.

Ischemic Injury

The 2018 AHA/ASA guidelines for the early management of patients with acute ischemic stroke [48] stress upon the use of isotonic fluids

rather than hypotonic fluids (might exacerbate ischemic brain edema). AHA/ASA recommendations for the management of cerebral and cerebellar infarction with swelling make similar recommendations advocating the use of isotonic fluids [49]. Balanced intravenous fluids being isotonic seem to be an attractive option in such scenarios.

Elective Supratentorial Craniotomy for Brain Tumors

The existing evidence, albeit sparse, indicates more stable electrolytes, particularly chloride, magnesium, calcium, and phosphate levels as well as a preserved acid-base balance with balanced fluids especially during prolonged elective supratentorial craniotomy, all distinct advantages over 0.9% NS. Day et al. published a study comparing normal saline with Plasmalyte as intraoperative maintenance fluid during craniotomy for excision of brain tumors [53]. Like the findings of the earlier studies, they find that the acid-base status and renal profile were better with Plasmalyte. Two novel findings of this study were the preservation of brain relaxation and a significantly lower level of neutrophil gelatinase-associated lipocalin (NGAL), a biomarker of kidney injury with the use of Plasmalyte for resuscitation.

Perceived advantages of balanced crystalloid solutions over non-buffered solutions are reflected in the British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP) [55] that recommend the use of balanced solutions for crystalloid fluid resuscitation or replacement.*Evidence level 1b*[1–6].

Major Spine Surgery

The combined physiologic effects of prone positioning and the risk of substantial blood loss pose patients undergoing multilevel spine surgery at high risk for intraoperative hemodynamic instability. Emerging evidence suggest that balanced crystalloids and third-generation colloids in balanced salt solution are potentially safer with no significant effect on coagulation when compared to crystalloids [56, 57].

Dose of Balanced Intravenous Fluids for Perioperative Replacement/Resuscitation: *How Much Is "Balanced?"*

As a general ordinance, intraoperative balanced fluids when used should be administered at a rate sufficient to replace the urinary and insensible losses. As a rough guide, 1 L of isotonic crystalloid and 1 L of hetastarch result in 250 ml and 750 ml of the intravascular volume expansion, respectively. Current data indicates that as long as normal serum osmolality and oncotic pressure are maintained and cerebral hydrostatic pressures are not markedly increased (e.g., due to true volume overload and elevated right heart pressures), volume replacement will not have any effect on cerebral edema and ICP.

In the critically ill neurological patient, the goal of fluid administration is to maintain near normal serum osmolality by repeated monitoring of this parameter. Any reduction in osmolality should be strictly avoided. When feasible, fluid management based on volumetric hemodynamic monitoring like CVP or pulmonary artery occlusion pressure (PAOP)-directed management and transpulmonary thermodilution (TPT) techniques [54] could provide real-time and more accurate guides to fluid management in the critically ill neurological patient.

Lactated Ringer's when administered in small volumes (not strictly isoosmotic, measured osmolality 252–255 mOsm/kg) are not likely to be detrimental, and can be used safely. However, when the clinical situation mandates large volume replacements (blood loss or other source of volume loss), a change to a more isotonic balanced fluid is advisable. With large volume loss, a combination of isotonic crystalloids and colloids may be the most prudent choice. The combined use of these fluids can avoid reductions both in serum osmolality and COP. Even when administered in a balanced substrate, hetastarch

should be used with caution due to coagulation factor VIII depletion when administered at volumes >1000 mL [52]. The newer formulation, pentastarch with minimal effects on coagulation, presents as a better alternative [51]. Future investigations to determine the end point of fluid resuscitation should focus on the parameters of cerebral perfusion and oxygenation where direct effects of systemic fluid management on the brain are examined, such as $PBrO_2$ [50].

The Clinical Equipoise

The SPLIT trial, the first large randomized controlled trial prospectively comparing the effects of a balanced solution (Plasma-Lyte 148) with those of 0.9% NaCl in critically ill patients, showed, unexpectedly, precise equipoise between the two treatments, although presenting important limitations [14]. However, the small number of neurological patients included in this study makes it difficult to draw appropriate conclusions in the neurocritically ill.

Conclusion

Indubitably, intravenous balanced fluids are gaining a foothold in clinical neurosurgery owing to their multitude of physiologically relevant advantages. However, the actual translation of such physiological effects into clinically relevant outcomes is still unclear, especially in the high-risk neurosurgical population (sepsis, trauma, AKI) exposed to larger amounts of such fluids.

Moreover, the "ideal" intravenous balanced solution incorporating all the defined characteristics (electrolyte content equal to plasma with maintenance of acid-base equilibrium) is yet to be made available.

Awaiting multicentric high-quality research on the potential mechanisms underlying their clinical effects and patient-centered clinical outcome in neurosurgery, such fluids continue to be considered as "drugs" and must be used with consideration to physiological rationale, clinical supporting evidence, and awareness of the adverse effects.

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Part III

Fluids: Monitoring Fluids

Invasive Versus Non-invasive Haemodynamic Monitoring

Summit D. Bloria, Ankur Luthra, Rajeev Chauhan, and Sameer Sethi

Abstract

Appropriate haemodynamic monitoring and management is necessary for neurological patients. Various modalities of haemodynamic monitoring, both invasive and non-invasive, are available. Each of these devices has their advantages and shortcomings. In this chapter, we give a brief overview of the many haemodynamic monitoring devices available for use in neurological patients.

Keywords

Haemodynamics · Goal-directed fluid therapy Stroke volume variation · Central venous pressure · PICCO · LiDCO

Introduction

Patients with neurological insults suffer from significant alterations in haemodynamic parameters. Many patients with acute ischaemic stroke, aneurysmal subarachnoid haemorrhage, traumatic brain injury, etc. have increased intracranial pressure and present with sudden hypertension and bradycardia. Fluid and electrolyte imbalance is also very common in neurological patients as a direct result of neurological injury, due to altered consciousness, effect of diuretics and various other causes. Appropriate haemodynamic monitoring and maintaining haemodynamic parameters within recommended levels is essential for better clinical outcome in neurosurgical patients, both during intraoperative period and during ICU stay [1, 2].

There are various modalities of haemodynamic monitoring and are usually classified as invasive or non-invasive. The most common invasive and non-invasive haemodynamic monitors are enumerated in Table 1. In this chapter, we begin by describing the various haemodynamic monitors and follow it by a discussion on the merits and demerits of various haemodynamic monitors.

Invasive Haemodynamic Monitors

1. Arterial cannulation—Invasive arterial blood pressure monitoring allows beat to beat of blood pressure monitoring and regulation in addition to providing access for arterial blood gas analysis. Common arteries that are cannulated include radial, dorsalis pedis, brachial, femoral, etc. A modified Allen's test is

S. D. Bloria
Division of Neuroanaesthesiology, Department of Anaesthesia and Intensive Care, PGIMER, Chandigarh, India

A. Luthra (✉) · R. Chauhan · S. Sethi
Department of Anaesthesia and Intensive Care, PGIMER, Chandigarh, India
e-mail: zazzydude979@gmail.com

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usually performed prior to cannulation of radial artery to rule out inadequate collateral circulation. Before cannulation of the artery, the pressure–tubing–transducer system should be nearby and already flushed with saline. The pressure transducer measures blood pressure on the basis of Wheatstone bridge principle. The transducer is usually calibrated to atmospheric pressure level prior to initiation of pressure monitoring. Many devices analyse the arterial waveform to estimate cardiac output and other haemodynamic parameters. Complications of arterial cannulation include arterial thrombosis, hematoma, nerve damage, necrosis of digits, etc.

Table 1 Various invasive and non-invasive haemodynamic monitors

Invasive haemodynamic monitors	Non-invasive haemodynamic monitors
Arterial cannulation	CNAP™ finger cuff
Arterial waveform-based devices—PICCO, LiDCO, FloTrac	
Central venous monitoring	Electrical bioreactance cardiography
Pulmonary artery catheter (PAC)	Thoracic electrical bioimpedance (TEB)
Transesophageal echocardiography (TEE)	The ccNexfin system
The NICO system	
PRAM (pressure recording analytical method)	

The fast flush test is used to calculate the damping coefficient and the natural frequency of the invasive blood pressure monitoring system as depicted in Fig. 1. A square wave is generated when the fast flush valve is squeezed. After the fast flush has finished, the whole transducer system returns to baseline. It does this as a harmonic oscillator, 'bouncing' a few times before actually coming to rest

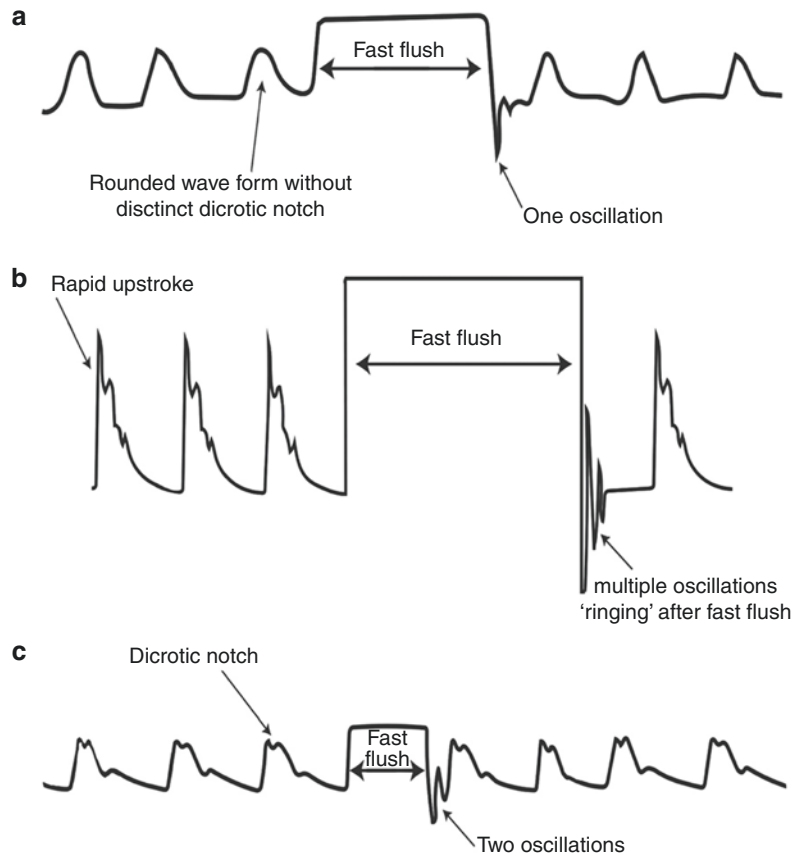

Fig. 1 Arterial waveform and the fast flush testing. (**a**) The square loop test. An overdamped waveform will have only one oscillation after the square wave, and the dicrotic notch will disappear. (**b**) Underdamped lines will have multiple oscillations after the square wave, and multiple notches can be seen in the waveform. (**c**) A properly damped arterial line will have two to three oscillations immediately after the square wave disappears. The tracing will then return to a normal arterial waveform. A distinct dicrotic notch should be present

(Fig. 1c). This 'bounce' effect is used to find out the resonance characteristics of the system. At least, there should be one 'bounce' oscillation. If the system fails to oscillate, there is too much damping (Fig. 1a). Also, there shouldn't be greater than two oscillations; a system which oscillates too much is underdamped (Fig. 1b).

2. Arterial waveform-based devices—Classified as those requiring calibration and those not requiring calibration. The former include PiCCO and LiDCO, while the latter includes FloTrac.

PiCCO (Fig. 2)

It stands for pulse index continuous cardiac output. The calculation of cardiac output using PiCCO requires insertion of central venous line and an arterial line. The arterial catheter of PiCCO has a thermistor 5 mm from its tip; in addition the device consists of an injection device which is connected to the distal tip of a central venous catheter. The artery cannulated most commonly is femoral artery, while radial, brachial and axillary arteries are also used infrequently. The measured and derived values are demonstrated on a monitor.

After connecting the monitor to venous and arterial lines, calibration is started. Calibration consists of three injections of 15–30 ml of cold normal saline in an interval of 5 min; the procedure needs to be repeated every 8 h. Studies have demonstrated that PiCCO has accuracy comparable to that of PAC [3]. An advantage of PiCCO over LiDCO is that PiCCO also provides information about intrathoracic blood volume index, an important measure of fluid responsiveness. Also, complications associated with the use of PiCCO have been rare [4].

LiDCO

The device was developed by LiDCO plus (LiDCO, Cambridge, UK). An arterial and a central/peripheral access is necessary for the operation of device. It uses lithium dilution to calibrate a pulse pressure analysis algorithm. The LiDCO system consists of a disposable lithium sensitive sensor which is connected to an existing arterial cannula. A connector sends a signal from the sensor to a monitor. A

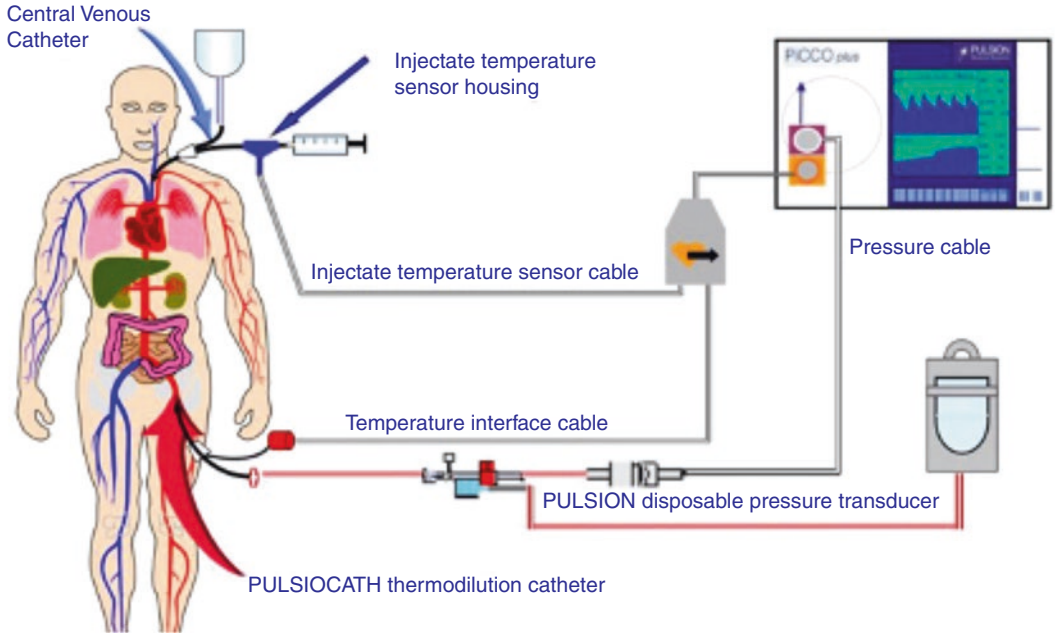

Fig. 2 The PiCCO system

small dose of lithium chloride (20–40 micromol/kg) is injected as an intravenous bolus, and cardiac output is derived from the dilution curve. In addition to the changes in cardiac output, the device also tells about pulse pressure variation (PPV) and stroke volume variation (SVV). LiDCO requires calibration every 8 h.

Patients with aortic valve pathologies, patients on lithium therapy and patients on intra-aortic balloon pump may not demonstrate accurate values when using LiDCO. There is evidence of successful application of LiDCO in paediatric patients [5].

FloTrac (Fig. 3)

FloTrac was introduced by Edwards Lifesciences in 2005. It does not require calibration. The FloTrac sensor is connected to an arterial line, and the FloTrac monitor displays cardiac output, stroke volume, stroke volume variation and systemic vascular resistance. It is an easy-to-use device but the accuracy of measurement gets affected in patients with arrhythmias, in patients with aortic valve disease and in haemodynamically unstable patients. While some studies have demonstrated accuracy of FloTrac comparable to that of PAC, others have highlighted its shortcomings in selected patient populations [6–8].

VolumeView

The VolumeView system was introduced by Edwards Lifesciences in 2010. The system consists of a thermistor-tipped arterial cannula, a monitor interface and a PreSep oximetry central line catheter. The various parameters displayed on the monitor include cardiac output, stroke volume, stroke volume variation, systemic vascular resistance, global end-diastolic volume, intrathoracic blood volume, pulmonary vascular permeability index and extravascular lung volume. Nakwan et al compared VolumeView and echocardiography in estimating global ejection fraction in septic patients and found that VolumeView provided a reliable estimate of ejection fraction in septic shock patients [9].

3. Central venous monitoring—A central venous access in a neurological patient allows measurement of central venous pressure (CVP), fluid administration and administration of high osmolarity drugs.

   Coagulopathy, infection at insertion site, right heart vegetations or tumours are contraindications to central line insertion. Subclavian and internal jugular veins are the most common sites of central venous cannulation. The line insertion can be landmark guided or ultrasound guided. Complications of central line insertion include pneumothorax, accidental arterial puncture, pleural effusion, arrhythmias, bloodstream infection, etc.
4. Pulmonary artery catheter (PAC) (Fig. 4)—It is a four-lumen catheter and has a thermodilution sensor. PAC is around 110 cm long and 4–8 Fr in calibre. PAC allows determination of central venous pressure (CVP), right atrial pressure, right ventricular pressure and pul-

Fig. 3 FloTrac monitor

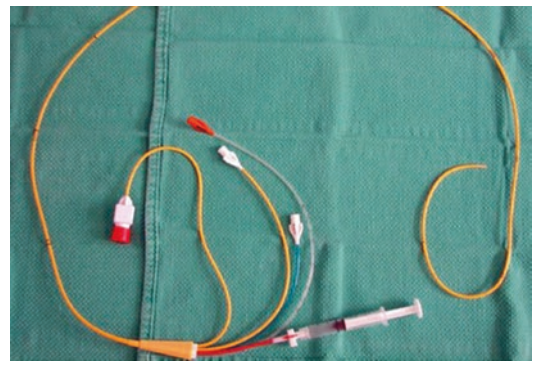

Fig. 4 Pulmonary artery catheter

monary artery pressure and allows calculation of cardiac output.

The four lumens are as follows:

(a) First, to inflate the catheter tip with air.
(b) Second, an accessory infusion port which ends 30 cm from the catheter tip.
(c) Third, the distal port which ends at the catheter tip and is used to measure pressures during catheter insertion.
(d) Fourth, the proximal port which ends 60 cm from the catheter tip. It measures right atrial pressures once the catheter tip is in the pulmonary artery.

Also, there is a thermistor which is used to measure cardiac output using thermodilution.

Coagulopathy, right heart endocarditis/tumours and left bundle branch block are contraindications to PAC insertion.

The method of PAC insertion consists of acquiring central venous access using Seldinger technique. The distal port is connected to a transducer that is zeroed to the patient's midaxillary line. The guide-wire is inserted after vein puncture and PAC sheath is threaded over the guidewire. The PAC is then inserted and advanced until a central venous waveform appears at a length of around 15 cm. The tip balloon is then inflated and the PAC is then advanced while observing the pressure waveform and values. Pulmonary artery is usually entered at a length of around 35–45 cm. A chest x-ray can be used to later demonstrate the correct positioning of the PAC.

Complications of PAC insertion include pneumothorax, arterial puncture, air embolism, arrhythmias, infection, etc.

Calculating Cardiac Output (CO) from PAC

Calculating CO from PAC utilizes the principle of thermodilution. 2.5–10 ml of cold fluid is injected into the right atrium and the change in temperature of blood at PAC tip is sensed by the thermistor. Plotting the temperature with time on x axis provides the thermodilution curve and area under the curve is equal to cardiac output.

Trans-oesophageal Echocardiography (TEE)

Trans-oesophageal echocardiography provides real-time activity of the heart. Cardiac output can be calculated TEE by measuring cross-sectional area of the left ventricular outflow tract and multiplying it with the velocity time integral (VTI). In addition, TEE can tell about valvular abnormalities and guide regarding volume status, ejection fraction and various other parameters. However, TEE requires administration of sedation/anaesthesia. Also there is a risk of complications associated with insertion of probe into the oesophagus. Also, manipulating the probe is difficult intraoperatively during neurosurgery as the access to the mouth is lost after the patient is draped and surgery begins. TEE has been used to detect intraoperative venous air embolism during sitting craniotomies, to detect patent foramen ovale and to guide ventriculo-atrial shunt insertion, but use of TEE as a haemodynamic monitoring device has not been investigated [10, 11]. During mechanical ventilation, TEE could not perform as good as PAC for CO determination [12].

The NICO System

The NICO system is based on the partial CO_2 rebreathing technique; i.e. it uses exhaled carbon dioxide as an indicator and applies Fick's principle. The cardiac output measurement is fulfilled by data interpretation that is collected by the proprietary sensors that measure airway pressure, flow and concentration of CO_2, and then combining these signals to calculate CO_2 elimination. The NICO system can be applied only in mechanically ventilated patients who are sedated and paralysed.

The NICO system showed good concordance with PAC when used in critically ill patients [13]. Carretero et al. compared calculation of cardiac

output using the NICO system with pulmonary artery catheter during cardiopulmonary resuscitation and found a high degree of agreement between the two techniques [14].

PRAM (Pressure Recording Analytical Method)

This system uses just an arterial line to provide information about CO, SVV, PPV and SVR. PRAM technology is based on the principle that, in any given vessel, volume changes occur mainly because of radial expansion in response to pressure variations [15].

PRAM is a non-calibrated pulse contour method. When compared with Doppler echocardiography for estimation of cardiac output in trauma patients, the two methods showed good agreement [16]. PRAM has also been found useful in estimating cardiac output in sepsis patients [17]. In paediatric patients aged 1 month–18 years, PRAM provided reliable estimates of cardiac output when compared with Doppler echocardiography [18]. However, in critically ill children, there was an unacceptably poor agreement between transpulmonary ultrasound dilution and PRAM [19].

Non-invasive Haemodynamic Monitors

There are multiple methods that have been devised for the measurement of blood pressure and cardiac output minimally invasively or non-invasively. The oldest method of haemodynamic monitoring is the non-invasive oscillometric method that utilizes an air-filled pressure cuff. But because of inaccuracy and variability of measurements, these devices are not dependable in acute conditions and don't provide any reliable information about the cardiac function. It consists of a cuff which is air-filled that can inflate on the subject and measure the blood pressure either manually by the operator or automatically by the device itself. When the blood pressure is measured manually, it can be achieved using the palpation auscultation technique. In the palpation technique, the operator palpates the radial artery when the measurement is being carried out in the arm and deflates the cuff. The pressure where the pulses are felt is the systolic pressure. The primary advantage of this method is being quick and does not require any sophisticated instrument, but the disadvantage is that it does not measure the diastolic blood pressure. When the auscultation technique is used, the cuff pressure is increased beyond the systolic blood pressure that has already been measured using the palpation technique, following which a stethoscope is placed on the concerned artery and the Korotkoff sounds are auscultated. The first sound corresponds to the systolic blood pressure, while the few last muffled sounds correspond to the diastolic blood pressure. This technique requires the operator to be well trained. The automated system using a applies the same technique, and inflates the cuff to an already set pressure and then decreases the pressure slowly. The oscillations and sounds are then detected by the machine which corresponds to systolic and diastolic blood pressures. Mean arterial pressure corresponds to the maximum oscillations. The algorithms that these machines use are proprietary and dependent on their corresponding manufacturers.

Finger Cuffs for Continuous BP Monitoring

Many companies have introduced finger cuffs which allow continuous BP monitoring and also provide information about other haemodynamic parameters like CO, SVR, SVV, SV, etc. These can be attached to middle phalanx of the finger for a period up to 8 h, after which the finger should be changed. These devices are based on volume clamp method. The cuffs provide similar pressures on either side of the arterial wall by clamping the artery to a fixed volume. There is some evidence of these devices providing feasible estimates of BP in ICU patients, although some studies have

shown these devices to be inferior to invasive BP monitoring as well [20, 21].

Special sized finger cuffs have been designed for paediatric patients and their accuracy checked with invasive blood pressure monitoring to find that these finger cuffs work well in paediatric patients as well [22]. When employed in preterm neonates, it was suggested that while finger cuffs were of limited value in estimating absolute blood pressure, the cuffs are useful in identification of beat-to-beat changes in systolic BP [23]. Another study found finger cuffs to be reliable for measurement of blood pressure in preterm infants [24].

These devices have been used intraoperatively also. When used in patients undergoing Caesarean section under subarachnoid block, the device was found to detect hypotensive episodes which the non-invasive blood pressure monitoring would have missed [25].

The ccNexfin System

Introduced by Edwards Lifesciences in 2007, it has a new version called the ClearSight system. The system consists of finger cuffs which wrap around the middle phalanx and measure blood pressure non-invasively using the volume clamp method. From the finger pressure waveform (received from the finger cuffs), the device reconstructs the brachial pressure waveform, and then cardiac output is estimated using the pulse contour method. The various haemodynamic parameters achieved using the ccNexfin system include blood pressure, stroke volume, cardiac output, stroke volume variation and systemic vascular resistance.

The ccNexfin system showed good correlation with pulmonary artery catheter in studies [26, 27].

Use of ClearSight system during heart valve interventions and cardiovascular surgery has been found to be useful, is simple and saves time [28, 29]. The use of ClearSight system for haemodynamic management during kidney transplantation has been reported [30].

Thoracic Electrical Bioimpedance (TEB)

TEB is a non-invasive alternative to monitoring of haemodynamic parameters including cardiac output, stroke volume and cardiac index. A low amplitude electrical signal is sent across the thorax. There are electrodes placed on the thorax which measure the impedance. Stroke volume is calculated on the basis of impedance change generated by the pulsatile flow and the time intervals between the changes. Surgical cautery, arrhythmias and fluid in thoracic cavity affect the accuracy of the device.

There is paucity of literature on accuracy of TEB in specific group of patients [31]. Elwan et al. found huge differences in cardiac output measured using Doppler and TEB in emergency care [32]. In normal adults, cardiac output measured using Doppler and TEB was found to be comparable [33]. A significant correlation between echocardiography and transthoracic electrical bioimpedance in the systemic haemodynamic assessment in patients with cirrhosis was observed [34]. Sabharwal et al. used TEB to determine haemodynamic changes after administration of mannitol in neurosurgical patients [35]. In aneurysmal subarachnoid haemorrhage patients undergoing surgery, non-invasive electrical velocimetry (EV) device based on the thoracic bioimpedance was compared with transpulmonary thermodilution to guide fluid therapy. The authors found that the cardiac index calculation using the two methods yielded different values in these patients [36].

Electrical Bioreactance Cardiography

Available with the name of NICOM system, the electrical bioreactance is a safe, non-invasive and continuous monitor. The basic principle is determination of change in frequency of electrical resistivity across the thorax. The system consists of four paired electrodes which are placed on the chest. One of the two paired electrodes injects an

AC current of 75 kHz, while the other electrode detects the electrical signal. On the basis of analysis of the current injected and detected, along with analysis of time delay between the two signals, the NICOM system determines phase shift, and stroke volume is determined from the phase shift signals. Clinical and preclinical data demonstrates the feasibility of using blood flow-related phase shifts of transthoracic electrical signals to perform non-invasive continuous CO monitoring. NICOM is said to get affected by electrical cautery signals and the accuracy gets affected at low flows [37]. In colorectal surgery patients, oesophageal Doppler-guided GDFT was found to be comparable to NICOM-guided GDFT [38]. NICOM system was found to have an acceptable accuracy with thermodilution in ICU patients in a multicentre study [39].

Goal-Directed Haemodynamic Management in Neurosurgery and the Neuro-ICU

Concept of Fluid Responsiveness

The estimation of intravascular volume status in neurological patients remains difficult. The traditional methods of volume estimation and fluid administration like central venous pressure and Holliday-Segar formula have been proven to be insensitive [40]. This gave way to the concept of 'fluid responsiveness'.

Fluid responsiveness is defined as an increase of stroke volume of 10–15% after the patient receives a 'fluid challenge' of 500 ml of crystalloid over 10–15 min. Fluid responsive patients have 'preload reserve' and will have an increase in stroke volume (and usually cardiac output) when fluid is administered. The presumption is that increased cardiac output will cause increased oxygen delivery (DO2) and increased tissue oxygenation.

Goal-Directed Haemodynamic Management (GDHM)

GDHM utilizes cardiac output (CO) monitoring techniques to guide clinicians for administering fluids, vasopressors and inotropes, both intraoperatively and in critical care settings. The aim of GDHM is to optimize tissue perfusion. The concept was initially suggested by Shoemaker et al. who reported a trend of decreased mortality following high-risk surgery when goal-directed haemodynamic management was used [41]. Various modalities have been described to guide GDFT including use of pulmonary artery catheter (PAC), trans-oesophageal echocardiography (TEE), arterial pulse waveform analysis, photoplethysmography, venous oxygen saturation and tissue oxygen saturation. Luo et al. showed that intraoperative GDHM strategy in high-risk patients undergoing brain surgery resulted in a shorter ICU length of stay and reduced costs, and also the postoperative morbidity was reduced [42].

The importance of optimization of intravascular volume in neurological patients cannot be overemphasized. Both hypovolaemia and hypervolaemia have been found to be associated with poor outcomes in neurological patients [43, 44]. However, determination of volume status in these patients remains difficult. Hence, using dynamic tests for determination of fluid responsiveness and administering fluids till patients are fluid responsive can help optimize volume status in these patients. Some indicators of fluid responsiveness include:

(a) A pulse pressure variation of more than 12%
(b) Inferior vena cava (IVC) diameter <2 cm and respiratory variation in IVC diameter of >50%
(c) A systolic pulse variation of more than 10%
(d) A systolic volume variation of more than 10%
(e) A left ventricle outflow tract—velocity time integral of >12%

Various authors have demonstrated the effectiveness of GDHT in neurosurgery. Wu et al. compared two fluid protocols based on different stroke volume variation (SVV) cut-offs for goal-directed fluid therapy (GDFT) during supratentorial brain tumour resection and found that during GDFT for supratentorial brain tumour resection, fluid boluses targeting a lower SVV are more beneficial than a restrictive protocol [45].

Hasanin et al. compared pulse pressure variation-guided fluid therapy during supratentorial brain tumour excision with standard intraoperative fluid therapy and demonstrated that GDFT therapy leads to increased intraoperative fluid administration and improved peripheral perfusion without increasing brain swelling [46].

Presently, the evidence demonstrating improved outcomes in patients undergoing non-cardiac surgery who are administered GDFT is thin [47]. Similarly, improved outcome in neurosurgical patients due to GDFT is yet to be proven. Further studies will be necessary to determine if the use of GDFT actually improves the outcome in these patients.

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Goal-Directed Fluid Therapy

Matthew T. V. Chan and Chee Sam Chan

Abstract

Goal-directed fluid therapy is the administration of fluid, vasopressors, and inotropes to optimize hemodynamic parameters for better tissue perfusion. Current practice uses cardiac output, systolic, or pulse pressure variations as the targets to follow. However, none of these measures indicate cerebral physiology. Electroencephalogram, evoked potentials, and cerebral oximetry may be used to guide fluid therapy. Nevertheless, the evidence for these monitors to improve patient outcomes remains inconclusive. There are numerous barriers in implementing goal-directed fluid therapy during anesthesia and caring for critically ill patients. Further trials should define the goals to target, and feasibility in implementing protocol. More trials are required to define the benefit and risk ratio in adopting the goal-directed fluid therapy in specific patient populations.

Keywords

Goal-directed fluid therapy · Cardiac output monitoring · Pulse pressure variation · Cerebral oximetry · Electroencephalogram

Goal-directed fluid therapy is a concept where administration of fluid, vasopressors, and inotropes is targeted to achieve an optimal hemodynamic parameter for better tissue perfusion [1]. In high-risk surgical patients, Shoemaker and colleagues reported a lower rate of postoperative complications, fewer deaths, earlier discharge from the hospital and the intensive care unit, and shorter duration of ventilation when perioperative cardiac index and oxygen delivery were increased to >4.5 L/min/m^2 and >600 ml/min/m^2, respectively [2]. The extraordinary results had drawn a lot of attention, and the approach has since extrapolated to various scenarios. In this respect, goal-directed fluid therapies have been studied extensively for the treatment of critically ill patients and during major surgery. In contrast, few studies have evaluated goal-directed fluid therapy in neurosurgical patients. In this chapter, we reviewed the clinical utility of goal-directed fluid therapy in patients having neurosurgery and receiving neurocritical care.

M. T. V. Chan (✉)
Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong,
Hong Kong Special Administrative Region, China

Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital,
Hong Kong Special Administrative Region, China
e-mail: mtvchan@cukh.edu.hk

C. S. Chan
Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong,
Hong Kong Special Administrative Region, China

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Which Goal to Direct Therapy?

An integral part of goal-directed fluid therapy is to establish a "goal" to guide interventions. Ideally, the goal has to be clearly defined and prognostically important and can be measured accurately and noninvasively. Figure 1 shows the common parameters that have been used to gauge tissue perfusion during surgery.

Traditional Goals

Arterial pressure is the primary determinant for driving tissue perfusion and is a standard monitor in contemporary anesthesia [3]. The major drawback of using arterial pressure is that there is no consensus on the minimum arterial pressure required to maintain organ function. In this respect, over 130 definitions on hypotension had been reported in the

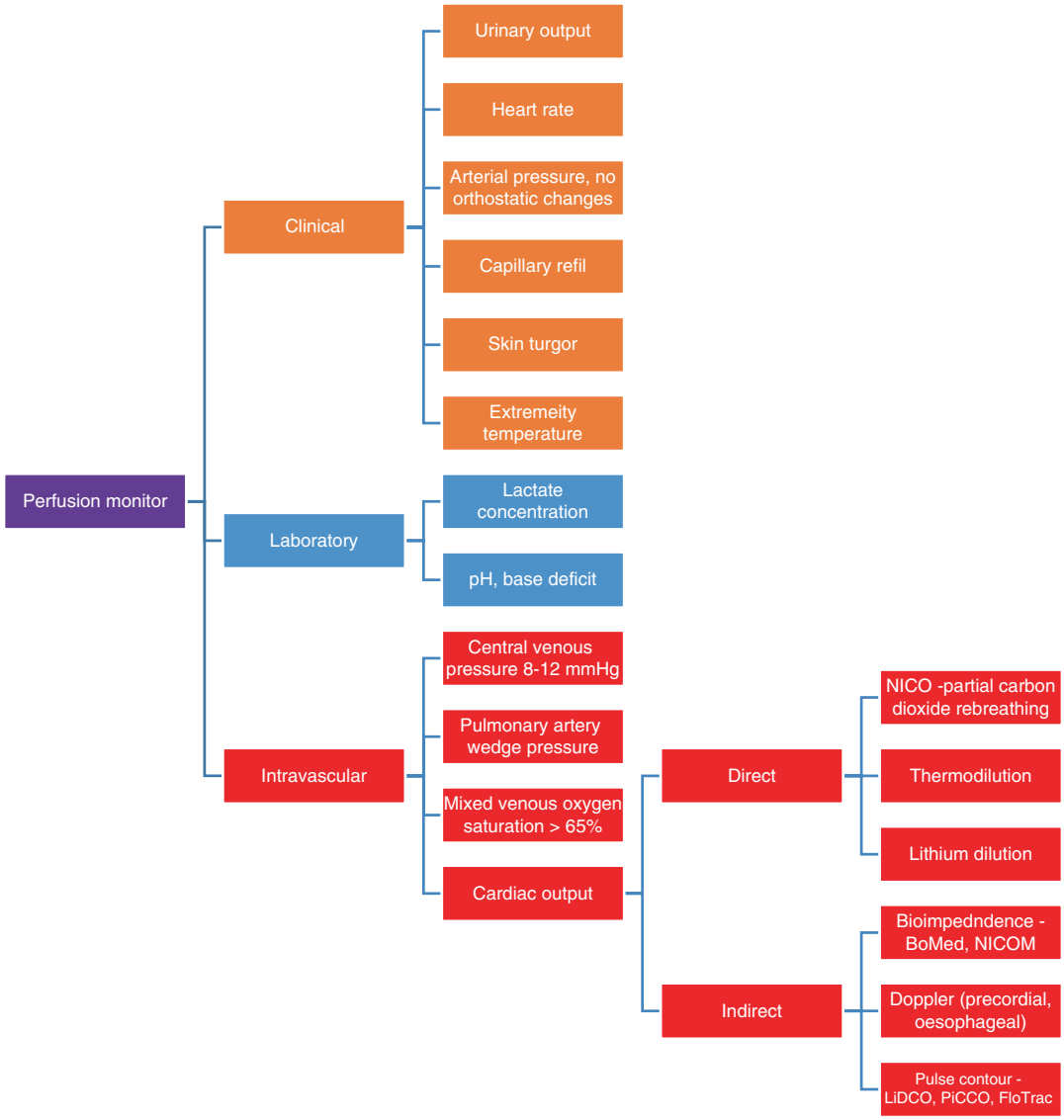

Fig. 1 Monitors for tissue perfusion

literature [4]. Nevertheless, multiple cohort studies, systematic reviews, and meta-analyses have shown an increased risk of postoperative adverse events with mean arterial pressure <65 mmHg or systolic arterial pressure <90 mmHg for >10 min [5–8]. In a randomized controlled trial (RCT), individualized blood pressure management with systolic arterial pressure maintained within 10% of baseline (n = 147) reduced the risk of postoperative organ dysfunction by 27% (95% confidence intervals, CI: 6–44%) compared with standard care (treating hypotension only when systolic arterial pressure was <80 mmHg, n = 145) [9]. Anesthesiologists may also monitor end-organ dysfunction using urine output, acid-base balance, and plasma lactate concentration. These measures however lack temporal resolution, require long turnover time, and tend to worsen only after significant hypoperfusion.

Cardiac Filling Pressures

Alternatively, anesthesiologists were accustomed in measuring cardiac filling pressures, such as central venous pressure and pulmonary artery occlusion pressure, to guide fluid therapy. As a measure of cardiac preload, it is assumed that an optimized filling pressure would be important to improve cardiac output and tissue perfusion. However, the absolute filling pressure is dependent on valvular pathology and ventricular compliance and is therefore a poor predictor for volume status or fluid responsiveness [10, 11].

Cardiac Output

Cardiac output is a surrogate marker of tissue oxygen delivery. Conventional measurement uses the indicator (e.g., cold saline, lithium, or indocyanine green) dilution technique, producing intermittent values, and requires insertion of invasive pulmonary artery catheter [12]. Recent technology development has allowed minimally invasive and beat-to-beat measurements of cardiac output [13, 14]. Currently, four methods are commercially available:

1. Impedance cardiography

Transthoracic electrical bioimpedance (TEB) measures the resistance to a high frequency and low voltage current passing through the thorax. The rhythmic changes of impedance correspond to the variations in aortic blood volume during successive cardiac cycles. Therefore, variations in cardiac output will be reflected by the change in TEB [15]. Clearly, TEB signals are affected by electrical interference and may undermine the utility of the device.

2. Doppler ultrasound

The Doppler technique measures blood flow velocity through the aortic valve and the descending thoracic aorta using suprasternal and esophageal probe, respectively [16]. Cardiac output is therefore the product of flow velocity, reference cross-sectional area, and heart rate.

3. Arterial pressure waveform and pulse contour analysis

It has been long recognized that pulse pressure is directly proportional to stroke volume [17, 18]. Currently, three commercially available monitors have been developed to determine cardiac output based on arterial pulse contour. The LiDCO monitor (LiDCO, London, UK) applies the PulseCO™ algorithm to account for aortic impedance, arterial compliance, and peripheral vascular resistance in order to estimate beat-to-beat cardiac output [19, 20]. LiDCO requires regular calibration using subtherapeutic doses of lithium for dye dilution-derived cardiac output [20]. Similarly, PiCCO monitor (PULSION Medical Systems AG, Munich, Germany) uses a proprietary algorithm to analyze the systolic component of the arterial pulse [21]. Intermittent (transpulmonary) thermodilution-derived cardiac output is required for calibration. The Vigileo-FloTrac system (Edwards Lifesciences, Irvine, CA) measures cardiac output with standard arterial catheter attached special proprietary transducer. In contrast to the other monitors, FloTrac does not require additional calibration [22].

In addition, the arterial pressure waveform monitoring allows anesthesiologists to access fluid responsiveness. In this respect, variations in arterial pressure (5–10 mmHg) during respiration are normal phenomena due to the transmission of intrathoracic pressure. In spontaneously breathing patients, arterial pressure decreases with inspiration and increases with expiration. The reverse occurs in mechanical positive pressure ventilation, where pulmonary blood volume is shifted to the left ventricle during inspiration and therefore increases arterial pressure with an increase in preload. The increase in intrathoracic pressure also decreases right ventricular filling, and will decrease arterial pressure subsequently. In patients with hypovolemia, variation in arterial pressure is exaggerated, and therefore derived indices from the arterial waveform (e.g., stroke volume, systolic pressure, and pulse pressure variation) could be used to guide fluid administration (Fig. 2).

4. Partial rebreathing method

In this method, brief and step changes in carbon dioxide elimination is compared to the

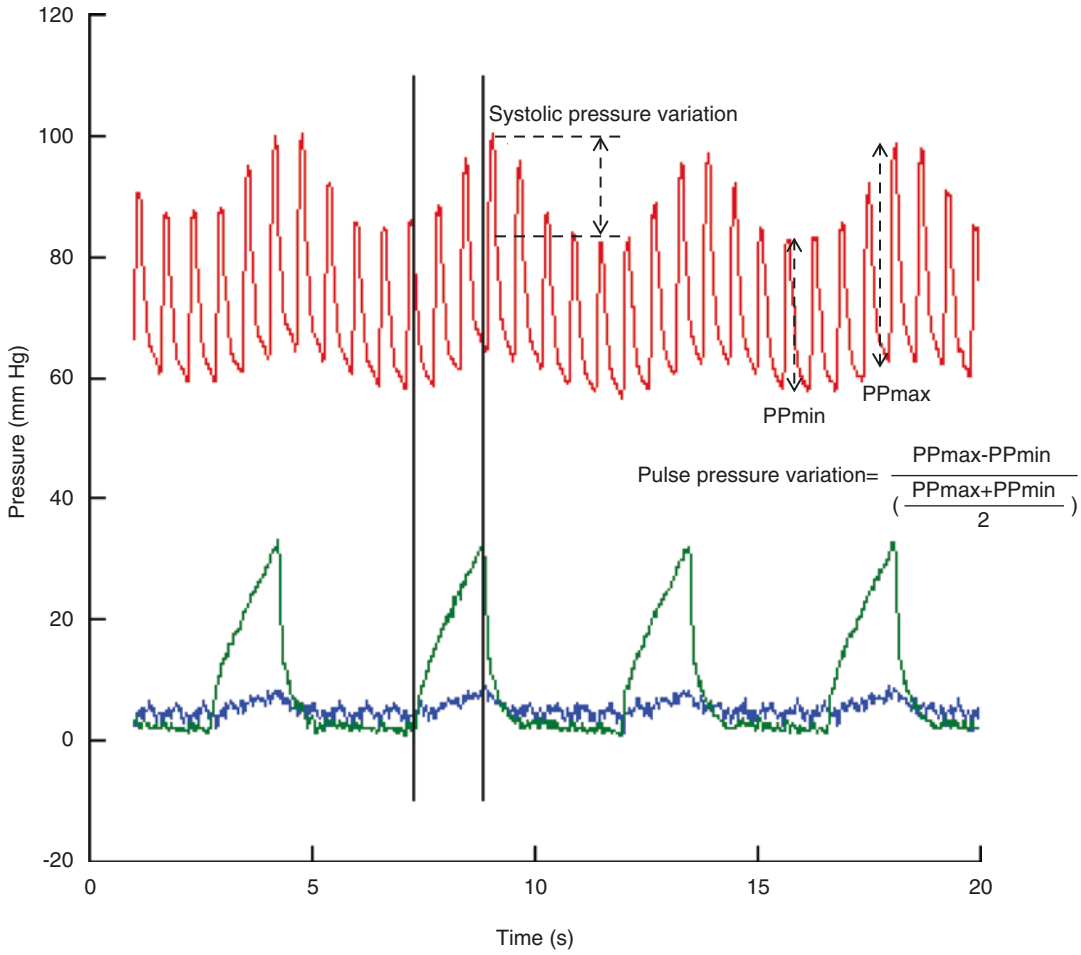

Fig. 2 Changes of arterial pressure with mechanical ventilation. Systolic pressure variation is the difference in systolic pressures at end-inspiration and end-expiration. Pulse pressure variation is the ratio between the difference and the mean of maximum and minimum pulse pressure. Red tracing, arterial pressure; blue tracing, central venous pressure; green tracing, airway pressure. Arterial, venous and airway pressure tracings courtesy of Dr. Robert Linton and Dr. Nick Linton (http://www.foxlinton.org/cardiac_output/PCOpages/spv2.html)

changes in end-tidal carbon dioxide tension [23]. The differential Fick method measures pulmonary blood flow and would only indicate cardiac output if the shunt fraction remains constant during the measurement period. Potentially, the technique could be integrated into anesthetic ventilator providing automated breath-to-breath cardiac output readings [24].

Measures of Cerebral Physiology

It should be noted that all the aforementioned technology measure systematic perfusion, and do not indicate cerebral physiology. Nevertheless, several modalities have been developed to measure cerebral hemodynamics, oxygenation, and electrophysiology (Table 1) [25], majority are designed for monitoring head-injured patients.

1. Intracranial pressure

Intracranial pressure (ICP) can be measured by inserting a catheter into the ventricles, at the subdural or epidural spaces. In addition, a fiber-optic sensor could be inserted to measure the parenchymal ICP [26]. There are risks associated with ICP monitoring. The reported rate for bleeding and infection ranged from 0.5–2% to 1–5%, respectively [27]. Nevertheless, ICP monitoring has been commonly used in the management of severe head injury [28, 29]. It remains difficult to decide on the ICP threshold that will require treatment. In the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) trial, strategies aiming to maintain ICP <20 mmHg in severe traumatic brain-injured patients did not improve 6-month mortality, functional, and cognitive performance [30].

Table 1 Cerebral monitors

Modality	Uses	Drawback
Intracranial pressure	• Measure ICP with catheter (or microsensor) insertion into the ventricle, parenchymal and epidural or subdural pressure measurement • Cerebrospinal fluid drainage from ventricular catheter	• Tract hemorrhage • Infection
Cerebral perfusion		
Transcranial Doppler	• Measures cerebral blood flow velocity	• Operator dependent • Availability of acoustic window • Fixation of probes for continuous monitoring
Cerebral oxygenation		
Jugular venous oximetry	• Measures global cerebral oxygenation	• Invasive catheter insertion • Contamination with extracranial circulation • Carotid puncture • Jugular vein thrombosis
Brain tissue oxygen monitoring	• Measures regional cerebral oxygenation using electrochemical-based probe or fluorescence-based probe	• Tract hemorrhage • Infection
Near-infrared spectroscopy	• Estimates cerebral tissue oxygen saturation by measuring the relative concentration of oxyhemoglobin and deoxyhemoglobin in a small region of the brain	• Contamination with extracranial circulation
Cerebral biochemistry		
Cerebral microdialysis	• Measures regional tissue biochemistry (lactate, pyruvate, glucose	• Tract hemorrhage • Infection
Cerebral electrophysiology	• Measures scalp electroencephalogram, somatosensory evoked potential	• Operator dependent for acquisition and interpretation • Delayed response

2. Cerebral blood flow

Measurement of global cerebral blood flow (CBF) requires imaging technique (e.g., xenon CT). However, regional CBF could be determined by using bedside transcranial Doppler. This is a measure of flow velocity, and the measurement is operator dependent, requiring appropriate acoustic bone window and specific mounting devices for continuous monitoring. Nonetheless, cerebral blood flow velocity has been used to determine cerebrovascular reactivity of the major cerebral vessels, for adjusting lung ventilation and arterial pressure targets during the management of head-injured patients [31]. In addition, transcranial Doppler can be used to detect vasospasm and hyperemia (Table 1). In carotid endarterectomy, the Doppler signal can be used to detect microemboli during arterial clamp release [32, 33]. However, it is unclear what might be the optimal CBF flow velocity to target.

3. Cerebral oxygenation

Global cerebral oxygenation could be determined by sampling of the venous blood drained to the dominant (90% right sided) jugular bulb [34]. A decrease in jugular venous oxygen saturation < 50% is thought to indicate brain ischemia. However, this measurement lacks spatial resolution. Several companies have since produced non-invasive cerebral oximeter that measures regional cerebral oxygenation using electromagnetic radiation (e.g., near-infrared) [35]. It should be noted that cerebral oxygenation is a relative measurement. Furthermore, the commercially available cerebral oximeters use different algorithms and the readings cannot be directly compared. Others have inserted a parenchymal probe with a Clark electrode to measure tissue oxygen tension. Tissue oxygen tension <20 mmHg is generally considered as critical [36].

4. Cerebral biochemistry

Cerebral hypoxia and ischemia lead to anaerobic metabolism, cellular damage, and release of excitatory amino acids. This will lead to a depletion of glucose store and an increase in lactate, lactate-to-pyruvate ratio, glutamate, and glycerol concentrations. By inserting a microdialysis catheter into the brain, it is possible to measure the concentrations of these metabolites and to gauge the extent of cerebral insult within a small brain region [37]. There are, however, no consensus on the thresholds to intervene. Nevertheless, cerebral microdialysis helps clinicians to understand the pathophysiology associated with brain injury and has been used as a surrogate marker for evaluation of new drugs for neuroprotection [38, 39].

Goal-Directed Algorithms

After establishing the goal of interest, the next step is to design an algorithm so that appropriate treatments can be implemented to achieve these goals. Hemodynamic goals (e.g., arterial pressure, cardiac output, pulse pressure variation) are commonly managed with fluid challenges including a combination of colloid or crystalloid. In a systematic review and meta-analysis of 24 RCTs on goal-directed fluid therapy in patients having major surgery (n = 3861), intraoperative use of colloid was significantly higher in the goal-directed group compared with controls, mean difference (95% CI): 467 (331–603) ml [40]. In addition, the administration of vasopressors or inotropes is getting popular to achieve these goals (Fig. 3).

In the management of neurocritical care patients, other measures, such as supplemental oxygen, hyperventilation, hypothermia, pentobarbital coma, osmotic therapy, and anticonvulsant, are used to achieve the goals (Fig. 4) [41].

Outcomes of Goal-Directed Therapy

Targeting Hemodynamic Variables

Using the hemodynamic targets, >100 studies have evaluated the effectiveness of goal-directed fluid therapy to improve outcomes after surgery [42]. There were also >20 systematic reviews and

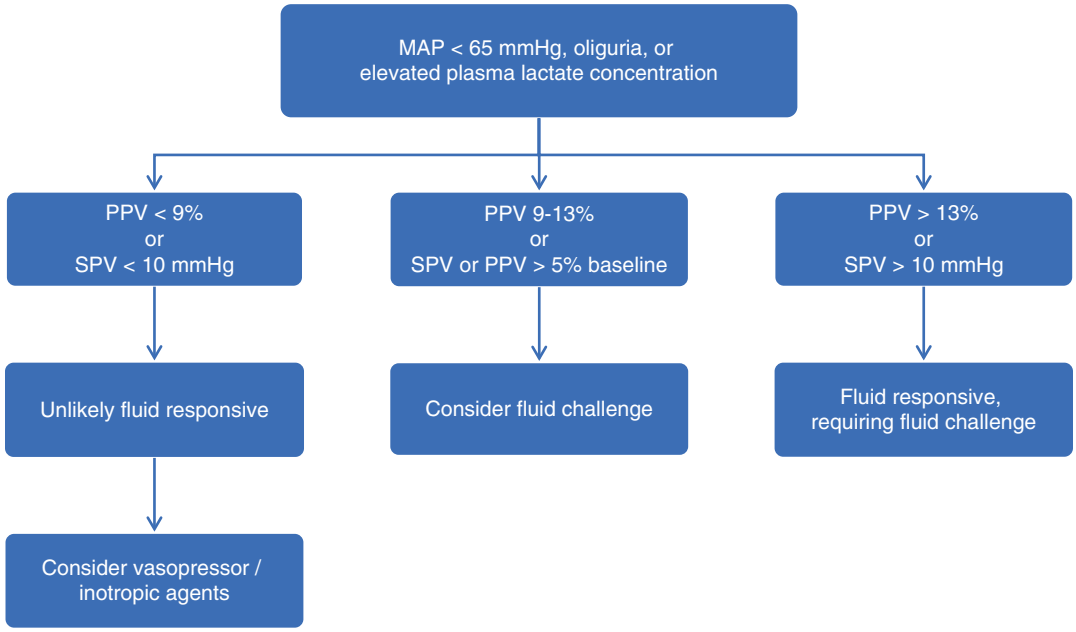

Fig. 3 Typical algorithm of goal-directed therapy using systolic pressure variation (SPV) and pulse pressure variation (PPV) in patients receiving general anesthesia with mechanical ventilation

meta-analyses summarizing these results. Using different combinations of studies on various outcomes, these analyses showed that goal-directed fluid therapy reduced rates of postoperative ileus [43–46], sepsis or infection [47–49], postoperative cardiovascular complications [50, 51], renal failure [48], or any complications [46, 52, 53]. Goal-directed fluid therapy also reduced hospital stay and duration of intensive care unit admission [45, 54–57], and there was a decrease in hospital or 30-day mortality, compared with controls in noncardiac surgery [58–61]. In cardiac surgery, overall complication rate and hospital stay were reduced with goal-directed fluid therapy [62]. Other meta-analyses, however, demonstrated no difference between groups [48, 53, 63–70]. Only few trials had studied goal-directed fluid therapy in neurosurgery [71–74]. Three trials had studied craniotomy [71–73] and one on spine surgery [74]. Only two trials reported postoperative outcomes [71, 72]. With limited sample size (total 208 patients), goal-directed fluid therapy reduced a composite of complications (sepsis, stroke, renal impairment, and all-cause mortality), 17% vs 35%, odds ratio (95% CI): 0.38 (0.20–0.73), $p = 0.004$, $I^2 = 0.0\%$.

Nevertheless, in an attempt to pool all 110 trials, Kaufmann and co-workers report large amount of heterogeneity, and it was not possible to perform meta-analysis. Furthermore, the results were sensitive to the studies included, sample size of individual trial [median (interquartile range) size = 40 [30–64] patients per group], monitors or targets chosen, and analytical methods used. Clearly, a large RCT is required to resolve the controversy whether target-guided therapy will improve postoperative outcomes [75, 76]. Two trials are currently ongoing. The FLuid Optimisation in Emergency LAparotomy (FLO-ELA) trial will randomize 7646 patients, ≥50 years to have anesthesia guided by stroke volume variation or control (ISRCTN14729158). Similarly, the OPtimisation of Peri-operaTive Cardiovascular Management to Improve Surgical outcomE II (OPTIMISE II) trial recruits 2502 patients having elective gastrointestinal surgery [77]. OPTIMISE II trial compares 30-day infection in patients receiving fluid and low-dose ino-

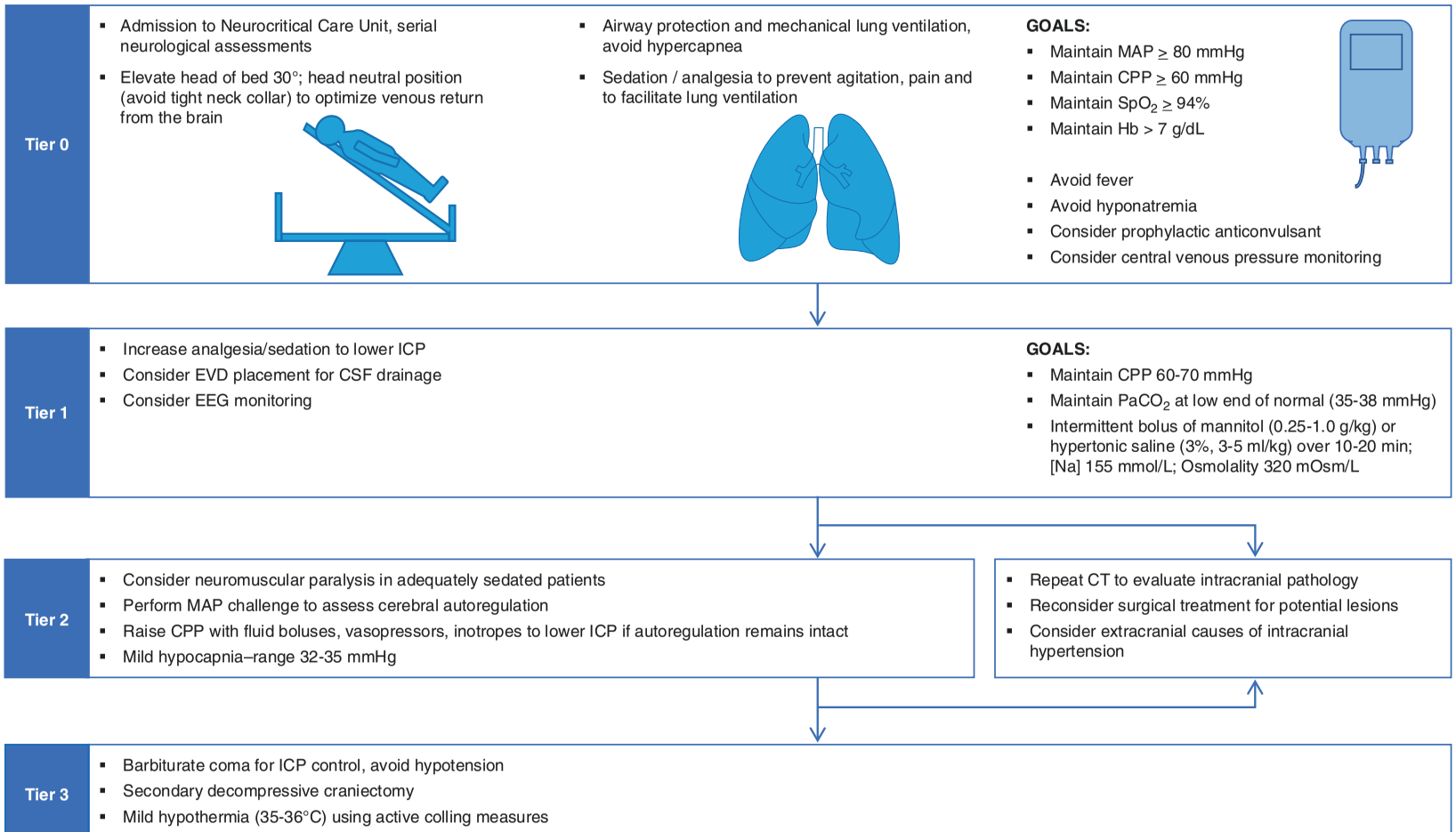

Fig. 4 Treatment algorithm (adopted from the Seattle International Severe Traumatic Brain Injury Consensus Conference) for patients with severe brain injury guided by intracranial pressure monitoring [41]. Patients who did not respond will require higher tier of treatments. MAP mean arterial pressure, CPP cerebral perfusion pressure, SpO_2 arterial oxygen saturation, Hb hemoglobin, $PaCO_2$ arterial partial pressure of carbon dioxide, ICP intracranial pressure, EVD external ventricular drain, EEG electroencephalogram, [Na] plasma sodium concentration, CT computed tomography

tropes (dobutamine or dopexamine) to achieve the targeted stroke volume variation or usual care. The results will inform the role of hemodynamic-guided target therapy on postoperative outcomes.

Targeting Cerebral Variables

Electroencephalogram (EEG) is the commonest cerebral monitor during surgery. EEG-guided anesthesia is thought to be useful in avoiding excessive anesthetic administration and may improve postoperative outcomes. Several trials have evaluated the effect of EEG monitoring in reducing postoperative deaths. The Perioperative Quality Initiative (POQI)-6 conference gathered a number of international, multidisciplinary experts to review the literature on the clinical utility of EEG [78]. In nine trials (ten publications [79–89], n = 8512) that examined postoperative mortality, EEG-guided anesthesia did not reduce all-cause death rate, 14.1% vs 15.1%, relative risk (95%CI): 0.95 (0.80–1.12), P = 0.528, I^2 = 38.4%. Since this systematic review, another large RCT was published. The Balanced Anesthesia trial randomized 6644 patients to receive deep or light anesthesia based on bispectral index (BIS) EEG monitoring. The death rate at 1 year after surgery in the deep anesthesia group (7.2%) was not different from the light anesthesia group (6.4%), p = 0.223. Figure 5 shows the updated meta-analysis. In 15,156 patients, the pooled relative risk (95%CI) was 0.94 (0.82–1.07), p = 0.339, I^2 = 32.79%.

Alternatively, anesthesiologists have used cerebral oximetry to guide anesthetic administration. In a systematic review and meta-analysis of 15 trials (n = 1822), there was no convincing evidence that monitoring improved outcomes, primarily related to the lack of events [35, 90]. Nevertheless, cerebral oximetry monitoring might improve cognitive performance at 1 week after surgery and reduce intensive care unit stay by 5.5–6.9 h (n = 379) [90].

The effect of goal-directed fluid therapy for the management of patients requiring neurocritical care remains less well defined [25]. Majority of

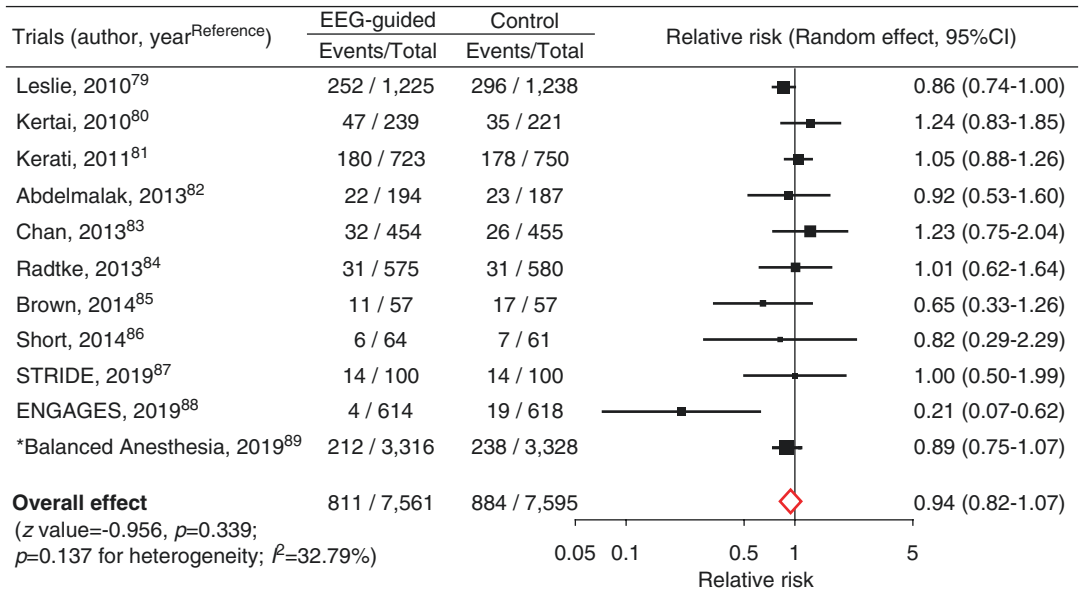

Fig. 5 Forest plots of trials comparing the risk for long-term mortality after surgery in patients receiving EEG-guided or routine care anesthesia. *Patients in the control group received deeper anesthesia; CI, confidence interval; EEG, electroencephalogram; ENGAGES, Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes; STRIDE, A Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients

the current guidelines recommend multimodality monitoring including ICP, cerebral autoregulation, oximetry, and intracerebral microdialysis [28, 29, 91, 92]. Nevertheless, the quality of evidence underlying these recommendations was low. Majority studies reported association and did not demonstrate causal relationship between goal-directed therapy and outcomes in neurocritical care patients. In particular, it is unclear what would be the minimum monitoring required and the targets that should be adopted (Table 1). Further outcome trials would be required before goal-directed fluid therapy could be widely adopted.

Conclusions

There are numerous barriers in implementing goal-directed fluid therapy during anesthesia and caring for critically ill patients. Further trials should define the goals to target, and feasibility in implementing protocol. Large RCTs are required to define the benefit and risk ratio in adopting the goal-directed fluid therapy in specific patient populations.

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Part IV

Fluids: Special Considerations

Perioperative Fluid Management for the Neurocritically Ill Patient

Maeve Muldowney and Abhijit Vijay Lele

Abstract

Fluid management strategies in patients requiring neurological/neurosurgical critical care may differ depending upon clinical scenarios. This chapter discusses the fluid considerations in treating neurologically ill patients as they transition from the prehospital setting to the operating room and the intensive care unit. This is described in the context of common neurological emergencies such as arteriovenous malformations, seizures, and brain tumors.

Keywords

Neurocritically ill · Traumatic brain injury · Prehospital · Perioperative fluid · Fluid resuscitation · Balanced crystalloid

M. Muldowney
Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA, USA

A. V. Lele (✉)
Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA, USA

Department of Neurological Surgery, Harborview Medical Center, Seattle, WA, USA

Harborview Injury Prevention and Research Center, Harborview Medical Center, Seattle, WA, USA

Neurocritical Care Service, Neuroscience ICU, University of Washington, Seattle, WA, USA
e-mail: abhijit2@uw.edu

Introduction

Management decisions made during the prehospital and perioperative resuscitation of patients with acute neurological injuries can have a profound and lasting impact on subsequent functional outcomes. A cornerstone in these patients' care is maintaining sufficient cerebral perfusion pressure, which depends on an appropriate circulating intravascular volume. However, fluid administration is not without risks; iatrogenic cerebral edema and sodium and glucose disorders can result. This chapter discusses the fluid considerations in treating neurologically ill patients as they transition from the prehospital setting to the operating room and the intensive care unit. This is described in the context of common neurological emergencies such as arteriovenous malformations, seizures, and brain tumors.

Arteriovenous Malformations (AVMs)

AVMs can have varied presentations, including spontaneous subarachnoid or intracerebral hemorrhage, seizures, focal neurological deficits, or even an incidental finding on neuroimaging performed for other indications. Like aneurysmal subarachnoid hemorrhage, patients with AVM may present emergently or electively for embolization or clipping of an AVM.

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The pathophysiology of AVMs is unique. The nidus is an abnormal vascular mass that connects an arteriolar and venous network without a normal intervening capillary bed. Blood may be preferentially shunted through this abnormal circuit to the disadvantage of neighboring capillary networks. These normal areas of brain parenchyma can exhibit relative hypoperfusion. However, there is evidence that cerebral autoregulation of these areas is shifted to the left, and blood flow can be regulated at lower ranges of pressure. The normal vascular beds in parallel with the AVM tend to be maximally dilated to preserve flow through their system.

Perioperative considerations for these patients are like that for any craniotomy. The maintenance of cerebral perfusion pressure (CPP) intraoperatively is vital to maintain flow through the normal capillary network. This should be achieved by ensuring patients are euvolemic. Once the euvolemic status is confirmed, mean arterial pressure and CPP can be optimized using vasopressor infusions. CPP is an important consideration to continue the perfusion of marginally perfused brain tissue served by normal vascular networks which are often maximally dilated.

In setting of a patient at high risk for intracranial pressure (ICP) elevation, clinicians should avoid hypotonic fluids, which can contribute to cerebral edema. Isotonic fluids are the fluid of choice to maintain normal serum osmolality. However, even isotonic fluids can, at large volumes, reduce the intravascular oncotic pressure and encourage interstitial cerebral swelling. For this reason, hypervolemia should be avoided.

The role of colloids is not well defined in these cases. Many practitioners avoid albumin due to the suggestion of increased mortality from data found in patients with traumatic brain injury. Hydroxyethyl starch can contribute to renal failure and coagulopathy. Although these findings were among different study populations, it is difficult to recommend their use at present, pending emerging clinical evidence of benefit.

These patients are additionally at risk of intraoperative AVM rupture and large volume blood loss, which should be prepared for as part of the anesthesia plan. Following rupture of an AVM, induction of hypotension may be necessary to facilitate surgical control of bleeding. Blood replacement should be based on the patient's premorbid status and degree of intraoperative blood loss. Like other neurological conditions, there is no definitive transfusion trigger currently.

Seizure Disorders

Pre- and Intrahospital Resuscitation of a Patient with a Seizure/Status Epilepticus

Patients with seizures and status epilepticus may have derangements in their metabolic profile with transient or persistent lactic acidemia, hypotension, fever, and acute kidney injury related to rhabdomyolysis. In these clinical scenarios, optimization of fluid resuscitation cannot be understated. Besides treating reversible causes of seizures [1], prompt administration of benzodiazepines, and anti-epileptic drug administration, aggressive fluid resuscitation must be considered. While the prehospital treatment is primarily focused on immediate seizure treatment with or without intravenous access [2], placement of large-bore intravenous access to facilitate balanced salt solution infusion may be considered in patients with ongoing status epilepticus [2].

Intraoperative Care of Patients During Epilepsy Surgery

Patients with a diagnosis of epilepsy who do not achieve adequate seizure control on two antiepileptic drugs (AEDs) may present for elective surgical management. Several procedures can be considered: resection of an epileptogenic focus, electrical isolation of a diseased area, or insertion of neuromodulation devices such as a vagal nerve stimulator. These surgeries may be performed under general or awake craniotomy, depending on the type of surgery, the location of the lesion of interest, and patient selection.

There are many aspects of epilepsy surgery that have implications for anesthesia, and a thor-

ough preoperative evaluation is required. The purpose of this review is to describe the fluid considerations for this patient group.

As these patients present electively for this type of surgery, euvolemia should be expected, but this may not be the case if fasting time has been prolonged. In line with American Society of Anesthesiologists guidelines, patients should be allowed clear fluids up to 2 h before surgery.

The aim of intraoperative fluid management should be to maintain an euvolemic state. Hypovolemia may reduce CPP, which is especially relevant if a patient is in the sitting position, which is often the case in an awake craniotomy. This can be exacerbated using mannitol, a potent diuretic. This diuresis should be expected when mannitol is given, and volume status should be continuously monitored. Hypervolemia can contribute to cerebral edema, elevating ICP, and worsening of operative conditions. Depending on patient comorbidities, it may also cause pulmonary edema, which may be challenging to manage, especially in the patient having an awake craniotomy where airway and ventilation are not secured.

Methods on how best to evaluate volume status are discussed elsewhere in this book, which leaves the question, which fluid is best for intraoperative maintenance? In general, an isotonic crystalloid is used for this purpose. Both balanced crystalloids and normal saline have been used. Due to the hyperchloremic acidosis incidence with normal saline infusion, we routinely use Plasma-Lyte (Table 1) in the operating room and in the neurointensive care unit.

Colloids are typically avoided, mainly on the findings of the post hoc analysis of the SAFE trial [3]. The applicability of this study's findings to other neurosurgical populations is unknown. Similarly, hydroxyethyl starches are avoided due to their association with renal impairment and coagulopathy.

Glucose-containing fluids should only be administered to correct hypoglycemia, with serial monitoring of blood glucose until normalized.

Brain Tumors

The most common clinical presentations of brain tumors are headache, focal neurological symptoms, and seizures. The causative lesion is subsequently discovered on neuroimaging. Brain tumors can be either benign or malignant, and malignant tumors can be either primary or metastatic. These patients may require surgery for biopsy for histological confirmation, or resection/debulking of the lesion.

Preoperative nausea and vomiting can occur, caused by either cerebellopontine angle tumors close to the vomiting center or elevations in ICP. The preoperative use of mannitol and other diuretics may further reduce intravascular volume. This will render patients hypovolemic, which should be corrected in the preoperative period to avoid hypotension following anesthesia induction. Depending on the tumor's nature and size, cerebral autoregulation may be impaired, meaning patients are directly dependent on CPP to maintain oxygen delivery to brain parenchyma. Hypotension should therefore be avoided. This can be achieved in part

Table 1 Relative composition and tonicity of crystalloid fluids to plasma

Conc (mmol/l)	Plasma	Plasma-Lyte	0.9% NaCl	Ringer's lactate
Na	140	140	154	130
K	4	5	–	4
Cl	102	98	154	110
Ca	2.5	–	–	3
Mg	1.1	3	–	–
Buffer		Acetate 27 Gluconate 23		Lactate 28
pH	7.35–7.45	4–8	4.5–7	6–7.5
Osmolarity (mOsm/l)	275–310	294	285	275
Tonicity	Reference	Isotonic	Isotonic	Isotonic

by ensuring patients are normovolemic at the outset and replacing any intraoperative losses. If vomiting has been protracted, electrolyte abnormalities can occur, which should also be corrected in the preoperative period.

Discussion with the neurosurgical team will reveal any concerns regarding elevated ICP. Hyperosmolar therapy may be required intraoperatively for brain relaxation, and it is essential to monitor urine output if mannitol is used. Most experts recommend the use of isotonic crystalloids for replacement and maintenance therapy. Hypotonic fluids may rapidly contribute to cerebral edema. Colloids may cross a disturbed BBB and have a similar effect. These patients may also have inadequate glycemic control in the perioperative period due to dexamethasone for tumor shrinkage. The treating anesthesiologist should anticipate the need for intraoperative IV insulin infusion to maintain blood glucose in the range of 100–150 mg/dl.

Differences in Choices if Crystalloids Used in the Prehospital, Emergency Room, Operating Room, and the Neurointensive Care Unit: An Argument Toward Using a Balanced Salt Solution in Neurointensive Care

As highlighted in the above scenarios, there is very little evidence to guide fluid choices. Much of the rationale for choosing or avoiding a particular fluid is based on theory rather than clinical trials or gleaned from evidence gathered among a different patient cohort. There may be intra- or interinstitutional preferences in selecting a particular fluid.

A recent randomized controlled trial [4] in the intensive care unit concluded that the use of balanced crystalloids for intravenous fluid administration appeared to reduce the composite outcome of inhospital mortality, new renal replacement therapy, and persistent renal dysfunction compared with the use of saline. In a small RCT [5], Roquilly et al. randomized 42 patients with spontaneous subarachnoid hemorrhage to a balanced salt solution or isotonic sodium chloride solutions. The most significant impact of the solution was developing hyperchloremic acidosis (95% in the saline group and 65% in the balanced salt group, a hazard ratio of 0.58). There were no differences in intracranial pressure or mortality. Similarly, Lehmann et al. [6] randomized 36 patients to normal saline, hydroxyethyl starch, or balanced crystalloid or colloid solutions. They concluded that treatment with saline-based fluids resulted in a more significant number of patients with hyperchloremia, hyperosmolality, and positive fluid balance >1500 mL early after SAH. At the same time, administration of balanced solutions did not cause more frequent hyponatremia or hypoosmolality.

Comparable results have also been reported in yet another randomized controlled trial on adult trauma patients. In this study, Young et al. [7] randomized 65 patients to either 0.9% NaCl or Plasma-Lyte. Compared with 0.9% NaCl, resuscitation of trauma patients with Plasma-Lyte resulted in improved acid-base status and less hyperchloremia 24 h postinjury.

To summarize (Table 2), to reduce the risk of hyperchloremic metabolic acidosis, we have Level I evidence supporting the use of balanced salt solutions in neurointensive care patients. Even though many randomized controlled trials include patients admitted to the neurointensive care units, the prevalent use of balanced salt solutions in the prehospital setting, emergency room, operating room, and neurointensive care units remains unknown and warrants further examination.

Table 2 Perioperative fluid management of the neurologically critically ill patient

Acute hemorrhagic stroke	
Prehospital	Expeditious transfer of patients to the nearest appropriate designated stroke center Do not delay transfer to establish routine IV access
Perioperative	*Arteriovenous malformation:* Aim for euvolemia Maintain cerebral perfusion pressure.
Seizures	
Prehospital	Emphasis is on seizure termination. IV access may not be required if the seizure has terminated by the time of EMS arrival IV access is required if the patient is in status epilepticus, but other routes can be considered initially
Perioperative	Balanced crystalloid recommended for maintenance during elective surgery
Brain tumor	
Prehospital	Diagnosis unlikely to be confirmed; may present as seizure or stroke mimic and should be managed accordingly Fluid deficit through inadequate oral intake and vomiting can be corrected with balanced crystalloid fluid
Perioperative	Isotonic fluid for resuscitation and intraoperative maintenance Hyperosmolar fluid may be required to manage ICP Anticipate hyperglycemia secondary to steroid use

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Fluid Management in Pediatric Neurosurgery

Ritesh Lamsal and Navindra Raj Bista

Abstract

Optimal fluid management is a cornerstone of pediatric neuroanesthesia. The primary aims of fluid therapy in pediatric neurosurgery are to maintain euvolemia and hemodynamic stability while avoiding dyselectrolytemia and imbalances in glucose and metabolic homeostasis. Hypervolemia, hypovolemia, dyselectrolytemia, and metabolic derangement can lead to significant morbidities in children. Fluid management requires careful consideration of the preoperative hydration and electrolyte status of the child, the nature of the surgery, potential for major blood loss, the need for osmotic diuretics, and the overall fluid balance. Isotonic crystalloids are the mainstay of fluid therapy in pediatric neurosurgical procedures. Intraoperative supplementation of dextrose-containing fluids is only required in some special circumstances. The volume and choice of osmotic fluids are guided by the specific needs of the surgery, institutional practice, and hemodynamic and biochemical parameters of the child.

Keywords

Colloid · Crystalloid · Fluid management · Isotonic · Neuroanesthesia · Neurosurgery · Pediatric

Introduction

Intravenous fluids should be treated as drugs that have specific indications, contraindications, and adverse effects. Even though the use of intravenous fluids is a fundamental component of neurosurgical anesthesia, the ideal fluid does not exist in current clinical practice. Fluid management in pediatric neurosurgery is challenging as it requires close attention to the child's fluid and electrolyte status, along with a continual assessment of the physiological response to fluid therapy. Ongoing surgical blood loss, hemodynamic perturbations, and concomitant use of osmotic diuretics increase the difficulty in assessing intravascular volume. There are also physiological issues in children that need careful consideration, such as the immaturity of the vital organs and the improper handling of water and electrolytes. This chapter will focus on the perioperative management of intravenous fluids in children undergoing neurosurgical procedures, including evidence-based use of various types of fluids, osmotic agents, and an overview of salt and water disorders. As there are only a limited number of large

R. Lamsal (✉) · N. R. Bista
Tribhuvan University Teaching Hospital, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal
e-mail: riteshlamsal@mmc.tu.edu.np

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studies concerning intravenous fluids in children undergoing neurosurgical procedures, many recommendations are extrapolated from similar studies in adults.

Pediatric Physiological Considerations

The important physiological considerations in children concerning the handling of fluids and the maturity of the organ systems are briefly described below.

Water Balance

Water content in the human body varies with age, gender, built, and the type of body tissue. The total body water relative to body mass is higher in children compared with adults and gradually decreases as the child grows. Total body water comprises nearly 80% of the body weight in premature infants, around 75% in full-term neonates, and 65% in infants older than 1 year [1]. The age-related changes in total body water are mainly due to the decrease in the extracellular fluid compartment.

Organ Systems

The renal system rapidly develops in the first month of neonatal life. At birth, the neonate's kidneys are unable to clear free water effectively or excrete sodium load [2]. Physiological feedback mechanisms, such as the renin-angiotensin-aldosterone system, are also underdeveloped in neonates [3]. Thus, neonates are extremely susceptible to developing dehydration, volume overload, and dyselectrolytemia if intravenous fluids are not carefully titrated to clinical effect. Similarly, newborn infants have a limited cardiovascular reserve. Any decrease in preload or an increase in afterload is not tolerated well because of poor compliance of the ventricles and an inability to increase the systolic ejection volume [4].

Preanesthetic Assessment

Preanesthetic examination generally provides the first opportunity for the anesthesiologist to assess the preoperative volume status of the child and plan the perioperative fluid strategy. Children undergoing neurosurgical procedures may be dehydrated because of fasting, decreased appetite and thirst, vomiting, use of osmotic agents, and altered consciousness. Clinical signs of dehydration in children include dry and cool skin, lethargy, sunken eyes, depressed fontanelle, decreased urine output, feeble pulse, and sluggish capillary refill time. A comprehensive assessment may not be possible in children undergoing emergency neurosurgical procedures.

Fasting Recommendations

Previous guidelines recommended prolonged preoperative fasting before general anesthesia to decrease the volume of the gastric content and prevent the risk of aspiration. In recent times, there has been a fundamental change in this approach with accumulating evidence of the detrimental hemodynamic, metabolic, and endocrine effects of prolonged fasting, coupled with our understanding that the incidence of pulmonary aspiration is very low in children [5–7]. Current pediatric guidelines recommend preoperative fasting of 1 h for clear fluids, 4 h for breast milk, and 6 h for solids before elective surgeries [8, 9]. It is prudent to minimize preoperative dehydration in children undergoing major neurosurgeries by judicious administration of intravenous fluids if oral feeding is not possible or appropriate, such as in patients with repeated vomiting, depressed consciousness, or loss of protective airway reflexes. There are no recommendations in the neuroanesthesiology literature

regarding the fasting interval in children who are at a potentially greater risk of pulmonary aspiration because of their neurological condition.

Intraoperative Fluid Management

The type, volume, and tonicity of administered fluids should be guided by the underlying pathophysiologic processes of the individual pediatric patient. The overall goals are to achieve euvolemia with a normal to slightly increased serum osmolality, maintain cerebral and peripheral tissue perfusion, and establish normal electrolyte and acid-base balance. The traditional approach of devising a perioperative fluid regimen in pediatric neurosurgery involves the correction of the preoperative deficits, maintaining basal metabolic requirements, and compensating for surgical bleeding.

Preoperative Deficits

Children undergoing major neurosurgical procedures require intravenous fluids to replenish the deficit caused by fasting and correct for possible gastrointestinal (vomiting), renal (diuresis), or cutaneous (burns, trauma) losses. Fluid management in premature neonates has to be meticulous as they can lose a lot of body water through their fragile and poorly keratinized skin [10]. Administration of anesthetic drugs in a volume-deficient child can lead to profound hemodynamic disturbances. There are also added concerns in children with neurological disorders because of potentially dysregulated salt-water homeostasis and concomitant use of osmotic diuretics. Although there are no standard guidelines regarding how preoperative deficits should be replenished intraoperatively, a typical practice is to administer half of the calculated fluid deficit in the first hour of surgery, and the remaining 50% of the deficit over the next 2 h. The total fasting deficit is calculated as the product of maintenance requirement per hour and the number of hours of fasting.

Maintenance Requirements

Fluid must be administered to replenish sensible and insensible losses and maintain the basal metabolic processes in the child. Cutaneous loss (premature skin, radiant warmer use, skin breaches like in neural tube defects) and respiratory tract loss (tachypnea, use of dry oxygen, high-flow gas flow systems) contribute to most of the insensible losses in pediatric neurosurgery. The most common method used to calculate basal maintenance fluid requirement in children is based on energy expenditure indexed to body weight, as first described by Holiday and Segar [11]. An easy way to approximate this requirement is 4 ml/kg/h fluids for the first 10 kg of body weight, 2 ml/kg/h fluids for the next 10 kg of body weight, and 1 ml/kg/h for the remaining body weight of the child.

Blood Loss

In major neurosurgical procedures, there can either be sudden acute bleeding or slow but continuous bleeding over a prolonged period. In both situations, the overall blood loss may be profound with significant physiological consequences. An accurate estimate of blood loss is difficult in pediatric neurosurgery; concealed hemorrhage, such as in drapes, pads, and sponges, can be easily underestimated. The overall goals in a child with active intraoperative bleeding are to maintain hemodynamics and oxygen-carrying capacity and to prevent and treat hyperfibrinolysis and dilutional coagulopathy.

There are no clear recommendations regarding the "transfusion trigger," or the hemoglobin/hematocrit threshold for initiating transfusion in pediatric neurosurgery. The decision to transfuse packed red cells can be based on several variables, like the child's hemodynamic parameters, the acuity of the bleeding, estimated blood loss, comorbid illnesses, and the stage of the surgery. Serial estimation of the hematocrit is helpful to guide blood transfusion and estimate the total blood lost. Additional crystalloids should be

given to maintain intravascular volume until the threshold of red cell transfusion is reached. The current best evidence suggests that the optimal crystalloid-to-blood volume ratio is approximately 1.5:1 [12]. As children have poor physiological reserves and cannot mount adequate compensatory responses to acute bleeding, it is prudent to keep a lower threshold for blood transfusion compared with adults.

Types of Fluids

Table 1 enlists some of the important physical properties of crystalloids and colloids administered in the perioperative period. Isotonic crystalloids are the most commonly used intravenous fluids in perioperative care as they are inexpensive, easily available, and relatively nontoxic.

Crystalloids

Traditionally, hypotonic crystalloids were the most commonly used fluid in pediatric surgical procedures. This age-old practice was based on the general premise that renal handling of sodium load is poor in children and the liberal use of isotonic fluids results in hypernatremia. However, in children undergoing neurosurgical procedures, even mild hyponatremia can worsen cerebral edema and neurological condition. Children undergoing neurosurgical procedures also have multiple non-osmotic stimuli for the release of antidiuretic hormone, like nausea, vomiting, pain, stress, malignancy, dehydration, hypotension, and infection [13, 14]. Normal saline, Ringer's lactate, and proprietary balanced crystalloids are the most common intravenous fluids used in the perioperative period.

Several studies in hospitalized children show no benefit or even harm with the use of hypotonic maintenance fluids [15–19]. A recent meta-analysis found that in hospitalized children admitted to intensive and postoperative care, the administration of hypotonic maintenance fluids significantly increases the risk of hyponatremia compared with the use of isotonic fluids [20]. In another systematic review, the authors found that the use of isotonic fluids reduces the risk of hyponatremia in different types of surgical pediatric patients [21]. Postoperative hyponatremia in children after the use of hypotonic fluids is most pronounced in the first 24 h after surgery [21]. This risk may be prolonged ("late hyponatremia") if intravenous fluids are continued for a lengthy period during the postoperative recovery [22, 23].

Neonates, particularly those in the first few days of life, are the only group of children where the data supporting the use of isotonic fluids is less robust. One recently published retrospective study found that the use of hypotonic fluids (like 5% dextrose in 0.45% saline) for maintenance or replacement fluid therapy results in unsafe plasma sodium concentrations in neonates [24]. However, in a triple-blind randomized trial,

Table 1 Properties of intravenous fluids

Fluids	Osmolarity (mOsm/L)	Oncotic pressure (mmHg)
Normal saline	308	0
Ringer's lactate	273	0
20% mannitol	1098	0
3% saline	1024	0
5% dextrose	252	0
5% dextrose-normal saline	560	0
0.45% saline	154	0
6% hetastarch	310	31
5% albumin	290	19
Plasma	295	26
4% gelatin	283	20

Dathan and colleagues found that the risk of hypernatremia is significantly higher in neonates receiving maintenance isotonic fluids compared with hypotonic fluids [25].

Even though strong evidence supports the use of isotonic fluids over hypotonic fluids in pediatric neurosurgery (probably, except in neonates), data are scarce regarding the comparison between 0.9% saline and balanced crystalloids. Normal saline is slightly hyperosmolar (osmolarity: 308 mOsm/L) and helps to reduce brain water content. Normal saline use can lead to hyperchloremic metabolic acidosis because of an excessive rise in plasma chloride, dilution of plasma bicarbonate, and increased renal elimination of bicarbonate [26, 27]. However, hyperchloremic metabolic acidosis develops only after infusion of large quantities of normal saline [26]. In some centers, the slightly hypo-osmolar Ringer's lactate (osmolarity: 273 mOsm/L) is administered together with normal saline during neurosurgical procedures. There is preliminary evidence in intracranial tumor surgery that the strategy of combining normal saline with Ringer's lactate may have the benefit of obviating some problems when using either solution alone, such as high chloride load, absence of electrolytes, and hypo-osmolarity [28]. The use of proprietary balanced solutions is also increasing in neurosurgery. These solutions are often marketed as intravenous solutions that closely resemble the human plasma. In a recently published clinical trial, the use of balanced crystalloids (Plasma-Lyte A) in children undergoing craniotomy for brain tumors was associated with a safer electrolyte and acid-base profile compared with the use of normal saline [29]. In two similar studies, the use of balanced crystalloids (Sterofundin and Plasmalyte) provided better acid-base balance and electrolyte levels when used for intraoperative fluid therapy in adults undergoing elective craniotomy compared with 0.9% saline [30, 31]. However, neuroanesthesiologists need to remain vigilant as the use of commercially available "plasma-like isotonic fluids" in acutely ill children may still be associated with significant electrolyte disorders [32].

Colloids

Colloids are crystalloid solutions containing a high molecular weight substance that retains the solution in the intravascular compartment. Colloids commonly used in clinical practice are hydroxyethyl starch, gelatin, dextran, and albumin. The use of intravenous colloids for early fluid resuscitation or maintenance therapy is a long-standing controversy in perioperative medicine. Clinical practice concerning the use of colloids varies enormously between countries and among physicians. Several studies done in critically ill adult patients suggest that the use of synthetic colloids is associated with an increased need for renal replacement therapy, coagulopathy, and even a trend toward increased mortality [33–35]. The risk of renal impairment with the use of synthetic colloids is particularly striking in patients with sepsis. Based on the findings of these studies, the general trend in perioperative care has shifted from the use of colloids to crystalloids in both adults and children.

However, proponents of colloids argue that patients presenting for pediatric neurosurgery are usually different from critically ill patients. Neurosurgical patients generally have healthy organ systems with possibly no comorbid illnesses unlike children in critical care who can have hypotension, renal impairment, metabolic derangement, and sepsis. Furthermore, in pediatric neurosurgeries, fluids are administered over relatively short periods compared with critical care; short-term use of low-dose colloids is not associated with kidney injury [36].

Two important goals in neuroanesthesia are to maintain euvolemia and hemodynamic stability. Within a few minutes of infusion, crystalloids start to leave the intravascular compartment and can accumulate in various organs. In contrast, colloids stay in the intravascular compartment for several hours. In a randomized trial enrolling over 1000 adults undergoing abdominal surgeries, Kabon et al. [37] found that goal-directed intraoperative use of 6% hydroxyethyl starch did not increase the risk of renal toxicity, even up to 6 months postoperatively. The incidence of minor

and major complications was similar in patients who received either colloids or crystalloids. In another study, intraoperative goal-directed colloid therapy was associated with fewer postoperative complications compared with crystalloid therapy [38]. A recently published meta-analysis in surgical patients concluded that the perioperative use of hydroxyethyl starch for volume replacement therapy does not lead to an increase in postoperative mortality or kidney dysfunction [39]. Another meta-analysis of 55 randomized trials in critically ill patients concluded that crystalloids are less efficient than colloids at stabilizing resuscitation endpoints [40]. Feldheiser [41] found that when a goal-directed algorithm is used to optimize the stroke volume, intraoperative use of balanced hydroxyethyl starch is associated with better hemodynamic stability compared with crystalloid-based therapy. This finding may be particularly relevant in the context of pediatric neuroanesthesia.

There are very few studies that have assessed the relative safety of colloids and crystalloids in neurosurgical procedures. In a small study in adults undergoing sitting craniotomy, the administration of hydroxyethyl starch resulted in better cardiac and stroke volume indices compared with Ringer's acetate [42]. In neurosurgical procedures, the use of colloids also decreases the total intraoperative fluid requirement [42, 43]. Based on emerging evidence, colloids may be useful in neurosurgeries that have a substantial intravascular volume loss. Judicious administration of colloids in selected children undergoing neurosurgery may help preserve hemodynamic stability and obviate the need for large-volume crystalloid infusion to maintain intravascular volume. Older generation colloids should not be used as they are associated with kidney injury and coagulopathy. Colloids should be used at the lowest effective dose, for the shortest period, preferably guided by objective hemodynamic measures, ensuring the infusion is terminated once the hemodynamic goals are met.

Dextrose-Containing Fluids

Administration of dextrose-containing fluids with consequent hyperglycemia leads to diuresis, dehydration, worsening of ischemic brain or spinal cord injury, and poor post-neurosurgical outcomes [44]. Both the degree and duration of hyperglycemia are independent risk factors for poor outcomes [45]. On the other hand, acute hypoglycemia is associated with neuronal death and long-term neurodevelopmental manifestations, such as developmental delay, seizure disorders, visual processing problems, and cognitive difficulties [46–48]. Furthermore, hypoglycemic events are challenging to diagnose under anesthesia.

The physiological mechanisms to elevate blood glucose are less developed in children than adults. The guidelines of the American Academy of Pediatrics recommend the addition of dextrose to maintenance intravenous fluids in children to avoid hypoglycemia and lipolysis [49]. However, these guidelines do not address the issue of supplemental dextrose during neurosurgery. The stress of surgery and anesthesia on the child's physiology leads to several metabolic sequelae, such as increased secretion of counter-regulatory hormones, surge in catecholamines, the release of inflammatory cytokines, and relative insulin resistance that lead to elevated glucose levels [50, 51]. These sequelae may have a significant impact on the neurological outcome of children undergoing intracranial procedures [44]. Pietrini et al. [45] found that intraoperative infusion of glucose-free balanced solution allows better control of blood glucose without a significant risk of perioperative hypoglycemia in children older than 1 month undergoing posterior fossa tumor surgery. These principles suggest it is reasonable to use glucose-free intravenous fluids in most pediatric neurosurgical cases. However, the neuroanesthesiologist should perform frequent glucose monitoring and possibly supplement dextrose in children who are at risk, such as neo-

nates and premature infants and children with prolonged fasting, catabolic state, poor nutritional status, metabolic disorders, and lengthy surgeries. A background infusion of 1–2.5% dextrose may be sufficient in such cases [52, 53].

Osmotic Fluids

Osmotic therapy may be required in pediatric neurosurgery to relax the brain, lower intracranial pressure, and facilitate the surgery. Historically, mannitol has been the osmotic diuretic of choice in intracranial surgeries. Recently, the use of hypertonic saline is gaining popularity in pediatric neuroanesthesia, and it appears to be safe and effective [54–56]. There is some evidence that 3% hypertonic saline causes a greater reduction of intracranial pressure compared with 20% mannitol in children with acute central nervous system infections [57]. Studies in adults have also found that hypertonic saline has a more sustained effect on intracranial pressure compared with mannitol [58]. The recent guidelines for the management of pediatric severe traumatic brain injury also recommend the use of hypertonic saline in children with intracranial hypertension [59]. However, there are other studies comparing mannitol with hypertonic saline in children that have found no significant difference in intracranial pressure between the two groups, or clinical outcomes [60, 61].

Unfortunately, no large study has compared the efficacy of mannitol and hypertonic saline to improve the neurosurgical field or postsurgical neurologic outcomes in children. As there is a lack of evidence, it is difficult to recommend one therapy over another in pediatric neurosurgery. Hypertonic saline may be a better choice in children with hemodynamic instability, presence of hyponatremia, or renal impairment.

Perioperative Dysnatremias

Disorders of sodium and water are the most common fluid and electrolyte disturbances in pediatric neuroanesthesia and neurocritical care practice. Four distinct abnormalities can contribute to perioperative dysnatremias: inappropriate fluid therapy (iatrogenic), syndrome of inappropriate antidiuretic hormone (SIADH), cerebral salt wasting (CSW), and central diabetes insipidus (CDI). These disorders are most common in children undergoing surgeries for parasellar tumors, like craniopharyngioma and pituitary adenoma, and pose significant diagnostic and therapeutic challenges [62].

SIADH

SIADH usually occurs in the neurosurgical postoperative period due to the release of intracellular ADH from injured neurons [63]. It can be seen in up to 3% of all pediatric tumor patients undergoing craniotomy [64]. SIADH manifests as reduced urine output, elevated urine osmolality, and increased concentration of urinary sodium leading to euvolemic hypo-osmolar hyponatremia [65]. In most children with uncomplicated SIADH, fluid restriction alone suffices to treat hyponatremia. Children with symptomatic hyponatremia with features like cerebral edema, visual disturbances, focal neurologic signs, or respiratory distress should be treated with hypertonic saline.

CSW

CSW is a condition where there is a depletion of extracellular volume because of impaired renal handling of sodium and water. Acute neurological injury can lead to the loss of sympathetic stimulation to the kidneys and stimulate the release of natriuretic peptides [66]. CSW can be present in up to 4% of children following intracranial surgeries [67]. Both CSW and SIADH present with similar laboratory features of hyponatremia, hypo-osmolality, and high urine osmolality; however, patients with CSW are volume-depleted, which is an important feature to distinguish it from SIADH [68]. Other diagnostic features of CSW include polyuria and elevated urinary sodium [68]. Children with CSW

are treated with normal saline as the first-line therapy to restore intravascular volume and correct the hyponatremia.

CDI

CDI is an extremely common postoperative complication in children and adolescents after neurosurgical procedures involving the sellar and parasellar regions because of damage to the pituitary stalk [69]. However, with the advent of less invasive surgical approaches to the sella, such as endoscopic transsphenoidal decompression, the incidence of postoperative CDI has decreased in recent years [70].

CDI results from the inability to concentrate urine because of the deficiency of ADH. It can sometimes manifest during the intraoperative period, but is commonly seen within 24–48 h of the surgery [62]. The characteristic features of DI are plasma hyperosmolality, polyuria, the output of hypotonic urine, polydipsia, and hypernatremia [71]. Treatment of CDI varies with the severity of polyuria and hypernatremia. Children with only mild-moderate features can be treated with free-water correction and a low-solute diet. In more severe cases, the treatment of choice is desmopressin, which is a synthetic analog of the endogenous ADH with potent antidiuretic action and without the unwanted vasopressor activity [72].

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Fluid Management in Geriatric Neurosurgery

Indu Kapoor and Hemanshu Prabhakar

Abstract

Geriatric patient population is increasing in the present world because of better healthcare facility, advances in medicine, and growing researches. These patients are afflicted with various physiological age-related comorbidities. The physiological change in body fluid and electrolyte composition with age is also significant. Clinicians should be well aware of various types of fluids and its compositions and also the role of individual fluid in different types of surgeries with its advantages and disadvantages. In neurosurgical patients, normal saline is a preferred choice of fluid by neuroanesthesiologists because of its believed hypertonic nature (308 mOsmol/lt). More recently, a balanced salt solution (270–285 mOsmol/lt) has been successfully used in neurosurgery as well as in neuro-intensive care unit. However, there is no strong evidence of benefits of one fluid over another in geriatric patient population.

Keywords

Geriatric patient · Age · Neurosurgery · Fluid therapy · Normal saline · Balanced salt solution

I. Kapoor (✉) · H. Prabhakar
Neuroanaesthesiology and Critical Care,
All India Institute of Medical Sciences,
New Delhi, Delhi, India

Introduction

The geriatric population in the world is increasing day by day, so are the geriatric patients who are being treated or operated in hospitals for various diseases. The factors that have led to the escalating graph of geriatric population include better healthcare services, advances in medicine, growing surgical techniques, etc. Longevity however is associated with age-related acute illnesses and increase in the prevalence of chronic diseases and thus the accelerated load on healthcare providers and services. Typically, geriatric patients are afflicted with various age-related comorbidities involving multiple organ systems: hypertension, diabetes mellitus, cerebrovascular disease, heart disease, bronchitis, Alzheimer's disease, etc. Along with comorbidities, there is physiologic change in the body fluid and electrolyte composition with age. Many studies have demonstrated that the total body water percentage and intracellular fluid decrease with age [1–3]. Geriatric patients are more prone to water and electrolyte imbalance also because of physiologic alterations like reduced thirst, decreased ability to concentrate urine, and imbalances due to diseases like chronic kidney disease, diabetes mellitus, etc. Hence, this patient population is considered as a challenge while posted for surgery, since maintaining fluid and electrolyte balance during intraoperative period sometimes becomes very tricky and is directly

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related to patient's outcome. Clinicians should be well aware of various types of fluids and its compositions and also the role of individual fluid in different types of surgeries with its advantages and disadvantages. In neurosurgery (traumatic and nontraumatic), normal saline is a preferred choice of fluid by neuroanesthesiologists because of its believed hypertonic nature (308 mOsmol/lt). More recently, a balanced salt solution (270–285 mOsmol/lt) has been successfully used in neurosurgery as well as in neurointensive care unit. However, there is no strong evidence of benefits of one fluid over another in geriatric patient population. Fluid resuscitation either with crystalloid or colloid should be individualized. The choice of fluid, crystalloid, or colloid should depend on the patient's clinical status. At present, no literature is available comparing these two resuscitative fluids in geriatric patients.

In this chapter, we will discuss how water composition and distribution of geriatrics are different from adults and the fluid management in geriatric patients undergoing neurosurgical procedures. Though there are limited literature on this topic in geriatric patient population, we will answer the specific questions like types of fluids used in these patients undergoing neurosurgical procedures, their advantages and disadvantages, and current evidences. We will also review different fluid therapies that can be used during intraoperative period in these patients.

Body Water Distribution in Geriatrics

Body water distribution or percentage is affected by many factors; aging is one of them. Many studies have shown that aging process is associated with a decrease in total body water (TBW) and intracellular fluid (ICF) due to fat-free mass loss and an increase in extracellular water (ECW) and ECW/TBW ratio [1–4]. Most of the body fluid is inside the intracellular and extracellular compartment, but water is also inside the various body organs. Since muscle tissue and fat also contain 75% and 10% of water, respectively, following age-related loss of muscle and fat content, there is additional water loss from the body. The proportion of water in the body decreases continuously with age [5] (Fig. 1). Steen et al. suggest that 70- to 80-year-old males contain less than 60% water and 70- to 80-year-old females less than 50% water [6]. Hence, the hydration status in an adult simply cannot be applied to geriatric patients because of physiological changes in water distribution occurring with aging.

Variety of Fluids Used in Geriatrics

The commonly used fluids in patients undergoing neurosurgical procedure include normal saline and balanced salt solution because of their osmolarity close to that of blood. *Normal saline* is the

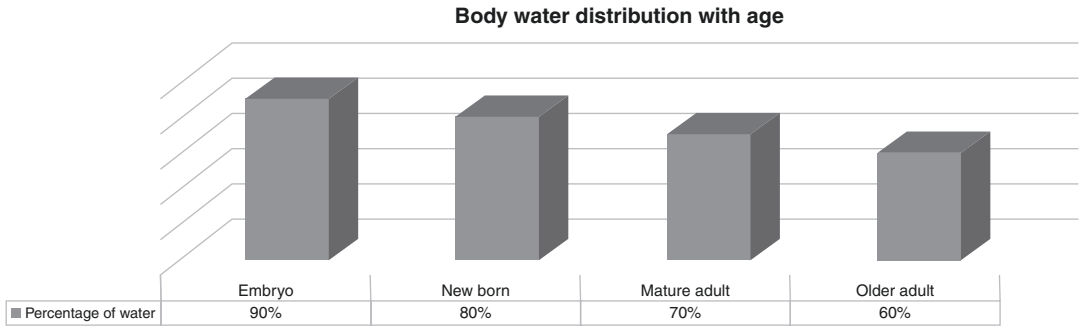

Fig. 1 Body water distribution with age

most commonly and frequently used fluid in this setting. Though slightly hypertonic, normal saline becomes isotonic once infused in blood due to dilution by plasma protein. The two major problems identified with the use of large volumes of normal saline are metabolic complications (hyperchloremic acidosis) and acute kidney injury, possibly as a consequence of the acidosis acting on renal vasculature and blood flow [7]. The normal saline-induced hyperchloremic acidosis has been suggested as a cause of brain stem ischemia due to its effect on renal blood flow [8, 9]. In geriatric patients, mild hyperchloremic acidosis is always found following normal saline infusion associated with prolonged postoperative recovery due to decreased gastric blood flow and intramucosal pH [10]. This makes the clinician more cautious while using normal saline in geriatric patients undergoing neurosurgery.

On the other hand, *balanced salt solution* has been found to provide significantly better control over acid-base balance, sodium, and chloride levels when used as intraoperative fluid maintenance and replacement during elective neurosurgery [11]. In other set of patients like trauma patients, compared with normal saline, resuscitation with balanced salt solution resulted in improved acid-base status and less hyperchloremia at 24 h post-injury [12]. In critically ill patients, among critically ill adults, the use of balanced crystalloids for intravenous fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal replacement therapy, or persistent renal dysfunction than the use of saline [13]. According to a meta-analysis by Hammond et al., resuscitation with balanced crystalloids demonstrated lower hospital or 28-/30-day mortality compared with saline in critically ill adults but not specifically those with sepsis. Balanced crystalloids should be provided preferentially to saline in most critically ill adult patients [14]. All these studies were conducted in adult patients [neurosurgical and non-neurosurgical]. Though commonly used, there is no strong evidence of benefits from normal saline which causes hyperchloremic metabolic acidosis in these patients. Further large trials are required to answer this query. Han et al. conducted a crossover study in 13 elderly men with bladder outflow obstruction due to benign prostatic hypertrophy, which had been alleviated by an indwelling bladder catheter while awaiting surgery, with a mean age of 73 years, who each received intravenous infusions of Ringer's acetate and of isotonic saline. Their study showed limited differences in fluid balance and renal function when Ringer's acetate or isotonic saline was infused in elderly men. Glomerular filtration rate was found to be increased in response to both fluids, though more after infusion of Ringer's acetate, indicating that balanced fluid is more readily excreted than normal saline [15]. To date, there is no study where normal saline and balanced salt solution has been compared in geriatric patients undergoing neurosurgical procedures during intraoperative period to assess the superiority of one over another. A good, large-sized randomized controlled trial is the need of the hour to find out suitable fluid for intraoperative period in geriatric patients, keeping in mind the optimal surgical condition required during neurosurgery and physiological alterations in total body fluid distribution in these patients.

Restricted Versus Liberal Fluid Therapy

Neurosurgical procedures are associated with major risk, especially in geriatric patients with their multisystem physiological decline and increased vulnerability to complications during intraoperative period. Despite of advanced surgical skills and perioperative care, intraoperative fluid therapy is one of the major factors which might influence the patient's recovery and outcome. Hasanin et al. conducted a randomized controlled trial where they enrolled 61adult patients scheduled for supratentorial brain mass excision and randomized them into either goal-directed fluid therapy [GDFT] group (intraoperative fluids guided by pulse pressure variation) and control group (standard care) [16]. They concluded that GDFT group during supratentorial mass excision had increased intraoperative fluid requirement and improved peripheral

perfusion without increasing brain swelling. GDFT also had increased urine output and low serum lactate level compared to control group. In an another study by Wu et al. in supratentorial tumor patients, where they compared arterial pressure continuous output (APCO)-derived stroke volume variation (SVV)-guided fluid management with control group on postoperative complications and outcome [17]. They observed that the intraoperative colloids and total infused fluid volume were significantly higher in APCO group than control group. The degree of brain edema at day 1 postoperative was not significantly different between the two groups. The lactate concentration at the end of surgery in the patients of APCO group was significantly decreased compared with baseline. Also, the incidence of postoperative complications was decreased in the APCO group. From above studies in adult patients, it is clear that fluid management based on dynamic parameters [SVV, PPV] has better patient outcome and less complications compared to liberal fluid group. The GDFT in geriatric patients undergoing non-neurosurgical procedure have shown that GDFT stabilized perioperative hemodynamics and reduced the occurrence of postoperative complications in these patients who underwent gastric cancer surgery compared to standard group. No significant differences were observed in mortality between the two arms [18]. According to a randomized controlled study by Liu et al. in geriatric patients undergoing radical resection of bladder cancer, the GDFT is beneficial for stabilization of hemodynamic status and maintenance of oxygen balance of supply and demand compared to control group [19]. Liang et al. investigated the influence of perioperative GDFT on the prognosis of elderly patients with benign prostatic hyperplasia and hypertension who received plasmakinetic energy transurethral resection of prostate (PKRP) surgery and observed that GDFT stabilized perioperative hemodynamics and reduced the incidence of postoperative complications in elderly patients who underwent PKRP [20], though the optimal fluid therapy in geriatric patients undergoing neurosurgical procedure remains unanswered.

The enhanced recovery after surgery (ERAS) protocols are increasingly applied in perioperative services worldwide [21]. The perioperative fluid management is one of the key elements of ERAS protocol, and the use of goal-directed fluid therapy (GDFT) is gaining popularity for the appropriate perioperative fluid/volume management [22]. The benefits of GDFT should be determined based on surgical and patient risk factors. Age is one of the factors, where fluid management in geriatric patients has to be very careful. The principle behind GDT is to maximize tissue oxygen delivery by achieving a maximum hemodynamic status with the required amount of fluid therapy. It is essential that an individualized GDFT plan should include optimization of patient's hemodynamic status and fluid requirement. Hence, a large randomized study is required to find out the effect of GDFT and liberal fluid therapy in geriatric patients undergoing neurosurgical procedures.

Current Evidence

At present, literature search does not reveal any study where different types of fluids have been compared to find out their effect on outcome and prognosis of geriatric patients undergoing neurosurgical procedures. Neither are the studies where different fluid therapies have been compared and assessed for their effect on outcome or mortality in this set of patients. Further, a good quality research is required to find out the most suitable fluid and fluid therapy in these patients.

Conclusion

Since dehydration, loss of thirst, weight loss, and malnutrition are common problems for aging patients, undergoing major surgical procedures like neurosurgery would be an add-on to the already physiologically altered bodily system to regulate and conserve water and electrolyte in the body. Hence, knowledge and awareness among clinicians play an important role in achieving improved outcome in these patients.

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Fluid Management in Pituitary Surgery

Zulfiqar Ali, Iqra Nazir, Shazia Anjum, and Hemanshu Prabhakar

Abstract

Patients with pituitary tumours undergoing transnasal, transsphenoidal or transcranial surgical resection are prone to develop disorders of sodium and water homeostasis as a result of damage to the hypothalamic-pituitary axis. The common water metabolism disorders encountered in clinical practice are diabetes insipidus (DI), syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and less commonly seen cerebral salt-wasting syndrome. Diabetes insipidus is characterised by the formation of larger quantities of urine in the first phase due to the development of diabetes insipidus, followed by a second phase of SIADH and a third phase due to recurrence of DI. These water and electrolyte abnormalities last for a brief duration in the postoperative period but require a meticulous monitoring. Diabetes insipidus is characterised by thirst and polyuria. Laboratory characteristics show an increased serum osmolarity and hypernatremia, associated with production of urine with low specific gravity. Postoperative SIADH is characterised by a decreased serum osmolarity and an increased urine hyperosmolarity and hyponatraemia. Cerebral salt-wasting is infrequently encountered in clinical scenarios after pituitary surgery. It is characterised with excessive natriuresis and extracellular volume depletion. A combined approach and coordination between an endocrinologist, an intensivist, a surgeon and a neuroanaesthesiologist are necessary for the optimal management in patients undergoing pituitary surgery.

Keywords

Fluid management · Pituitary tumours · Transsphenoidal surgery · Central diabetes insipidus · Polyuria · Syndrome of inappropriate secretion of antidiuretic hormone · Cerebral salt-wasting syndrome

Z. Ali (✉) · I. Nazir
Division of Neuroanesthesiology and Critical Care, Sheri Kashmir Institute of Medical Sciences, Srinagar, India
e-mail: zulfiqar.ali@skims.ac.in

S. Anjum
Department of Critical Care Medicine, Batra Hospital and Medical Research Centre, New Delhi, India

H. Prabhakar
Neuroanaesthesiology and Critical Care, All India Institute of Medical Sciences, New Delhi, Delhi, India

Patients with pituitary tumours undergo a myriad of water metabolism disorders in the perioperative period. These disorders result from dysregulation of, a major neuroendocrine system, hypothalamic-pituitary-adrenal (HPA) axis [1], arising as a result of the mass effect of the sellar mass or intraoperative manipulation of the hypothalamus, pituitary stalk or posterior pituitary

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gland, resulting in central diabetes insipidus (DI) and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Rarely cerebral salt-wasting syndrome (CSWS) is also seen during postoperative period [2].

Anatomical and Physiological Basis of the Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic nuclei in the supraoptic and paraventricular region synthesise the arginine vasopressin (AVP). The prohormone arginine vasopressin is packed into vesicles and transferred via hypothalamic-hypophyseal axis for storage in the posterior pituitary gland [3]. A rise in the plasma osmolality, any factors decreasing the blood pressure or circulating blood volume, leads to the release of AVP into the blood circulation to adjust the osmotic equilibrium [4]. The circulating AVP binds to AVP-V2 receptors in the collecting tubules of the kidney. There results an activation of the cyclic AMP-mediated signal transduction stimulating the insertion of aquaporin-2 (AQP2) channels into the apical membrane of the collecting duct in the kidneys. The collecting duct becomes permeable to water, thereby facilitating the passive absorption of water.

Additionally, vasoconstriction in blood vessels induced by circulating AVP results in an increased blood pressure [1]. Multiple studies have shown that DI may have an incidence from 0.5% to 25% and SIADH from 9% to 25% in the postoperative period [5, 6].

Diabetes Insipidus

Postoperative diabetes insipidus is one of the commonly prevalent water metabolism disorders seen after pituitary surgery [7]. In a series of 1571 patients with pituitary adenomas undergoing surgery, DI developed in 31% within the first 24 h after surgery and 17% after 3 days [8]. The prevalence may be lower (10% and 20%) for pituitary tumours confined to the sella turcica and elevated (60–80%) for surgical resection of large tumours [8].

Clinical Features

Polyuria and thirst are the immediate symptoms observed in the postoperative period. They are characteristically seen immediately in the first 48 h after surgery. The urine output may vary the prevalence, predictors and patterns of postoperative from 4 L to 20 L per 24 h depending upon the mild or complete absence of ADH deficiency [9]. *Adipsic DI* characterised by an impaired sense of thirst may lead to severe dehydration and hypernatremia. It may be seen in hypothalamic damage after extensive surgery with giant craniopharyngiomas and adenomas [10]. Transient *DI* occurs due to mild and reversible injury to pituitary stalk and lasts for 24–48 h after surgery. *Permanent DI* results due to irreversible damage of the pituitary stalk [11]. Untreated diabetes insipidus may lead to volume depletion and hyperosmolality, resulting in irritability, confusion and coma.

In the triphasic pattern, three consecutive phases of water metabolism disorder have been observed. The initial stage of DI occurs for 5–7 days. The second phase is characterised by SIADH which lasts for 2–14 days. SIADH occurs due to the release of AVP from the degenerated neurons from the posterior pituitary, leading to decreased serum sodium levels and decreased serum osmolality [12]. The third phase is characterised by a development of permanent diabetes insipidus due to depletion of AVP synthesising neurons [13]. Biphasic pattern is characterised by the presence of only the initial two stages of water metabolism characterised by diabetes insipidus and SIADH.

Laboratory Findings

The biochemical features show an increased serum osmolality accompanied by a decrease in urine osmolality. Serum electrolytes need to be monitored closely if the urine output is more than 300 mL/h for 2 consecutive hours and if the urine-specific gravity is $\leq$1.005. Diabetes insipidus is expected if serum sodium rises to 146 mEq/L or higher. In an alert healthy patient, serum Na may not increase beyond 150 mEq/L, as the osmotic stimulus may be accompanied by

Table 1 Grading of postoperative diabetes insipidus

Grade		
I	*Probable transient* DI	Symptoms of diabetes insipidus are short lived and settle within 48 h
Diabetes insipidus requiring treatment:		
II	*Transient* DI	Symptoms last <2 weeks
III	*Persistent* DI	Symptoms >2 weeks but < 6 months
IV	*Chronic*	Symptoms last for >6 months

DI diabetes insipidus

an increased intake of fluids due to the feeling of thirst experienced; in the postoperative period, de Vries et al. [9] classified the postoperative diabetes insipidus from grade 1 being the probable to grade IV characterised by chronic persistent diabetes insipidus lasting for more than 6 months (Table 1).

Treatment of Postoperative Diabetes Insipidus

Mild diabetes insipidus in the postoperative period is treated by sufficient intake of water. Patients are advised to drink orally whenever they feel thirsty. This compensates for the increased urine output and helps in maintaining the serum sodium levels. The fluid balance (urine output and oral intake) and the serum electrolytes are closely monitored every 3 hours to gauge the fluid status of the patient.

When the fluid loss (urine output is increased to more than 300 mL/h for 2 consecutive hours) exceeds the patient's ability to drink and the serum sodium levels increase to 146 mEq/L or higher, injection vasopressin is administered at 5–10 units IM/SC every 8–12 hours. A continuous intravenous infusion can alternately be started at 0.0005 unit/kg/hr initially and the dose doubled every 30 min to reach the desired effect with the total dose exceeding 0.01 unit/kg/hr. Vasopressin use has the drawbacks of (1) the need for intramuscular or subcutaneous administration and (2) anti-vasopressin antibodies which appear and cause a secondary increase in urine output which is resistant to ADH treatment [14].

Desmopressin can be administered orally (50–100 μg tablets), sublingually (30–60 μg), through intranasal spray (5–10 μg) or as a parenteral formulation (intravenous or subcutaneous dose of 2–4 mcg/day divided q12hr). The dose is repeated once after repeating the urine osmolality (<200 mosm/l), specific gravity (<1.005) and increased urine output (>2.5 ml/kg/h for >2 h) [9].

Risk Factors for Postoperative Diabetes Insipidus

Sigounas et al. [15] found that the incidence of diabetes insipidus in the postoperative period is very low. Permanent diabetes insipidus was observed in 2.7% and transient diabetes insipidus in 13.6% of patients undergoing minimally invasive pituitary surgery. Factors found to be responsible for the occurrence of diabetes insipidus were Rathke's cleft cyst histology, cerebrospinal fluid leak and previous nonendoscopic lesion resection. It was observed that increased levels of serum sodium to more than 145 mmol/L during first 5 days after surgery was a sensitive (87.5%) and a specific (83.5%) marker for the development of permanent postoperative diabetes insipidus [9, 15].

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Hensen and colleagues [8] observed that hyponatraemia was a very frequent complication observed in patients. The authors found a biphasic pattern characterised by polyuria and hyponatraemia in 53 (3.4%) patients and a triphasic pattern characterised by polyuria-hyponatraemia-polyuria in 18 (1.1%) patients.

Postoperative SIADH is characterised by a decreased serum osmolarity (<270 mosm/kg) and an increased urine hyperosmolarity (>100 mosm/kg) and hyponatraemia (serum sodium less than 130–135 mEq/L) with urine sodium loss of more than 40 mmol/l (Table 2). A low serum uric acid may be seen due to renal loss of uric acid and a low serum creatinine due to the mild volume expansion [16].

Table 2 Diagnostic features of SIADH

Clinical presentation	Signs and symptoms
Asymptomatic	No symptoms and signs
Mild	Headache, irritability, lack of concentration, lethargy, vomiting
Moderate	Confused, restless, myalgia, anorexia
Severe	Altered consciousness/coma, seizures, extrapyramidal involvement
Physical examination	Absence of oedema Absence of signs of dehydration
Laboratory parameter	*Laboratory values*
Serum sodium	<135 mmol/L
Serum osmolality	<275 mOsm/kg
Urinary osmolality	>100 mOsm/kg in the presence of serum hypo-osmolality
Urinary sodium	>40 mmol/L

The main treatment for SIADH is by restriction of the fluids [17]. In an asymptomatic patient with mild hyponatraemia (>125 mmol/L), limitation of the fluid intake to less than 1000 mL and a liberal increase in salt intake are sufficient. In a patient with moderate hyponatraemia with serum sodium levels of 120–125 mmol/L or severe hyponatraemia with serum sodium levels less than 120 mmol/L (with no or minimal symptoms), chronic hyponatraemia should be slowly corrected. A restriction of fluid to less than 500 mL daily or an infusion of hypertonic saline (HS) is started. However, the increase serum sodium should be slow, at a rate of 0.5 mmol/L/h. In patients who present with seizures or altered consciousness or an acute onset of hyponatraemia, 3% saline infusion is started at an initial rate of 1 mmol/L/h for the first few hours. In case of volume overload, it is followed by a concomitant administration of furosemide [17].

Various drugs as demeclocycline and lithium have been tried in treating SIADH. However, there are no randomised clinical trials that have tried to study the efficacy of these drugs after transsphenoidal surgery. Demeclocycline has been implicated in the development of nephrogenic diabetes insipidus in patients with hyponatraemia secondary to SIADH. This leads to decreased urine concentration and increased levels of serum sodium.

Tolvaptan is helpful in the treatment of dilutional hyponatraemia [18]. It may be safely used following pituitary surgery with regular monitoring of serum sodium levels. A dose of 15 mg once daily is initiated which may be increased progressively to 60 mg/day [19, 20].

Cerebral Salt-Wasting Syndrome

Cerebral salt-wasting is very rarely seen after pituitary surgery. It is characterised with excessive natriuresis and extracellular volume depletion. The exact mechanism for cerebral salt-wasting is unknown. Various causative mechanisms as release of brain natriuretic factor, C natriuretic peptide and atrial natriuretic peptide have been postulated. It is believed that a decrease in sympathetic input to the kidneys may cause an increase in urinary sodium excretion. There is a hypovolemic hyponatraemia [21] caused by the release of brain natriuretic peptide—which is treated by the administration of hypertonic saline. The main features on which CSW can be differentiated from SIADH are weight (which may be increased or unchanged in SIADH and decreased in CSWS), serum osmolality (which is decreased in SIADH and increased or normal in CSWS), serum protein levels (which may be normal or high in CSWS) and hematocrit (which is low or normal in SIADH and increased in CSWS) [22]. A combined disorder of central diabetes insipidus and cerebral salt-wasting syndrome, though rare, has also been reported in the postoperative period following pituitary surgery and may be associated with a high mortality due to a delay in diagnosis and inadequate or delayed treatment [23].

Conclusion

The postoperative period in patients undergoing transsphenoidal or transcranial pituitary surgery is invariably characterised by water metabolism disorders which need to be identified and treated.

A multidisciplinary approach involving a neurointensivist, neuroendocrinologists and a neurosursurgeon to have a preoperative hormonal assessment of these patients is needed. Appropriate and timely management of these endocrinopathies and water metabolism disorders will help to decrease the morbidity and mortality of patients undergoing pituitary surgeries.

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Fluid Management in Aneurysmal Subarachnoid Hemorrhage

Charu Mahajan, Indu Kapoor, and Hemanshu Prabhakar

Abstract

Fluid management in aneurysmal subarachnoid hemorrhage is challenging in view of the associated conditions like neurogenic stunned myocardium (NSM) and neurogenic pulmonary edema (NPE) and the need to institute hypertensive therapy in patients who develop delayed cerebral ischemia (DCI). Fluid therapy should aim for maintenance of euvolemia that can be achieved by clinical assessment along with close hemodynamic monitoring. Both hypovolemia and hypervolemia have been found to be associated with poor outcome. In patients developing DCI, hypervolemia has to be induced through the use of isotonic crystalloid infusion. Evidence is still not strong enough for recommending the use of colloids as maintenance fluid, even though studies have shown that they are safe to use in aSAH patients without underlying renal disease.

Keywords

Fluid therapy · Goal-directed fluid therapy · Aneurysmal subarachnoid hemorrhage · Hemodynamic monitoring

C. Mahajan (✉) · I. Kapoor · H. Prabhakar
Neuroanaesthesiology and Critical Care,
All India Institute of Medical Sciences,
New Delhi, Delhi, India

Aneurysmal subarachnoid hemorrhage (aSAH) is a neurological emergency often associated with significant debility. Fluid forms an important part of early management, as patients often present with history of vomiting and altered consciousness resulting in a potentially dehydrated state. The development of associated neurogenic stunned myocardium and neurogenic pulmonary edema requires strict titration of fluid transfusion. Moreover, one of the unique features of aSAH is cerebral vasospasm and delayed cerebral ischemia (DCI) where optimization of hemodynamics is considered the foremost step. This makes it imperative to transfuse correct amount and type of fluid, which needs to be rationalized on the basis of available evidence.

How Much Fluid to Be Transfused?

Patients presenting in emergency department often have a raised blood pressure which is a compensatory response to elevated intracranial pressure (ICP) while, actually, patients may be in a hypovolemic state. Altered consciousness, coma, and neurological deficits predispose these patients to reduced oral intake while presence of vomiting and fever increases the fluid loss. Nakagawa et al. measured the changes in circulating blood volume in 73 patients during acute and very acute stages of SAH. The authors found that before surgery, patients in acute stage (within

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72 h of onset of SAH) had lower circulating blood volume (CBV), while those in very acute stage (within 6 h of onset of SAH) had similar CBV as other neurosurgical cases. On basis of these findings, authors suggested to maintain normovolemia in very acute stage and relatively hypervolemia during 3–5 days after surgery for patients who undergo surgery during acute stage of SAH [1]. The reduction in CBV is even more pronounced in patients with poor clinical grades [2].

On the other hand, positive fluid balance has been found to be associated with increased odds of transcranial Doppler vasospasm and prolonged hospital length of stay as well as poor functional outcome [3, 4]. In a retrospective study including 237 nontraumatic SAH patients, total daily amount of fluid and fluid balance were calculated over 15 days. The main fluids transfused constituted of nutritional compounds, IV drugs, and volume substitution. A higher daily fluid intake was associated with increased pulmonary fluid accumulation, prolonged mechanical ventilation, higher SAH, early brain edema score, development of anemia, DCI, and poor functional outcome [5]. The "triple-H therapy" propagated maintenance of hypervolemia as a modality for management of vasospasm for many years. Volume expansion leading to increase in cerebral blood flow (CBF) has been studied by several authors. In one such study, no difference in net fluid balance, mean global CBF, or measured blood volume was seen in patients receiving postoperative hypervolemic or normovolemic therapy [6]. Hypervolemia only increased cardiac filling pressures without resulting in increased CBF. The prophylactic hypervolemia thus does not confer any protection from delayed cerebral ischemia and has no role in the prevention of delayed ischemic neurological deficits (DIND) [6, 7]. However, on measurement of regional cerebral blood flow by positron emission tomography in patients having vasospasm, bolus of 15 ml/kg saline increased mean regional CBF in areas of the brain most vulnerable to ischemia [8]. This indicated that it had some beneficial effect when instituted therapeutically. The efficacy of triple H in improving outcome remains uncertain. A systematic review was carried out to study the effect of different components of triple-H therapy on cerebral perfusion. For analyzing the effect of prophylactic or therapeutic hypervolemia on CBF, seven studies were included [9]. When compared to baseline measurement, prophylactic hypervolemia did not result in significant change in CBF. Therapeutic hypervolemia resulted in a significant CBF increase (mean increase of 9 ml/100 gm/min) compared to baseline values in one of the studies [10]. Authors concluded that among three components, hypertension seemed to be more effective in increasing CBF than hypervolemia or hemodilution [9]. The American Heart Association/American Stroke Association and Neurocritical Care Society (NCS) recommend maintenance of euvolemia and normal circulating blood volume for the prevention of DCI [11, 12]. Prophylactic hypervolemia and intravascular volume contraction are not recommended. In patients with persistent negative fluid balance, fludrocortisone or hydrocortisone may be considered [12].

Right patient selection is one of the important factors for deciding about fluid management. For 413 patients enrolled in CONSCIOUS I trial, propensity scored-matched cohorts were assessed for development of DIND and outcome in those who received colloids between 3 and 14 days and had a positive fluid balance. The authors found that administration of colloids and positive fluid balance did not reduce the risk of DIND or DCI but was associated with worse 6–12-week functional outcome [13]. A negative fluid balance was associated with more infarcts in patients with severe angiographic vasospasm, while positive fluid balance was associated with worse outcomes. While Martini et al. found positive fluid balance to be associated with increased odds of vasospasm, Ibrahim et al. did not find positive fluid balance to be associated with DIND or delayed infarcts. Another recent retrospective study, including 223 aSAH patients, concluded that high early fluid input is associated with DCI [14]. This highlights the importance of judicious fluid management and careful identification of patients who need volume expansion.

Monitoring

Euvolemia as a goal for management is subject to individual interpretation and may highly vary if no monitor is used for guiding fluid administration. For maintenance of fluid balance, CBV needs to be monitored reliably. Volume replacement guided by clinical parameters like heart rate, blood pressure, and fluid balance is often unreliable. Central venous pressure is considered less reliable for volume assessment. Pulmonary artery catheter is a gold standard for cardiac output (CO) measurement but is not preferred these days because of its safety concern and cost. Similarly, serum sodium concentration may not be accurate enough to judge volume status of a patient. Patients with hyponatremia caused by cerebral salt-wasting (CSW) are hypovolemic, while that caused by syndrome of inappropriate antidiuretic hormone secretion (SIADH) are euvolemic. High brain natriuretic peptide is also unable to differentiate between hypovolemic and non-hypovolemic hyponatremic state after SAH [15]. This makes all these modalities less accurate for prediction of intravascular volume status. The use of radioactive isotopes for CBV measurement is reliable but impractical in clinical management. Pulse dye densitometry (PDD) is a noninvasive technique based on indicator dilution technique with pulse spectrophotometry, used for accurate estimation of CBV [16]. It measures the arterial concentration of injected indocyanine green by special PDD probes. However, for clinical management, we rely on dynamic monitors like echocardiography, passive leg raising, and other semi-invasive cardiovascular monitoring. Transesophageal echocardiography-derived parameters like superior vena cava collapsibility index (SVCCI) (>38%), aortic velocity time integral variability (>20%), and delta down (>5 mm Hg) have been found to be good predictors of fluid responsiveness in patients with aSAH [17]. Similarly, distensibility of the inferior vena cava (>16%) as measured by ultrasound is also a reliable predictor of fluid responsiveness in aSAH patients admitted in ICU [18]. The non-calibrated pulse contour systems like FloTrac, LiDCOrapid, and PulsioFlex use arterial pulse to calculate various direct and derived parameters like stroke volume, stroke volume variation, and cardiac index. Bedside transpulmonary thermodilution (TPT) technique has been found to be feasible and reliable for estimating cardiac index, global end-diastolic volume index (GEDVI), and extravascular lung water (ELW) on basis of which fluid management protocol can be devised [19]. The PiCCO (pulse index continuous cardiac output) device uses pulse contour analysis along with TPT to measure cardiac preload, cardiac output, afterload, contractility, and volume responsiveness. These monitoring devices have been found to be of great help in aSAH patients to understand the volume changes. TPT performed in poor-grade aSAH patients has shown higher ELW, pulmonary vascular permeability, and systemic vascular resistance (SVR) indices, indicating a heart failure-like afterload mismatch. Patients with DCI were found to have decreased GEDVI (hypovolemia) in the early stage of SAH [20]. GEDVI <822 ml/m and >921 ml/m best correlate with development of DCI and severe pulmonary edema, respectively [21]. As compared to TPT, cardiac index obtained from FloTrac is less reliable and underestimates CI but is an acceptable indicator for preload [22]. Other noninvasive monitors based on bioreactance have also shown to be reliable in initial studies [23].

Simonassi et al. conducted a systematic review and meta-analysis to understand whether standard compared with advanced hemodynamic monitoring can improve patient management and clinical outcomes after aSAH [24]. The authors found incidence of DCI was lower in advanced compared with standard hemodynamic monitoring group. Rest, there were no differences in neurological outcome, fluid intake, or development of pulmonary edema. Based on the results, these authors have proposed a flowchart to guide clinicians in decisions regarding the use of advanced hemodynamic monitoring in aSAH patients. Basic hemodynamic monitoring like ECG, invasive arterial pressure, and serial troponin measurement has been suggested in initial period in all patients. The use of advanced hemodynamic monitoring is suggested in (a) patients with poor SAH grade (WFNS grades 4–5); (b) those requir-

ing high dose of inotropes/vasopressors; (c) patients having cardiovascular complications (raised troponin values, abnormal wall motion, and/or ejection fraction <40%); (d) those having pulmonary complications (neurogenic pulmonary edema, respiratory failure); as well as (e) those developing neurological complications such as DCI and vasospasm (diagnosed clinically/radiologically).

The SAH guidelines state that monitoring of volume status may be beneficial and it is reasonable to monitor volume status in certain patients with recent aSAH by combination of CVP, pulmonary wedge pressure, and fluid balance [11]. Vigilant fluid balance management should be the basis for monitoring intravascular volume status, and no specific modality of noninvasive or invasive monitoring technology can be recommended over clinical assessment [12]. Also, CVP lines should not be placed solely for CVP measurement, and fluid management based solely on CVP measurement is not recommended [12]. Routine use of pulmonary artery catheters is also not recommended as it incurs risk and lacks clear benefit [12]. The European Society of Intensive Care Medicine (ESICM) guidelines recommend assessing the efficacy of fluid infusion in SAH patients with DCI using a multimodal approach that includes arterial blood pressure and reversal of neurological deficit as the main endpoints [25].

Goal-directed fluid therapy (GDFT) has been observed to be better than standard therapy for correction of fluid and hemodynamic derangements. It helps in earlier recognition and better management of dehydration and hemodynamic derangements [26]. For patients with poor SAH grade, early GDFT using TPT lowers the rate of DCI (5% vs 14%) and improves functional outcome when compared to standard therapy [27]. In a recent RCT, GDFT focusing on normovolemia and induced hypertension was found to be superior to standard therapy in terms of reduced rate of DCI after SAH along with a better 3-month functional outcome [28]. The authors used induced hypertension rather than hyperdynamic/hypervolemic therapy, based on current guidelines. GDHT is believed to improve not only the microcirculatory parameters but possibly also the microcirculation, which can be beneficial in prevention of DCI. Also, TPT-based hemodynamic management has shown better cognitive function compared with standard (pressure-based parameters and clinical examination) hemodynamic management in one of the studies [29]. Table 1 shows overview of studies using GDFT in aSAH patients.

The occurrence of systemic complications of aSAH like NPE and NSM is associated with poor outcome. TPT enables measurement of extravascular lung water and pulmonary vascular permeability index (PVPI) along with other cardiac indices enabling better management [32, 33]. This has been found to be helpful in understanding different etiologies (permeability or hydrostatic) of pulmonary edema, thus assisting with appropriate fluid management during NPE. The PVPI is high and GEDV low without cardiac dysfunction in permeability edema, while in hydrostatic edema, CO is low and GEDV high with cardiac dysfunction and without PVPI elevation [32].

Type of Fluid

The use of hypoosmotic fluids (0.45% saline and dextrose containing fluids) after acute brain injury is discouraged because of the risk of increase in brain edema and intracranial pressure. For the same reason, lactated Ringer's solution being hypoosmolar can cause increase in cerebral edema if infused in large volumes. The AHA/ASA SAH guidelines and the Neurocritical Care Society recommend against the use of large volumes of hypotonic fluids and intravascular volume depletion and prefer volume replacement with isotonic crystalloid [11, 12]. Hyponatremia is quite common in SAH patients, and it has been shown to increase incidence of brain swelling, cerebral vasospasm, and even mortality. The type of fluid infused can significantly affect sodium levels. To elucidate whether sodium content of the fluid infused affects mortality and morbidity in SAH patients, a clinical trial has been undertaken which is estimated to be complete by 2023 [34]. Isoosmolar crystalloid (0.9% saline) or hypertonic crystalloid (hypertonic saline) can shift water from the brain tissue into

Table 1 Studies utilizing goal-directed fluid therapy in aneurysmal SAH patients

	Patients	Intervention	Comparator	Results
Chui et al. (2022) [26] RCT	40 adult patients with aSAH within 5 days of aneurysm rupture undergoing endovascular coiling	Goal-directed therapy (GDT) guided by noninvasive cardiac output monitoring	Standard therapy	GDT resulted in earlier recognition and more consistent treatment of dehydration and hemodynamic derangements
Ali et al. (2019) [29] Cohort comparison study	84 aSAH patients admitted to ICU	Transpulmonary thermodilution (TPT) monitor-measured flow-based parameters	Traditional pressure-based hemodynamic parameters and clinical examination	TPT monitor-based hemodynamic management provides better cognitive outcome as assessed by MoCA score
Mutoh et al. (2009) [30] comparative study	116 patients with SAH who underwent surgical clipping and were diagnosed with vasospasm	Transpulmonary thermodilution (PiCCO plus)	Conventional fluid management protocol guided by pulmonary artery catheter thermodilution	Both techniques showed close agreement. Patients managed by PiCCO appear to have a therapeutic advantage over conventional methods for a better clinical course with less cardiopulmonary complications
Mutoh et al. (2014) [27] RCT	160 patients treated within 24 hours after subarachnoid hemorrhage	Early GDT guided by preload volume and cardiac output monitored by transpulmonary thermodilution	Standard therapy guided by fluid balance or central venous pressure or uncalibrated, less-invasive CO monitoring in patients with DCI	For patients with poor clinical grade, those who received early GDT had a significantly lower rate of DCI and mRS of 0–3 at 3 months than those who received standard therapy
Bloria et al. [31] (2021) RCT	50 adult patients undergoing surgical clipping	GDFT using left ventricular outflow tract velocity time integral (LVOT-VTI) measured by transesophageal echocardiography	CVP-guided fluid management	GDFT maintained blood pressure with lower volumes of intravenous fluid with no adverse impact on outcome

RCT randomized controlled trial, *aSAH* aneurysmal subarachnoid hemorrhage, *MoCA* montreal cognitive assessment, *CO* cardiac output, *DCI* delayed cerebral ischemia, *mRS* modified rankin scale, *CVP* central venous pressure

intravascular compartment, thus reducing cerebral edema. Hypertonic saline (23.5%) in dose of 2 ml/kg, when administered to poor-grade SAH patients, is associated with an increase in arterial blood pressure, cerebral perfusion pressure, flow velocity, brain tissue pH, and brain tissue oxygen content along with decrease in ICP [35]. Hypertonic saline has been found to be as effective as mannitol at reducing increasing ICP in aSAH Patients [36].

The hyperchloremia associated with saline infusion can lead to acute kidney injury (AKI) resulting in increased morbidity and mortality [37]. The incidence of hyperchloremia has been observed to be about 64% (Cl > 109 meq/l) with 60% developing levels >115 meq/l. This is associated with increased risk of AKI, prolonged ICU stay, and in-hospital mortality [38]. In a recent study, Sadan et al. compared the effect of two hypertonic solutions with different chloride content (23.4% NaCl versus 16.4% NaCl) on serum chloride concentrations in SAH patients who have already developed hyperchloremia (serum Cl > 109 mmol/L). Authors found both these solutions to have similar effects on ICP reduction. The chloride load and AKI rate were significantly less in 16.4% Nacl/Na-acetate infusion [39].

Balanced salt solutions include crystalloids as well as hydroxyethyl starch (HES) solutions. These fluids decrease the risk of hyperchloremic

acidosis in brain-injured patients as compared to saline solutions [40]. Lehmann et al. randomized 36 SAH pateints to receive either normal saline or balanced crystalloid and colloid solutions for 48 hours. Saline-based fluids led to more rate of hyperchloremia, hyperosmolality, and positive fluid balance >1500 ml early after SAH. Hypoosmolality and hyponatremia were not more frequent in the balanced solution group [41]. HES has been associated with development of renal insufficiency in patients having sepsis. But no association between application of HES and development of AKI has been found especially in aSAH patients with intact renal function and without an elevated baseline creatinine [42, 43]. Administration of colloids during the DIND risk period has not been found to be beneficial in terms of reduction of DIND and delayed infarcts [13]. Albumin has been used in aSAH patients to induce hypervolemia and was found to improve clinical outcome. A phase I pilot study conducted at six North American sites investigated the safety and tolerability of 25% human albumin in patients with subarachnoid hemorrhage. Albumin in dose up to 1.25 g/kg/day was administered for 7 days, and it was tolerated by patients without any major complications. Doses higher than this resulted in significant cardiovascular complications. However, as guidelines no longer recommend induction of hypervolemia, its utility for this aspect is doubtful. More trials are required to investigate its neuroprotective action in human trials [44].

To conclude, fluid therapy should target maintenance of euvolemia that can be achieved by clinical assessment along with close hemodynamic monitoring. Both hypovolemia and hypervolemia have been found to be associated with poor outcome. In patients developing DIND, hypervolemia has to be induced through the use of isotonic crystalloid infusion. Evidence is still not strong enough for recommending the use of colloids as maintenance fluid, even though studies have shown that they are safe to use in aSAH patients without underlying renal disease.

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Fluid Management in Traumatic Brain Injury

John Dawson, Pouya Entezami, and Archana Mane

Abstract

The major goal of perioperative and critical care management of traumatic brain injury patients is to prevent secondary injury. Understanding the various choices for fluid management in the prehospital and preoperative stages is essential in minimizing secondary injury to the brain and providing optimal care to patients with traumatic brain injury. Adequate fluid resuscitation is focused on maintaining cerebral perfusion pressure and oxygen delivery to the brain. The major types of resuscitative fluids are crystalloids, colloids, and blood products. Balanced crystalloids such as plasma-lyte and lactated ringers are relatively hypotonic and carry a theoretical risk for worsening cerebral edema. Given these factors, normal saline is the preferred IV fluid for management of the TBI patient. Regarding red blood cell transfusion, the classic approach has been to transfuse red blood cells (RBCs) in patients with TBI to maintain a hemoglobin (Hb) level greater than 10g/dl or hematocrit greater than 30% for the theoretical principle of maintaining optimal oxygen-carrying capacity. However, more recently, clinical practice has moved toward a restrictive transfusion strategy (maintaining Hb concentrations ≥7g/dl) after studies showed liberal transfusion strategies (Hb ≥10g/dl) may be unnecessary or perhaps even harmful in the general critical care setting. Hyperosmolar therapy is a common tool in the armamentarium used to manage raised ICP. There is little consensus regarding the exact agent, administration (bolus vs infusion), and timing/duration of administration. Commonly used options for hyperosmolar agents include mannitol and hypertonic saline. This chapter highlights the current recommendations in the fluid management of patients with traumatic brain injury.

Keywords

Etiology of TBI · Incidence and burden of TBI · Primary and secondary brain injury · Preoperative and intraoperative fluid management · Crystalloids vs. colloids in TBI · Brain Trauma Foundation · Lund concept · Blood-brain barrier · Cerebral perfusion · Intracranial pressure · Blood pressure parameters

J. Dawson
Department of Anesthesiology, Albany Medical College, Albany, NY, USA

P. Entezami
Department of Neurosurgery, Albany Medical College, Albany, NY, USA

A. Mane (✉)
Department of Anesthesiology, Albany Medical College, Albany, NY, USA

AMC Anesthesiology Group, Albany, NY, USA
e-mail: manea@amc.edu

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Introduction

Traumatic brain injury (TBI) occurs when neurological dysfunction and damage result from a force transmitted to the head or body. The US Department of Veterans Affairs and the Department of Defense's Clinical Practice Guideline for Management of Concussion/mTBI (version 1.0, April 2009) define TBI as "a traumatically induced structural injury and/or physiologic disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event: any period of loss of or a decreased level of consciousness (LOC), any loss of memory for events immediately before or after the injury (post-traumatic amnesia [PTA]), any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.), neurologic deficits (weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient, or intracranial lesion" [1, 2].

An estimated 69 million individuals worldwide each year sustain a TBI of varying degrees. Proportionally, the number of TBIs resulting from road traffic collisions (RTC) was greatest in low to middle countries in Africa and Southeast Asia (roughly 56% of the population per year) and lowest in North America (25%). The incidence of RTC was similar in Southeast Asia (1.5%) and Europe (1.2%). The overall incidence of TBI was greatest in North America (1299 cases per 100,000 people) and Europe (1012 cases) and least in Africa (801 cases) and the Eastern Mediterranean (897 cases) [3].

In high-income countries, falls and RTCs are the most common causes of TBI, though RTCs dropped from 39% to 24% between 2003 and 2012, while falls increased from 43% to 54% (especially in the elderly) in a similar time period. Conversely, in low- to middle-income countries (LMIC), the population with the peak of TBI incidence is younger, highest in those ages 28–31 years old. Between 1,730,000 and 1,965,000 lives could be saved if global trauma care were improved in LMIC; this represents a significant disease burden. The ability to apply clinical research standards of high-income countries in LMICs represents an important future international research topic [4].

Brain Injury Classification

Brain injury is classified into various ways. Injuries can be focal or diffuse. Focal injuries consist of anatomic lesions such as subdural and epidural hematomas, or bleeding into the parenchyma or ventricles, and traumatic subarachnoid hemorrhage. Diffuse injuries, such as diffuse axonal injuries or hypoxic insults, may also occur.

Brain injuries may also be classified as primary or secondary. Primary TBI is the result of the forces of the trauma causing direct damage. The primary insult results in damage to brain tissue and impaired regulation of cerebral blood flow (CBF). It also causes oxidative stress, upregulation of inflammatory mediators, and vasospasm. These processes ultimately lead to cell death and generalized brain edema [5]. Secondary injuries can result from ischemia, increased intracranial pressure, and decreased cerebral perfusion pressure, all of which worsen the clinical situation. In the most severe injuries, this cascade can lead to brain herniation and death. Preventing this secondary damage is the goal of perioperative and critical care management of TBI patients.

Systemic insults (viz., hypotension, hypoxia, and hypercarbia) are associated with increased mortality. Management strategies focus on preventing secondary injury by maintaining adequate CBF and preventing hypoxia [6]. A substitute for CBF should be maintained utilizing principles based on the Monro-Kellie doctrine and CPP by optimizing mean arterial pressure (MAP) via fluid administration and vasopressors and/or decreasing ICP via sedation, bedside maneuvers, cerebrospinal fluid (CSF) drainage, hyperosmolar therapy, and even barbiturate coma or decompressive craniotomy (DC) in refractory cases. Clinical exam, direct ICP monitoring, and imaging as indicated all help guide strategies to reduce ICP. New modalities such as brain tissue

Table 1 Glasgow Coma Scale (GCS)

Eye opening	Best verbal response	Best motor response
4: Spontaneous	5: Oriented	6: Obeys commands
3: To speech	4: Confused	5: Localizes across midline
2: To pain	3: Inappropriate words	4: Withdraws
1: No eye opening	2: Incomprehensible sounds	3: Flexion
	1: No verbal response	2: Extension
		1: No movement
Total GCS: 3–15		

oxygen (PbtO2) monitoring are yet understudied, but are promising in optimization of CBF [7, 8].

The Glasgow Coma Scale (GCS) is a commonly used tool to grade the severity of head trauma at the time of presentation (Table 1). The scale classifies the trauma as mild, moderate, or severe. Mild traumas (GCS 13–15) are the most common (75–85%) and are often seen in sports injuries and low-impact injuries (such as ground-level falls). In cases of moderate (GCS 9–12) and severe (GCS 3–8) TBI, a linear correlation to poor outcome is noted. This includes transient or even permanent neurologic deficits, with the most critical patients progressing to a vegetative state or death. While imperfect, GCS on arrival is commonly used to portend prognosis. Loss of consciousness (LOC) or post-traumatic amnesia (PTA) is also used to predict outcomes [9].

Sodium Homeostasis

In a healthy person, plasma osmolality is maintained within 2% of normal osmolality values (275–295 mOsm/kg). Increases in osmolality trigger the release of antidiuretic hormone (ADH) from the posterior pituitary and a sensation of thirst. ADH binds to V2 receptors of the collecting tubules causing reabsorption of water to restore plasma osmolality. The hypothalamic response to thirst is simultaneously stimulated causing the person to increase fluid intake. Pituitary damage secondary to TBI was reported as early as 1918 by Cyran and others, positing that tearing of blood vessels and stretching of nerves cause damage to the hypothalamus and pituitary glands, contributing to fluid balance aberrancies following TBI [10].

Disorders of sodium and fluid regulation are common in patients with a TBI. Serum osmolality, most easily affected by intravascular and extravascular salinity, is important for the control of cerebral edema and prevention of secondary brain injury. Serum sodium is regulated by body water adjustments and the release of arginine vasopressin (AVP). This hormone stored in the posterior pituitary is released by a stress response in TBI resulting in hypoosmolar states and triggering cerebral edema. Management of TBI patients requires meticulous management of serum sodium and fluid levels.

Hyponatremia is defined as serum sodium less than 135 mEq/L. The incidence of hyponatremia in TBI patients ranges from 9.6 to 51%, most commonly manifesting as urine sodium greater than 40 mEq/L. Causes of hyponatremia in TBI include cerebral salt-wasting (CSW), syndrome of inappropriate antidiuretic hormone secretion (SIADH), inadequate set intake, and damage to the pituitary gland. Hyponatremia can cause arrhythmias by altering the membrane potential and poses a danger from movement of water from the plasma to the brain cells causing the cells to swell and increasing the ICP [11]. Hyponatremia should be corrected by a maximum of 10–12 mmol/L on the first day and then 18 mmol/L over the next 2–3 days. Management of low serum sodium states in TBI is tricky. Restricting fluid could be dangerous considering it could lead to poor cerebral perfusion and cerebral ischemia [12]. Early use of fludrocortisone for the management of hyponatremia has successfully shown to decrease hospital stay [12].

Acute hypernatremia states with sodium levels greater than 145 mEq/L may need correction depending on the serum sodium levels and etiology. Causes of hypernatremia in TBI include diabetes insipidus (DI). In addition, TBI patients' poor cognitive status prevents adequate oral fluid intake to compensate for the losses, with resul-

tant severe dehydration and hypernatremia. Sodium-lowering agents include hypotonic sale, free water, and vasopressin. Correction helps bring the shrunken neuronal cell to its original size. Avoidance of cerebral edema that could result from this therapy is avoided by correcting the sodium levels gradually [12]. However, as discussed later, hypernatremia is a powerful tool in reducing ICPs if utilized and monitored appropriately.

Prehospital Fluid Management in TBI

The primary goal of perioperative management of TBI patients is to prevent secondary injury. Understanding the various choices for fluid management in the prehospital and preoperative stages is essential for optimizing care. Despite the growing understanding and treatment options for TBI patients, prognoses remain poor. Severity of the primary injury heavily determines the outcome with secondary injuries resulting in progressive deficits [13]. Hypotension remarkably worsens outcomes. Fluid administration is the most common method of resuscitation and treating hypotension in the field. Due to a lack of data, the optimal use of fluids is based on clinical scenarios and expert opinions [14, 15]. The choice of fluids to be given in the prehospital setting is a topic of debate at this time.

The Brain Trauma Foundation (BTF) strives to develop guidelines for the prehospital management of TBI. They concluded that maintaining systemic blood pressure greater than 90 mmHg by adequate fluid resuscitation (optimizing CPP) should be evaluated as frequently as possible [16]. Conventionally, isotonic crystalloids such as normal saline or lactated ringers are used. The solutes in these fluids are small enough to move freely between the intravascular and interstitial spaces. However, intravascular volume expansion is limited. Normal saline in large amounts may give rise to hyperchloremic acidosis. Hypertonic saline and volume expanders such as albumin may be used. The SAFE study (saline vs. albumin for resuscitation in TBI) conducted in 2004 compared the use of either 4% albumin or normal saline for fluid resuscitation and found no difference in outcomes at 28 days [17]. However, a post hoc follow-up study (SAFE–TBI) comparing intravascular fluid resuscitation in ICU patients with TBI with saline versus albumin demonstrated higher mortality rates among patients with severe TBI who received 4% albumin than those who received saline. At 24 months, there were significantly fewer favorable neurologic outcomes in the albumin group than in the saline group. Additionally, there were fewer favorable neurologic outcomes in patients with severe TBI in the albumin group than in the saline group. The authors suggest from their findings that in acute resuscitation of severe TBI patients, saline is preferable to albumin [18].

A different framework for fluid management than the BTF framework is the “Lund concept.” The “Lund concept,” originated in Sweden over 20 years ago, involves volume-targeted strategy for ICP control and is considered controversial. It operates on the premise of disruption of the blood-brain barrier and impairment of cerebral autoregulation after TBI and that therefore the transcapillary water exchange is determined by the differences in hydrostatic and colloid osmotic pressure between intracapillary and extracapillary compartments. The concept suggests that controlling the transcapillary osmotic and hydrostatic differences is the only way of inducing transcapillary reabsorption of interstitial fluid. It utilizes complex pharmacotherapy combinations involving α2-agonist clonidine, β1-antagonist metoprolol, low-dose thiopental, dihydroergotamine, and maintaining colloid osmotic pressure via albumin administration and red blood cell transfusion [19]. The Brain Trauma Foundation differs from this by stressing that brain damage is not dependent on fluids, but rather on CPP and the management of ischemia and secondary injury.

Fluid Management in Polytrauma Patients with Concurrent TBI

Administering volume therapy and hemostasis is critical in trauma patients with hemorrhagic shock. In a recent study, one group of patients was given 0–1000 mL of fluid, while the second group received 1500 mL. In patients with severe TBI, reduced volume therapy did not correlate to worse outcomes. Higher volumes did not improve neither mortality rates nor the GOS outcome (Glasgow Outcome Scale) [5]. However, administration of higher volumes was associated with reduced hemoglobin (Hb) and reduced coagulation capability. There was no significant reduction shown in mortality rate with increasing volumes. The study data did demonstrate that prehospital volume administration of more than 1500 mL does not improve mortality in severely injured patients with severe TBI.

Fluid resuscitation has been used aggressively in the past for trauma patients. The new approach for the treatment of traumatic hemorrhagic shock is known as damage control resuscitation (DCR). This strategy—used initially by the military—is being applied in civilian trauma care. The goal of DCR is to target conditions that exacerbate hemorrhage. The most commonly conceived elements of this include minimizing crystalloid resuscitation, permissive hypotension, hypothermia control, preventing acidosis, using antifibrinolytics, and blood product transfusion. Crystalloid administration is associated with increased inflammatory markers and increased neutrophil activation. This inflammatory response may create a detrimental situation with tissue leakage and hypotension. This vicious cycle is referred to as resuscitation injury, previously termed reperfusion injury. Permissive hypotension to decrease bleeding in trauma patients is practiced in many centers. It is important to note, however, that in patients with TBI, permissive hypotension is absolutely contraindicated. It has been shown that even a single episode of hypotension causes doubling of mortality in this patient population. Although there still remains some debate on the subject, any treatment resulting in hypotension in a TBI patient remains contraindicated at this time. This results in significant controversy and discussion amongst teams, especially in the acute phase of resuscitation of the polytrauma patient. Large-volume crystalloid resuscitation may lead to other situations including acute respiratory distress syndrome (ARDS), compartment syndromes, and coagulation problems [20]. Recommendations to take care of trauma patients with suspected TBI is to transport them to a level 1 trauma center without delay, with fluid administration kept to a minimum. In summary, the recommendation is to resuscitate patients with TBI to maintain a cerebral perfusion pressure between 50 and 70 mmHg.

Intravenous Therapy in TBI

Crystalloid Fluids

Maintaining normotension is as much a priority for TBI patients as it is for all critically ill patients. To this end, hemodynamic goals are centered around maintaining euvolemia and optimizing cerebral perfusion pressure. Balanced crystalloids such as plasma-lyte and lactated ringers are relatively hypotonic and carry a theoretical risk for worsening cerebral edema. Given these factors, normal saline is the preferred IV fluid for management of the TBI patient. The SAFE trial further lent evidence for the use of normal saline as the ideal fluid for the TBI patient [17].

Blood Product

The classic approach in TBI patients has been to maintain a hemoglobin (Hb) greater than 10 g/dl or hematocrit greater than 30% by transfusing red blood cells (RBCs), theoretically to maintain optimal oxygen-carrying capacity [21]. However, after studies showed that liberal transfusion to Hb ≥10g/dl may be unnecessary or even harmful in critical care, clinical practice has recently moved toward a more restrictive strategy of transfusing to maintain Hb concentrations ≥7g/dl. Managing coagulopathy is a central component of TBI management. Patients on anticoagulation should

receive reversal agents to prevent worsening of intracranial hemorrhage. While there is insufficient evidence for platelet administration guidelines, a commonly accepted threshold for transfusion includes platelets <75,000/microL.

Osmotic Therapy

Hyperosmolar therapy is a common tool in the armamentarium used to manage raised ICP. There is little consensus regarding the exact agent, administration (bolus vs infusion), and the timing/duration of administration [22]. Some clinicians use hyperosmolar therapy as needed, while others administer it in all TBI patients [23]. Mannitol affects serum osmolality and along with induced hypertonicity is the mainstay in the medical management of raised ICPs [24]. Osmotic therapy is chosen when patients are symptomatic from cerebral edema and/or have a measurable increased ICP (usually greater than 22 mmHg). Osmotic therapy aims to create an osmolar gradient across the blood-brain barrier. Water is drawn across the barrier which leads to a decrease in brain volume and subsequent decrease in ICP. The efficacy of hyperosmolar therapy diminishes with time which limits the prolonged use of such therapies. Mannitol's short duration of action limits its long-term use in the critical care environment. Mannitol is administered in boluses of 0.25–1 g/kg every 4–6 h. Mannitol carries a higher risk of volume depletion leading to hypovolemia and hypotension. As with other therapies, serial laboratory testing is required.

The Brain Trauma Foundation (BTF) presently recommends that 20% mannitol in a dose of 0.25–1.0 mg/kg be used to decrease ICP. "The rationale for doing so is to maintain sufficient recognition of the potential need for hyperosmolar therapy to reduce ICP, while acknowledging that more research is needed to inform more specific recommendations." Due to the incomplete evidence regarding hypertonic therapy, official recommendations do not yet exist. Monitoring requirements include analyzing serial serum electrolytes (every 4–6 h), kidney function, and serum osmolality.

Hypertonic Saline

Options for hypertonic saline include gradual administration of 3% NaCl and boluses of 23% NaCl. An infusion of hypertonic saline is titrated to an initial sodium goal of 145–155 mEq/L. Potential adverse effects include circulatory overload leading to pulmonary edema and hyperchloremic metabolic acidosis. Boluses are used when there is a concern for impending cerebral herniation, typically given in 30-mL boluses infused over 10 min. Theoretically, hypertonic saline has several advantages over mannitol, particularly the fact that hypovolemia and volume depletion do not occur with hypertonic saline, making it the safer choice for the trauma patient with ongoing blood loss, hypovolemia, or hypotension. Potential adverse effects include pulmonary edema and circulatory overload, as well as increased chloride burden which may result in non-anion gap metabolic acidosis [25].

Conclusion

The understanding of fluid resuscitation and management in TBI patients in the prehospital, surgical, and critical care settings plays a vital role in achieving the best possible outcomes for this particularly challenging patient population. Though the prognosis for severe TBI patients remains poor, resuscitation of patients in the acute phase combined with a thorough understanding of the available management options is required.

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Fluid Management in Spine Surgery

Mohamed Samy Abdel Raheem

Abstract

Perioperative fluid therapy (PFT) is an important component of perioperative care of patients undergoing major surgical procedures. Notably, spine surgery is one of those complex procedures. In addition to the well-recognized risks and limitations of PFT in major surgeries, spine surgery is associated with unique patient and surgical factors that render PFT a real challenge. These factors include: the patient's preoperative morbid status, the extent of the surgical procedure, the impact of patient position, the operative blood loss, and the high necessity to maintain spinal cord perfusion. This chapter is intended to discuss the perioperative fluid and blood management of patients undergoing spine surgery in view of the associated challenges and the current available evidence.

Keywords

Spine surgery · Fluid therapy · Perioperative

Introduction

Spine surgery is increasingly used to treat patients with spine instability, tumors, congenital deformity, infections and degenerative diseases [1]. Anesthetic management of patients undergoing spine surgery involves several challenges owing to the patient's premorbid conditions [2], the effects of position during surgery [3], the anticipated blood loss [4], the need to maintain spinal cord perfusion and function [5], and the risk of serious postoperative complications [6–8]. Perioperative fluid therapy (PFT) is an integral part of the overall anesthetic management. Nevertheless, the fluid management strategies, in general, have been a subject of a considerable debate involving the volume and the type of fluid as well as some myths regarding the replacement of losses. Though several studies have investigated PFT during major surgical procedures, those related to spine surgery are scarce.

This chapter is intended to discuss the perioperative fluid (including blood) management of patients undergoing spine surgery, considering the aforementioned challenges and highlighting the current available evidence. Therefore, it is crucial to shed some light on the factors that govern the management strategy including the current status of the long-standing fluid management controversy, the role of PFT as an important component of the enhanced recovery after surgery pathways (ERASPs) [9], as well as the impact of

M. S. Abdel Raheem (✉)
Department of Anesthesia and Intensive Care, Asyut University, Assiut, Egypt
e-mail: msraheem@doctors.org.uk

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certain surgical and patient factors on PFT and hence on the postoperative outcome.

Current Status of the PFT Debate

Perioperative Fluid Therapy

Perioperative fluid therapy is a fundamental component of perioperative management and greatly influences the postoperative outcome. The goals of PFT are to maintain euvolemia, cardiac output, organ perfusion, and oxygen delivery [10]. In addition, PFT should maintain the balance between colloid oncotic pressure and capillary hydrostatic pressure and preserve the integrity of the endothelial glycocalyx. A damaged glycocalyx causes leucocyte adhesion, platelet aggregation, and increased vascular permeability leading to interstitial edema [11]. Despite extensive research, the optimal PFT strategy is still controversial and debated.

Perioperative hypovolemia decreases blood flow to vital organs; the resulting vasoconstriction further impairs organ and tissue perfusion leading to ischemia. On the other hand, excess intravenous fluid therapy causes tissue edema and may impair organ system function with a higher incidence of postoperative complications [12].

Liberal, Restrictive, or Goal-Directed?

Liberal fluid therapy strategy is the traditional "textbook recipe" of infusing large volumes of fluids based on a general formula involving body weight, extent of surgical trauma, and some outdated concepts. Considering that the preoperative patients are hypovolemic as a result of preoperative fasting, the need to replace third space losses and the use of bowel preparation (if any) as well as the replacement of blood loss by three times a volume of crystalloids are currently disputed.

Studies have shown that healthy patients maintained a normal blood volume even after prolonged fasting [13], that the third space has never been proven [14] and is merely an artificial construct from the past [15], and that mechanical bowel preparation for colorectal surgeries showed no real difference in terms of outcome and can be abandoned [16]. Furthermore, in a systematic review, the common belief that intravascular losses require three times volume replacement with crystalloids (3:1 ratio) as opposed to colloids has been regarded as an overestimate and that the ratio of 2:1 or less should be considered [17].

In addition, perioperative management of blood volume changes mandates a careful assessment of several clinical and physiological variables [10]. Intraoperative hypotension during general and neuraxial anesthesia is not always a result of hypovolemia. Hypotension can be induced by anesthetic agents, positive pressure ventilation, and surgical factors. Therefore, it should not be automatically considered as a trigger for fluid administration regardless of its etiology [18, 19].

In a retrospective analysis, autopsy of 13 cases with fatal postoperative pulmonary edema revealed hypervolemia with no other causes of death [20]. In 1999, the National Confidential Enquiry into Perioperative Deaths (NCEPOD) highlighted overhydration as a risk factor leading to postoperative death. Therefore, careful fluid management in vulnerable patients was recommended by the NCEPOD [21]. Postoperative fluid-induced weight gain was linearly associated with a higher mortality [15]. The reported complications of liberal PFT including interstitial edema, organ dysfunction, adverse outcome, and mortality triggered the need for a more restrictive strategy for PFT.

Restrictive fluid therapy strategy was investigated in comparison to the liberal strategy in terms of the associated complications, the impact on postoperative outcome, and the in-hospital length of stay (LOS). Several randomized controlled studies looked at those variables with conflicting results ranging from a better outcome favoring the restrictive strategy [22–24], a harmful effect associated with fluid restriction [25, 26] particularly renal hypoperfusion [27] or no difference in outcome [28, 29]. More recently, a large international randomized controlled trial was published (the RELIEF study). It included 3000 patients undergoing major abdominal sur-

gery. A restrictive approach aiming at a net zero fluid balance was compared to the liberal strategy. The authors concluded that as opposed to the liberal strategy, the restrictive approach did not result in a higher rate of disability-free survival but was associated with a higher rate of acute kidney injury [30]. However, those studies varied in their design, the type of fluid administered, the definition of the restrictive approach, and the outcome variables [11]. As a result, the comparison between both strategies were not well defined and did not yield enough evidence to generate evidence-based guidelines [31]. On the contrary, they created more questions than answers [32]. As a result of the conflicting results, the goal-directed therapy (GDT) [33] emerged as an alternative approach. The aim of GDT is to avoid the complications of hypovolemia or hypervolemia by administering fluid according to the actual need of each patient.

Goal-directed strategy (*GDT*) aims at individualizing the PFT to achieve a set of hemodynamic goals; the net fluid volume required to reach such goals depends on the patient's individual fluid responsiveness. Traditional hemodynamic measurements do not have the ability to guide fluid administration in this settings [11]. A healthy patient may lose up to 25% of the blood volume without a noticeable decrease in blood pressure or an increase in heart rate. Moreover, neither the central venous pressure value nor the rate of its change can accurately predict fluid responsiveness [34]. On the other hand, more sensitive, yet minimally invasive, hemodynamic monitors including esophageal Doppler and arterial waveform analysis (pulse pressure variation and stroke volume variation) have been used to detect fluid responsiveness. The use of esophageal Doppler to guide fluid responsiveness was associated with a favorable postoperative outcome in several surgical settings [35–37]. Therefore, esophageal Doppler was recommended for use in the UK (NICE) [38], the USA (Medicare) [39], and Europe (ERASPs) [40] to guide fluid therapy in major surgical procedures. In a multicenter randomized controlled trial (FEDORA trial) [41], the effect of GDT on postoperative complications in low- and moderate-risk surgical patients was investigated. The findings revealed that esophageal Doppler monitor-guided GDT resulted in reduced postoperative complications and shorter hospital LOS in low- and moderate-risk patients undergoing intermediate risk surgery, with no difference in mortality. Nevertheless, in a recent randomized controlled trial (RCT) [42], restrictive and GDT strategies were compared in patients undergoing major abdominal surgery. Both strategies were associated with similar incidence of moderate to severe postoperative complications. More recently, a 20-year systematic review was conducted to investigate the overall incidence of complications when GDT was used as opposed to controls. The authors reported that irrespective of the volume of fluid infused, GDT approach reduces postoperative complications but not perioperative mortality [43]. Therefore, the uncertainty still exists concerning the relative benefits and superiority of the restrictive and GDT strategies.

Enhanced Recovery After Surgery Pathways (ERASPs) Recommendations

Enhanced recovery after surgery pathways were developed aiming at optimizing the patients' postoperative outcome through maintaining normal physiology in the perioperative period while reducing the incidence of postoperative complications and readmissions [44]. PFT is one of the main components of ERASPs that implements the current evidence-based practices of fluid management. Optimizing PFT starts in the preoperative period, through the intraoperative phase, and continues to the postoperative period. ERASPs' preoperative goal is to render the patient euvolemic prior to surgery. Intraoperative goals are to provide the optimal fluid management that preserves the intravascular volume while avoiding crystalloid-induced excess salt and water uptake. Postoperatively, the aim is to allow early resumption of oral fluid intake, avoiding intravenous fluid unless clinically indicated [9]. Preoperatively, ERASPs recommend encouraging patients to consume carbohydrate-containing clear fluid until 2 h prior to induction

of anesthesia. Intraoperatively, achieving euvolemia is recommended using an individualized approach. ERASP guidelines stated that GDT approach may be suitable for some patients; otherwise, a restrictive zero-balance approach may be reasonable. However, targeting a perioperative zero balance was criticized for being associated with a higher incidence of acute kidney injury [30]. Recently, a "moderately" restrictive approach was suggested with a net fluid balance of 1–2 L at the end of surgery [45]. Postoperatively, initiation of early oral intake and avoiding intravenous fluid therapy are recommended [46]. Postoperative weight gain is a marker of high morbidity and mortality [15]. Therefore, ERAPs recommended avoiding a weight gain of more than 2.5 kg [47].

Surgical and Patient Factors

Spine surgery comprises a wide range of procedures for surgical management of deformities, infection, neoplasms, degenerative changes, and trauma that may involve spine stabilization. Spine surgical procedures may be lengthy, involve multiple vertebral levels, entail certain patient positioning, and result in excessive blood loss. Significant blood loss during spine surgery can result in hemodynamic changes that may jeopardize the spinal cord perfusion leading to drastic consequences. Moreover, complex spine surgeries may be performed on elderly patients with frailty and reduced physiological reserve, oncology patients with significant comorbidities, or trauma patients with associated injuries. These surgical and patients' factors increase the complexity of PFT for spine surgery patients. Therefore, their fluid management strategy should be tailored and individualized considering the current recommendations for PFT as well as the impact of surgical and patient factors on fluid management.

Surgical Factors

Blood Loss

Multilevel, reconstructive, and spine fixation procedures are associated with significant blood loss that requires allogenic blood transfusion [48]. In major spine surgery, blood loss from decorticated bone, osteotomies, and muscle stripping may reach 10–30 $ml \cdot kg^{-1}$ [49]. Prone position and high intra-abdominal pressure [50], the number of spine levels involved [49] and tumor surgery [51] is associated with higher blood loss. Significant blood loss and allogenic transfusion result in higher incidence of postoperative morbidity, adverse outcome, and hospital LOS [52]. In the USA, a retrospective analysis of closed claims following surgical procedures revealed that spine surgery represented 14% of the claims involving massive hemorrhage [53]. Therefore, it is imperative to implement preventive measures to minimize blood loss as well as the need for allogenic blood transfusion using pharmacological and non-pharmacological techniques. Careful patient positioning to avoid intra-abdominal pressure increase and reduce venous engorgement at the operated spine segment can reduce blood loss per vertebral level by about 50% [54]. In addition to good surgical techniques, anesthetic techniques aiming at maintaining stable hemodynamics within the limits of normal range of the individual patient, providing adequate analgesia, and avoiding hypervolemia are needed to avoid excessive blood loss during spine surgery. The intraoperative use of controlled hypotension for spine surgery is not recommended in view of several limitations including the lack of consensus regarding the hemodynamic thresholds as well as the time limits for its use and its associated complications including postoperative delirium and cognitive dysfunction, postoperative neurological deficits, ischemic strokes, postoperative visual loss (POVL), and acute myocardial and kidney injury [54]. Cell saver use is used by many centers to reduce the need for allogenic blood transfusion; however, studies revealed conflicting data regarding its value in this context. In a recent meta-analysis, cell saver use was associated with reduced number of units transfused intraoperatively; however, there was no difference in the postoperative or the total number of units transfused [55]. Pharmacological techniques for reducing blood loss include the use of tranexamic acid (TXA) as a fibrinolytic agent. Recently, TXA use in patients undergoing

long-segment spine fusion surgery resulted in reduced intraoperative blood loss and postoperative transfusion requirement with no increase in the thrombotic complications [56, 57]. Point-of-care devices (thromboelastography and thromboelastometry) can be used to aid diagnosis and guide management of blood loss-induced hemostatic derangements [58].

Prone Position

Prone position is frequently used for spine surgery. Studies revealed that prone position is associated with a significant reduction in cardiac output and cardiac index without affecting other hemodynamic parameters [3]. Nevertheless, prone position can result in a mechanically induced increase in intra-abdominal and airway pressures. The increase in both pressures can significantly compress the inferior vena cava, reduce venous return and cardiac output, and engorge the valveless epidural venous plexuses. As a result, it is associated with increased intraoperative blood loss [59, 60], impaired spinal cord perfusion [61], and a higher incidence of lower limb thrombosis [62]. Moreover, prone position can be associated with other serious complications including airway and facial edema leading to delayed extubation and POVL. Spine surgery accounted for 70% of the non-ophthalmic causes of visual loss as a result of ischemic optic neuropathy or central retinal artery occlusion [63]. Though it was reported that the incidence of delayed extubation or reintubation was less in spine surgery patients when a restrictive fluid strategy was implemented [64], the association between PFT and POVL remains controversial [65].

Spinal Cord Perfusion and Function

Hypovolemia, hypotension, and low cardiac output during spine surgery can lead to spinal cord ischemia. Moreover, certain spine surgical procedures, such as scoliosis surgery, can jeopardize the spinal cord blood supply. Impaired spinal cord perfusion is detrimental to its function leading to serious neurological complications [66]. The risk of such complications ranges from 1 to 2% being higher in combined approaches, revision procedures, severe deformity correction, and intraoperative hypotension [67]. Intraoperative monitoring (IOM) of the spinal cord somatosensory (SSEP) and motor evoked potentials (MEP) is therefore essential in major spine surgery for the monitoring of the spinal cord function [68] and the immediate detection of abnormalities. This combined monitoring approach is associated with a higher sensitivity and specificity for detecting neurological damage during deformity correction in adult [69] and young patients [70]. In hypovolemic-hypotensive animal models, an increased latency of MEP and a decreased amplitude of SSEP were reported with a return to the baseline values when the blood volume was restored. Moreover, the duration of hypotensive episode was found to have a significant impact on the neurological outcome [71]. In a retrospective study, hypotension during spine deformity surgery was found to be the commonest cause of MEP changes indicating spinal cord ischemia. Restoration of blood pressure values was timely correlated with reversal of these changes in MEP [72]. In order to reverse its effects on spinal cord function, it is important to manage hypotension depending on its etiology whether hypovolemia or vasodilation. In hypovolemic hypotension, restoration of the mean arterial pressure using vasopressors did not reverse the MEP changes as it did in hypotension due to vasodilation [73] emphasizing the importance of augmenting the blood flow and oxygen delivery to the spinal cord rather than merely increasing the mean arterial pressure [74]. In order to obtain reliable results, the electrophysiological changes derived from SSEP and MEP monitoring should be carefully interpreted. In addition to some surgical factors, it is prudent, therefore, to consider the anesthetic factors that may affect either their latency, amplitude, or both. All inhalational anesthetic agents result in a dose-dependent reduction in the MEP amplitude [75]. Cortical-evoked responses are more vulnerable to the effects of anesthetic agents than the spinal-evoked ones. Similarly, MEP are more susceptible to the effects of anesthetic agents compared to SSEP [76]. Though a bolus dose of propofol has a potent suppressant effect on cortical responses, total intravenous anesthesia (TIVA) using propofol has been recommended to mitigate the effects of inhalational anesthetic agents on MEP [77].

TIVA using propofol with fentanyl or remifentanil provided adequate MEP recordings in 97% of patients who were neurologically intact [78]. The use of depth of anesthesia monitors such as bispectral index (BIS) has been recommended [79, 80] during TIVA to avoid burst suppression and meanwhile to prevent awareness [81].

Patient Factors

Certain patient-related factors can add to the complexity of PFT. Frail patients, those with spine injury as part of poly-trauma, and oncology and cardiac patients are more prone to develop complications as a result of PFT.

Frailty

There are increasing numbers of elderly and frail patients undergoing spine surgery. Frailty, a geriatric syndrome, is associated with adverse postoperative outcome and poor functional and cognitive recovery [82]. Frail patients are sensitive to hypovolemia and dehydration with a limited ability to concentrate urine and handle the sodium load induced by PFT [83]. While young patients can excrete up to 300-mmol sodium per liter of urine, frail patients are lacking this ability [84] highlighting the need for administering enough water to allow the excretion of the osmolar load. N-terminal pro-brain natriuretic peptide (NT-proBNP) increases with age as well as with cardiac diseases, and its high preoperative levels can predict adverse outcomes [85]. In the elderly, ERASPs recommend meticulous regulation of PFT, keeping the net fluid balance close to zero with near normal electrolyte homeostasis and providing enough water and glucose supply [86, 87].

Spine Injury as Part of Poly-trauma

In poly-trauma patients, international guidelines recommend a restrictive PFT strategy and permissive hypotension until bleeding is controlled [88]. A systolic blood pressure target of 60–70 mmHg for blunt trauma and 80–90 mm Hg for penetrating trauma with slow infusions rather than large boluses of crystalloids [89] are recommended. In traumatic hemorrhagic shock, permissive hypotension is safe and reduces mortality; however, it is contraindicated in patients with traumatic brain injury (TBI) [90]. Both hyperemia and ischemia, resulting in high or low cerebral perfusion pressures, respectively, are deleterious leading to increased mortality in head injury patients. A systolic blood pressure >90 mmHg or a mean arterial pressure >80 mm Hg is recommended to maintain cerebral perfusion using small volumes (100–200 ml) of fluids [91]. In patients with spinal cord injury, similar approach is recommended by keeping mean arterial pressure between 85 and 90 mmHg in the first week after injury [92]. However, optimal spinal cord perfusion pressure and autoregulation range vary not only between patients but also temporally. Therefore, analogous to the cerebral hemodynamic management in TBI patients, individualized "targeted" perfusion therapy of the injured cord should be implemented rather than applying fixed hemodynamic targets for all patients [93]. Moreover, in acute spinal cord injury patients, neurogenic shock, cardiac disturbances, and hyponatremia are not uncommon rendering PFT more challenging in such cases. Therefore, individualized GDT using fluids, vasopressors, or inotropes guided by multimodal hemodynamic and neuromonitoring should be considered [91, 92].

Oncology and Cardiac Patients

Monitoring-guided individualized GDT seems also appropriate in high-risk oncology patients [94] and those with cardiac disease [95].

Conclusion

Spine surgery is increasingly used to manage patients with different pathological conditions. In spine surgery patients, PFT presents a real challenge in view of its impact on their outcomes; the uncertainty regarding the ideal type and volume of fluid to be used; the unique surgical, anesthetic, and patient factors; and the lack of evidence-based guidelines specific to this type of surgery. Moreover, the optimal strategy for PFT, in general, is still debated despite extensive

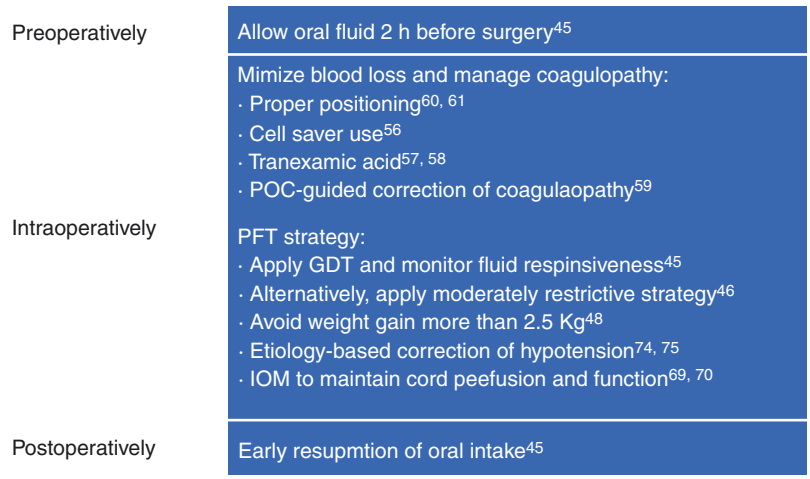

Fig. 1 Currenty available guidelines to guide fluid therapy in spine surgery

POC: Point-of-care testing. GDT: Goal-directed therapy. IOM: Intraoperative monitoring of spinal cord function

research. Therefore, applying the currently available guidelines and recommendation (Fig. 1) for PFT while considering the various factors specific to spine surgery are pivotal in order to prevent complications and improve outcome. The current body of evidence supports applying the ERASP guidelines for PFT, implementing an individualized GDT in major spine surgery and high-risk patients, targeting a moderately restrictive strategy rather than a zero-balance approach, and using measures to reduce intraoperative blood loss including TXA. In addition, considering the impact of positioning on hemodynamics, using intraoperative monitoring of spinal cord function, and implementing an etiology-based management of hypotension are mandated to prevent complications. More research is awaited in this field to refine the evidence-based guidelines for PFT management in spine surgery patients.

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Fluid Management in Neurosurgical Patients with Coexisting Cardiac Diseases

Manee Raksakietisak

Abstract

Neurosurgical patients with underlying cardiac diseases are very sensitive to fluid management. They need careful preoperative cardiac evaluation regarding myocardial ischemia, significant arrhythmia, valvular heart disease, and heart failure. Presence of heart failure in preoperative period will increase perioperative cardiac morbidity. Some may have heart failure. Some may have euvolemia or even hypovolemia. Fluid assessment and fluid responsiveness in cardiac patients are very important. Fluid challenge can be given in cardiac patients. In responders, hemodynamic parameters will change to favorable results. Bedside echocardiogram and passive leg raising (PLR) test are excellent tools for assessing fluid responsiveness. In patient with hypovolemia and hypotension, resuscitation fluid should focus on rapid restoration of circulating volume. Intraoperative hypotension can be minimized with goal-directed fluid combined with protocol management. Postoperative IV fluid requirements should be low in most cases. Fluid balance chart and serum electrolytes should be checked. Cardiac complications (myocardial ischemia, atrial fibrillation, and heart failure) occur commonly, and some neurological conditions such as neurogenic stunned myocardium (NSM) can cause myocardial dysfunction. Appropriate fluid and blood pressure management may decrease or prevent major cardiac events.

Keywords

Cardiac complications · Cardiac patient · Fluid assessment · Fluid responsiveness · Goal-directed therapy (GDT) · Hypotension

Introduction

Fluid management of neurosurgical patients with coexisting cardiac disease is a great challenge to anesthesiologists in perioperative period. Patients with underlying cardiac diseases are very sensitive to fluid management. Too much fluid can cause congestive heart failure. Too little fluid leads to inadequate preload, low cardiac output, hypotension, and poor tissue perfusion. Intravascular volume of neurosurgical patients can be altered by several etiologies, such as receiving diuretics (mannitol and furosemide) to reduce intracranial pressure or to provide brain relaxation. Anesthetics cause systemic vasodilatation and relative hypovolemia. Surgery can also result in massive bleeding. Development of diabetes insipidus (DI) or syndrome of inappropriate

M. Raksakietisak (✉)
Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
e-mail: manee.rak@mahidol.ac.th

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antidiuretic hormone (SIADH) secretion during perioperative period may further lead to fluid and electrolyte imbalance [1]. This chapter provides details about administering fluid in cardiac patients during perioperative period for neurosurgical procedures.

Preoperative Assessment of Cardiac Patients

Apart from neurological assessment, cardiac patients need careful preoperative evaluation regarding cardiac function and pathologies such as myocardial ischemia, significant arrhythmia, valvular heart disease, and heart failure. Presence of heart failure in preoperative period will increase perioperative cardiac morbidity. Stabilization of cardiac function and treating pulmonary congestion should be done before elective surgery. Evaluations with respect to exercise tolerance and functional capacity are also very important. They determine perioperative risk, need for invasive monitoring, and special postoperative care. Some may need further cardiac test or intervention [2–7].

Symptoms, signs, and investigation of patients with heart diseases are shown in Table 1.

Table 1 Symptoms, signs, investigation, and interpretations [2–7]

	Interpretation
History	
Breathlessness, orthopnea, nocturnal dyspnea Palpitation, dizziness, syncope Severity and triggers of dyspnea and fatigue	Symptoms of heart failure Symptoms of heart failure To determine NYHA class
Presence of chest pain, history of CAD History of long-standing or poorly controlled hypertension	Symptoms of coronary ischemia Hypertensive heart disease, diastolic dysfunction
Exercise capacity, physical activity	Functional capacity
Weight: loss or gain	GI dysfunction (cachexia) or fluid overloaded
Medication adherence	Access for medication, follow-up
Salt-containing diet	Sodium retention
Physical examination	
Blood pressure (supine and upright)	Hypertension or hypotension (postural change)
Pulse: tachycardia, irregularity, narrow pulse pressure	Signs of heart failure, arrhythmias
Tachypnea, lung crepitation Jugular venous pressure, hepatojugular reflux	Signs of heart failure Identify congestion
Size and location of apical impulse S 3 gallop Cardiac murmur Hepatomegaly, ascites, peripheral edema Cooled lower extremities, oliguria	Ventricular enlargement Ventricular dysfunction Structural heart disease Fluid overloaded Inadequate cardiac output
Investigation	
Electrocardiogram (ECG)	Ischemic pattern, left ventricular hypertrophy (LVH)
Chest X-ray	Cardiomegaly, congestion, Kerley B line, pleural effusion
Blood test: cardiac troponin, BNP or NT-proBNP Other blood test: hemoglobin and WBC—sodium, potassium, urea, creatinine (with eGFR), liver function tests (bilirubin, AST, ALT, GGTP), glucose, HbA1c, lipid profiles	Myocardial ischemia, heart failure For initial assessment for other organ functions
Echocardiogram Other cardiac testing such as cardiac magnetic resonance, stress imaging, coronary angiography (according to cardiologist and guidelines)	Structural heart, ventricular function, volume status, hemodynamic parameters Myocardial structure and function

CAD coronary artery disease, *NYHA* New York Heart Association, *BNP* B-type natriuretic peptide, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *WBC* white blood cell, *eGFR* estimated glomerular filtration rate, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGTP* gamma-glutamyl transpeptidase, *HbA1c* hemoglobin A1c

Fluid Assessment and Fluid Responsiveness

Fluid assessment and fluid responsiveness in cardiac patients are very important. Only half of hypotensive patients respond to fluid resuscitation [8]. Some cardiac patients may have heart failure and overloaded intravascular volume. However, some may have euvolemia or even hypovolemia. Hypovolemia is common during perioperative period due to several factors such as overuse of diuretics (thiazides or furosemide or mannitol or combination of diuretics), and/or inadequate intake, and/or severe nausea or vomiting (in case of raised intracranial pressure) and/or ongoing blood loss in multiple trauma [1]. Despite advance in laboratory investigations and imaging technology, careful history taking and meticulous physical examination are essential for fluid status evaluation [9].

Common symptoms, signs, monitoring, and investigation for fluid status evaluation and fluid responsiveness are shown in Table 2 [8–13]. However, many symptoms and signs are too general and not specific to hypovolemia or hypervolemia. In those cases, some investigations may be needed. For example, hypotension can be caused by several factors, not only from hypovolemia. In hyperglycemic state, renal insufficiency or use of diuretics, SIADH or DI, urine output may be an inaccurate measure of volume status and resuscitation.

Fluid challenge can be given to cardiac patients with low systolic blood pressure (SBP <90 or 100 mmHg) or low mean arterial pressure (MAP <60 or 70 mmHg), with tachycardia (heart rate >90 or 100 beats/min), or with other signs of hypovolemia (Table 2). Crystalloid or colloid (in cases with no acute kidney injury or no sepsis) can be given in a bolus with volume of 4–10 mL/kg

Table 2 Assessment of fluid status and fluid responsiveness [8–14]

History	Monitoring (noninvasive or invasive)
Hypovolemia	Vital signs or national early warning scores (NEWS)
Fluid loss via urine, the gastrointestine, or the skin	Fluid balance chart, weight
Blood loss	Blood urea nitrogen, creatinine, electrolytes
Low or inadequate intake	Urine output
Hypervolumia	Stroke volume variation or pulse pressure variation (if indicated)
Excessive intake in patients with heart failure or chronic kidney disease	Cardiac output (if indicated)
Excessive fluid resuscitation	Central venous pressure (CVP) or pulmonary capillary wedge pressure (PCWP) (if indicated)

Physical examination	Investigation
Hypovolemia	Hypovolemia
Altered mental status	Elevated hematocrit
Dry mucous membranes	Low bicarbonate level
Poor skin turgor	Increased base deficit
Tachycardia (heart rate >90/min)	Increased lactate level
Hypotension (systolic blood pressure <100 mmHg or orthostatic changes)	Increased blood urea nitrogen/creatinine ratio
Capillary refill >2 s	Increased urine osmolality or concentrated urine
Peripheries cold to touch	Decreased fractional excretion of sodium
45° passive leg raising suggests fluid responsiveness	
Weight loss	
Hypervolumia	Hypervolemia
Weight gain	Chest X-ray (lung congestion)
High jugular pressure	Echocardiography (large left ventricular volume, large IVC diameter)
Hepatomegaly, ascites, peripheral edema	
Lung sound (rales or crepitation)	Lung ultrasound (B line and pleural effusion)

National early warning scores (NEWS) = score developed by the Royal College of Physicians (UK) by using six physiologic parameters: respiratory rate, oxygen, temperature, systolic blood pressure, pulse rate, and consciousness

(100–500 mL or more) to most patients [8–12]. However, in cardiac patients with impaired cardiac function, a slower bolus rate is preferred. However, when infusion time was longer than 30 min, proportion of responder was decreased [8]. In responders, hemodynamic parameters (macrocirculation) will change to favorable results such as increasing in blood pressure, increasing in cardiac output, or decreasing in pulse rate. Microcirculation such as lactate, prolonged capillary refill time, and mottling score will also be improved [10, 11]. Frequent monitorings and re-evaluation are essential for fluid adjustment.

Those with negative response to passive leg raising (PLR) test are unlikely to be fluid-responsive. PLR can be used in combination with other goal-directed fluid therapies [8].

In sick patients on ventilator with an arterial line, hemodynamic parameters such as changes in pulse pressure (ΔPP) during positive pressure ventilation or pulse pressure variation (PPV) can be used for fluid responsiveness. In patients who breathe spontaneously, PPV can be used in conjunction with a maneuver that increases intrathoracic pressures, i.e., Valsalva maneuver or passive leg raising test [12].

Bedside echocardiogram is another excellent tool for assessing fluid responsiveness. Disadvantages of echocardiogram are noncontinuous monitoring and high inter-operator variability. Pulse contour analysis or other noninvasive cardiac output monitoring can also be used for fluid responsiveness [8, 13].

Echocardiogram/Transthoracic Ultrasound for Fluid Management

Myocardial dysfunction in cardiac patients may be diastolic, systolic, or both systolic and diastolic dysfunctions. Some cardiac patients have abnormalities in valve function (stenosis or regurgitant or both) or arrhythmias. Preoperative echocardiogram gives some valuable details about cardiac volume, cardiac function, and valve abnormalities, but it is not always needed in every case of cardiac patients. However, echocardiogram is essential for cardiac patients with unstable hemodynamics or doubtful volume status [13].

Heart failure may result from disorders of pericardium, myocardium, endocardium, heart valves, great vessels, or other metabolic abnormalities. Most commonly, HF patients have left ventricular (LV) myocardial disease. Some patients have normal LV size and preserved ejection fraction (EF), whereas others have cardiac chamber dilatation and/or reduced EF [5–7].

Optimal filling volume for cardiac patient has a very narrow range. Outside this narrow range, stroke volume and cardiac output may be decreased because of hypovolemia or hypervolemia. When stroke volume has been optimized with adequate fluid and/or the use of inotropes, cardiac output will undoubtedly be improved providing good tissue perfusion. Optimum intravascular volume will also prevent reflex tachycardia from hypovolemia. Tachycardia increases myocardial oxygen consumption and puts patients with coronary artery disease at risk [5–7].

Positive pressure ventilation increases the size of inferior vena cava (IVC), while negative pressure reduces its size. A large, noncompliant IVC implies patient is not a volume responder. IVC diameter is easily and reproducibly measured 1–2 cm from right atrial junction using transthoracic ultrasound [13]. Lung ultrasound can be used for fluid status assessment. B line and pleural effusion suggest fluid overloaded [14].

Types of Fluid Management

Different indications need different types of fluid. In patient with hypovolemia and hypotension, resuscitation fluid should focus on rapid restoration of circulating volume, so high sodium (Na 130–154 mmol/L) containing fluid such as 0.9% NaCl or balanced salt solutions should be used [9, 10, 15].

From neurosurgical view point, crystalloids should be used as first-line resuscitation fluid. Synthetic colloids should not be used as resuscitation fluid regarding its affecting platelet function. Glucose-containing hypotonic solutions,

albumin, and other hypotonic solutions should not be used as resuscitation fluid [16].

Replacement fluid must mimic fluid that has been lost such as gastrointestinal loss from vomiting or urine loss from DI. Maintenance fluid must deliver basic electrolytes (approximately 1 mmol/kg/day of potassium, sodium chloride, and water 25–30 mL/kg) and glucose for metabolic needs (50–100 g/day of glucose to limit starvation ketosis) [9, 15].

Patient electrolytes also guide fluid management. For example, in patient with acute or symptomatic hyponatremia, a bolus of 100–150 mL of hypertonic saline (3% NaCl) over 10–20 min could be given. For a moderate symptom, use continuous infusion of 3% NaCl 0.5–2.0 mL/kg/h. However, in asymptomatic or mild hyponatremia, a slower rate of 3% NaCl or 0.9% NaCl can be used [17]. In patient with hypervolemic hyponatremia or cardiac patient with impending heart failure, hypertonic saline can be combined with loop diuretic. Frequent glucose and electrolyte monitoring is essential because electrolyte imbalance and hypoglycemia or hyperglycemia have deleterious effects on neurological function.

Dosage and duration are equally important for fluid management. For resuscitation, a bolus of 500 mL <15 min is recommended [9]. For replacement fluid, when cause of fluid loss is stopped, replacement is no longer needed. Final step in fluid therapy is to withhold fluid when it is no longer required, thus reducing the risk of fluid overload and deleterious effects [10]. In cardiac patient, invasive or sophisticated monitoring may be needed if, somehow, fluid responsiveness is in doubt.

Perioperative Fluid Management

To avoid a bolus fluid loading in cardiac patient, fluid deficit should be corrected or prevented before surgery.

Current guidelines allow intake of clear oral fluid up to 2 h before elective surgery [18]. For enhanced recovery after surgery (ERAS) guideline, carbohydrate-rich drink is suggested to be given 2–3 h before operation to decrease insulin resistance and avoid dehydration from prolonged fasting [19]. However, fluid may need to be restricted in patients with symptoms and signs of heart failure (HF). Symptoms and signs of HF are dyspnea, fatigue, limited exercise tolerance, and fluid retention. Cardiologist consultation is necessary in cardiac patients with acute heart failure. Elective surgery might need to be postponed because acute heart failure increases perioperative cardiac risk.

Intraoperative Fluid Management

Hourly fluid maintenance can be calculated by summation of fluid deficit + maintenance fluid + blood loss + surgical loss or third-space loss. Third-space loss remains unclear, and interstitial fluid loss is returned to circulation by lymphatic system. Interstitial fluid shift is related to endothelium glycocalyx. In sepsis or systemic inflammatory response, there is fluid leakage via endothelium glycocalyx. In conclusion, third-space loss is no longer included in calculation for fluid management [15].

Restrictive vs. liberal fluid therapy for major abdominal surgery (RELIEF) trial showed a high incidence of postoperative acute kidney injury (AKI) in restrictive group. Restrictive group received a <5 mL/kg bolus at anesthesia induction, followed by intraoperative crystalloid infusion at a rate of 5 mL/kg/h. Liberal group received a 10-mL/kg bolus at induction, followed by an intraoperative rate of 8 mL/kg/h [20]. Zero fluid balance is too restrictive, and a somewhat liberal approach may be needed. Therefore, evidence-based practices in non-thoracic surgeries are moving away from a restrictive fluid strategy toward maintaining euvolemic state or 1–2 L of positive fluid balance in general low-risk population [20, 21].

Individualized goal-directed fluid (GDT) therapy is proven to be beneficial in several outcomes. It can reduce mortality in high-risk patients or high-risk surgeries/procedures. GDT reduced rates of arrhythmia; however, myocardial infarction (MI), HF, and cardiac arrest were

not significantly different between groups. High-risk patients included cardiac patients and patients with severe comorbidities [22]. Most neurosurgical procedures are classified as moderate- or high-risk procedures with a great change of fluid during operation. Arterial line or invasive blood measurement is normally used in craniotomy and major spine surgery, so pulse pressure variation can be used for fluid responsiveness. For very sick cardiac patient with low ejection fraction, continuous cardiac output monitoring may be useful, not only for fluid titration but also for inotrope and vasopressor management [23]. Combining goal-directed fluid monitoring with protocol management (Fig. 1) may improve patients' outcome.

Intraoperative Hypotension

After anesthesia induction, many cardiac patients may experience severe hypotension because of preexisting hypovolemia, anesthetic-induced vasodilatation, and positive pressure ventilation. These patients are on ascending limb of Frank-Starling curve and will benefit from individualized, goal-directed intravascular fluid administration. Factors associated with post-induction hypotension are pre-induction systolic blood pressure, elderly, and emergency surgery [24]. A slow fluid bolus (10–20 min) at time of induction and a slow titration of anesthetic agents or using induction agents such as thiopentone or etomidate have

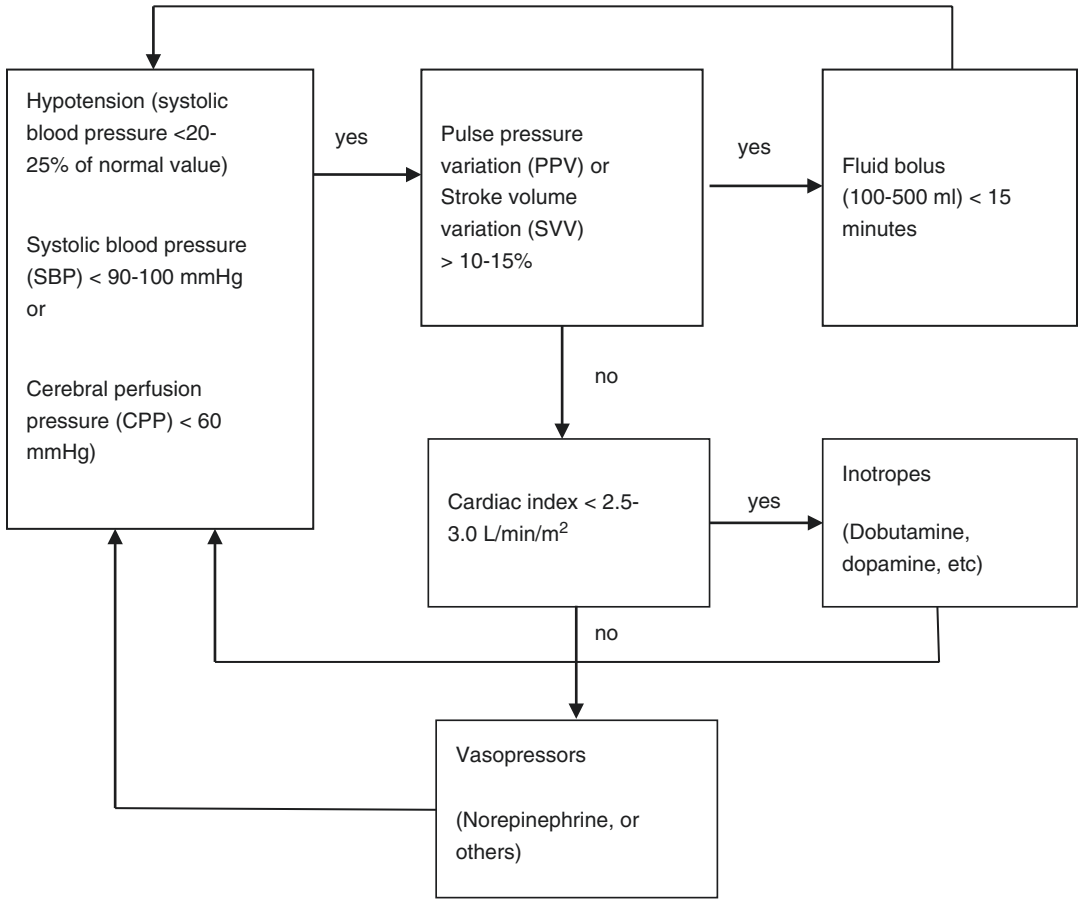

Fig. 1 Protocol for goal-directed fluid therapy in hypotensive patient

less myocardial depressant effect compared with propofol. A single dose of etomidate can decrease cortisol production, but adrenal insufficiency is unlikely [25].

Perioperative hypotension frequently occurs in critically ill or cardiac patients. Vasopressor and/or inotropic drugs should be prepared and ready for use. It has been shown in the study that intraoperative hypotensive episodes of as little as 1–5 min can be associated with an unfavorable outcome [26]. In contrast, routine use of vasopressor to prevent and treat hypotension might mark symptoms and signs of hypovolemia in some cardiac patients. In repeated hypotension despite adjustment in anesthetic agent, hypovolemia may be the cause, and fluid challenge might provide some benefits (Fig. 1).

To treat hypotension, balanced salt solution is preferred. However, acetate or lactate ringer solution is slightly hypotonic (273 mmol/L) which leads to cerebral edema. A large amount of 0.9% NaCl (308 mmol/L) leads to hyperchloremic metabolic acidosis. So mixed crystalloid can be used to avoid such side effects. However, hydroxyethyl starch (HES) solution can potentially cause acute kidney injury in septic patients. In hypovolemic or hemorrhagic patient, a small amount of colloid prior to transfusion can be given. Colloid lasts longer in intravascular space and reduces interstitial edema [21].

Blood Transfusion

There was no evidence that restrictive transfusion strategy (hemoglobin (Hb) 7 g/dL to 8 g/dL) affects 30-day mortality or morbidity (cardiac events, stroke, pneumonia, thromboembolism, infection) compared with liberal transfusion strategy (Hb 9 g/dL to 10 g/dL). There were insufficient data to draw a conclusion in clinical subgroups such as cardiac patients with acute coronary syndrome, myocardial infarction, or neurological patients with traumatic brain injury and stroke or patients with bleeding risk [27]. Recently published blood transfusion guidelines [28, 29] supported restrictive transfusion strategy. A restrictive red blood cell (RBC) transfusion threshold of 8 g/dL is recommended for patients undergoing orthopedic surgery and cardiac surgery and those with preexisting cardiovascular disease [28]. Implementation of patient blood management improved appropriate RBC utilization [29, 30].

For cardiac patient, acceptable level of hemoglobin is higher compared with other population, so triggering point for transfusion is 8 g/dL [28] or even higher. In neurosurgery, there were some evidences in patients with traumatic brain injury (TBI) and subarachnoid hemorrhage to study transfusion trigger of red blood cells. An Hb level <9 g/dL in patient with subarachnoid hemorrhage was associated with an increased incidence of brain hypoxia and cell energy dysfunction [31]. TBI patients with Hb concentration >9 g/dL were associated with an improved 6-month functional outcome [30, 31]. Clinical experiences played an important role in transfusion practice in neurosurgery.

Preoperative hemoglobin concentration is usually higher than normal due to fasting. Allowable blood loss from calculation is usually too high. In neurosurgical procedures, estimated blood loss is sometimes difficult due to irrigating fluid. Repeated hemoglobin measurement is essential during operation with ongoing blood loss. Interpretation of hemoglobin level should be adjunct with fluid status. A false high Hb level usually shows in acute hemorrhagic setting.

Hyperosmolar Therapy and Hemodynamic Changes

Hyperosmotic therapy (mannitol and hypertonic saline) is commonly used to reduce intracranial pressure and provide brain relaxation. Both agents increase osmolality and induce water shift through intact blood-brain barrier. They increase initially central venous pressure, cardiac output, cardiac index, lower systemic vascular resistance, and variable results with blood pressure [32, 33]. Administration of hypertonic saline heightens level of serum sodium and promotes a temporary reduction of potassium. In contrast, mannitol causes a transient acute dilutional hyponatremia

with a concomitant increase of potassium [34, 35]. Urine output is significantly higher in patients treated with mannitol.

In cardiac patients, hyperosmolar therapy can induce heart failure due to initial increase in intravascular volume and can cause significant hypotension after mannitol-induced diuresis. Fluctuation in intravascular volume can cause hemodynamic instability, so lower dose and slower rate of infusion of hyperosmolar therapy in these cardiac patients might provide more stable hemodynamics. Electrolyte abnormalities undoubtedly affect cardiac patients than general population. Hypokalemia and hypomagnesemia can precipitate cardiac arrhythmias.

Postoperative Fluid Management

Excessive fluid administration has a negative impact on recovery after major surgery. Patients recovering from major surgery typically have a 3–4-kg weight gain secondary to fluid and salt overload, manifesting as tissue edema [15]. However, restrictive vs. liberal fluid therapy in major abdominal surgery (RELIEF) trial showed a high incidence of postoperative acute kidney injury (AKI) in restrictive group or zero balance group. Study suggested maintaining euvolemic state or 1–2 L of positive fluid balance in general low-risk population [20]. Excessive fluid can slowly be self-eliminated in postoperative period or with the use of diuretics.

Postoperative intravenous fluid requirements should be low in most cases unless there are ongoing fluid and electrolyte losses such as DI in pituitary surgery. Patients should be encouraged to resume oral fluid as soon as possible after surgery. Intravenous cannula can be locked, but no administered fluid, only for parenteral antibiotics or other drugs.

Patient's fluid balance should be charted and serum electrolytes checked, especially after osmotic therapy. Regular postoperative assessment of patient's fluid status and requirements should include asking for thirst and looking for signs of hypovolemia or hypervolemia (Table 2). Urine output can be an unreliable monitor of fluid status in postoperative neurosurgical patients.

Goal-directed fluid therapy and fluid responsiveness can continuously be used in postoperative period. However, this period's fluid shift or fluid loss is less than intraoperative period. Cardiac patient who is hemodynamically stable can be managed with standard care.

Common Cardiovascular Complications

Cardiac complications occur commonly in perioperative period, especially patients with coexisting cardiac diseases. Perioperative myocardial infarction or injury occurs up to 3% in patients undergoing elective major noncardiac surgery [34, 35]. Troponin surveillance provides early myocardial injury detection, and its level relates to cardiac prognosis. Stable hemodynamics can be achieved with appropriate fluid and electrolyte management. Mean arterial pressure <55 mmHg increases incidence of myocardial injury after noncardiac surgery (MINS) [26].

Apart from cardiothoracic surgery, incidence of postoperative atrial fibrillation (AF) is 3–10% [34]. Precipitating factors are not always known, but catecholamine stress, myocardial ischemia, pain, hypovolemia or atrial stretch, hypoxia, and electrolyte disturbances have all been implicated. Loss of atrial contraction reduces stroke volume, and tachycardia may cause myocardial ischemia. Some patients with postoperative AF episodes are asymptomatic, but cardiac patients with limited or reduced cardiac function can frequently become hemodynamically unstable. This acute AF may need pharmacological or electrical cardioversion to restore sinus rhythm. Some patients who fail from rhythm control AF should benefit from rate-controlled AF. Postoperative AF should be treated the same way as AF from any other cause, and stroke risk should be assessed with a validated scoring system such as CHADS2-VASC and anticoagulation started if indicated [36]. However, after major neurosurgery, bleeding risk should be assessed before starting antico-

agulant. Atrial fibrillation is a leading cause of ischemic stroke from embolic event, but hemorrhagic stroke occurs from the use of anticoagulant. Management of arrhythmias is a shared responsibility of critical care intensivists and cardiologists. Arrhythmias may arise from intrinsic cardiac pathology or from secondary precipitating factors.

Majority of patients with postoperative heart failure also have preoperative heart failure. Heart failure is rare in noncardiac patient as a solely postoperative complication. Some of patients with acute coronary syndrome will develop systolic heart failure as a consequence of myocardial ischemia. Other causes are inappropriate fluid type and volume, perioperative lung injury as neurogenic pulmonary edema, preexisting renal impairment, and sepsis. Patients with preoperative diastolic dysfunction (long-standing hypertension with left ventricular hypertrophy) can experience postoperative pulmonary edema, myocardial infarction, and other major cardiac events. It has been suggested that using some forms of cardiac output monitoring to optimize stroke volume as well as avoiding tachycardia may lower cardiac morbidity [37].

Hypervolemia in triple-H therapy (hypervolemic, hypertensive, and hemodilution) was used to treat patients with delayed cerebral ischemia in postoperative period. However, it caused pulmonary edema without improving neurological outcomes. So hypervolemia is no longer recommended. In cardiac patients who are very sensitive to fluid overload, this therapy should not be used [16].

Some neurological conditions can cause myocardial dysfunction such as neurogenic stunned myocardium or neurogenic stress cardiomyopathy. It is characterized by ischemic electrocardiography (ECG) changes, increased cardiac biomarker, and reversible left ventricular dysfunction (cardiomyopathy) without evidence of epicardial coronary artery disease. It is related to subarachnoid hemorrhage or other neurologic etiologies. Neurogenic stunned myocardium sometimes can lead to cardiogenic shock and neurogenic pulmonary edema. Cardiogenic shock is treated with inotrope to optimize cardiac output and maintain cerebral perfusion pressure. Drugs that prolong QTc interval such as antidepressants should be avoided. Although this type of cardiomyopathy is reversible, patients with NSM exhibit poor outcome and high mortality [38].

Conclusion

Perioperative fluid management in cardiac patients is very crucial. Fluid should be optimized starting from preoperative period to intraoperative and postoperative period. Hemodynamically unstable cardiac patient may benefit from goal-directed individualized fluid therapy to prevent perioperative major cardiac events.

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Fluid Management in Neurosurgical Patients with Coexisting Pulmonary Problems

Mathangi Krishnakumar,
Mouleeswaran Sundaram, and Kamath Sriganesh

Abstract

Fluid and electrolyte management forms an integral part of care in neurosurgical patients. The complexity of hemodynamic monitoring and fluid therapy increases in patients with coexisting pulmonary disease. Understanding the pathophysiological changes in the pulmonary and nervous systems, drugs used in their management, and their impact on fluid physiology, and knowledge about choice and dose of fluid therapy, helps in appropriate decision-making regarding fluid management in neurosurgical patients with pulmonary problems.

Keywords

Fluid therapy · Assessment · Neurosurgery · Pulmonary problems · Hemodynamic monitoring

Introduction

Fluid management forms an important part of care in neurosurgical patients. The volume and composition of administered fluids become critical in neurosurgical patients with coexisting pulmonary pathologies as the fluid management strategies often compete with divergent requirements of brain and lung pathologies. In this chapter, we discuss fluid management in neurosurgical patients with coexisting pulmonary problems under the following headings: (1) pulmonary problems in neurosurgical patients, (2) fluid management in pulmonary diseases, and (3) fluid management in neurosurgical patients.

Coexisting Pulmonary Problems in Neurosurgical Patients

The pulmonary system is responsible for providing oxygen and removing carbon dioxide. Oxygen consumption of the brain is about 3.5 mL/100 g of brain tissue, which is about 20% of the total oxygen content. Utilization of oxygen is more in the gray matter compared to the white matter. Oxygen transport from the lungs to the brain depends on concentration gradient, alveolar gas exchange, solubility, and adequate tissue perfusion [1, 2]. Thus, any impairment of the lung function is likely to affect the brain function as well.

The practice of neuroanesthesia is aimed at providing optimal operative conditions and maintaining adequate cerebral perfusion and oxygenation [3]. Many patients with significant comorbidities are increasingly undergoing neurosurgical procedures in the recent years due to the

M. Krishnakumar · M. Sundaram · K. Sriganesh (✉)
Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, India
e-mail: sriganeshk@nimhans.ac.in

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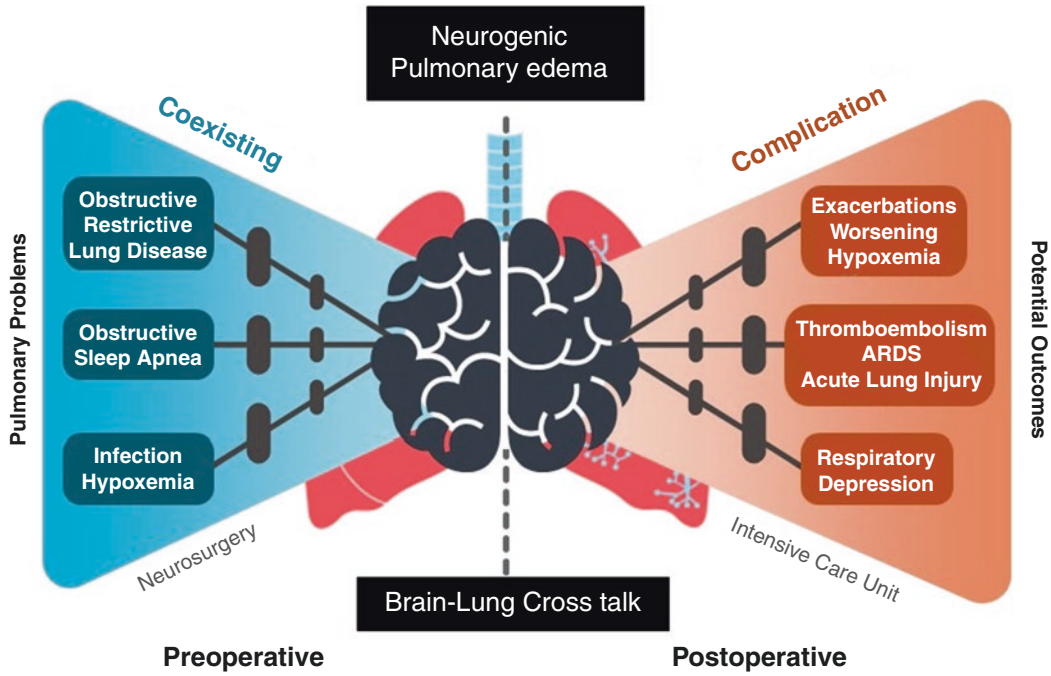

Fig. 1 Pulmonary problems in neurosurgical patients

advancements in neurosurgical, anesthesia, and monitoring techniques. Perioperative respiratory complications can contribute to increased morbidity and mortality and poor neurological outcomes. This risk increases in neurosurgical patients with coexisting pulmonary problems. Prolonged duration of neurosurgery and anesthesia, positive pressure ventilation, tube block from excessive secretions, loss of protective airway reflexes, respiratory muscle weakness, and cardiorespiratory dysfunction can contribute to adverse respiratory events in this population.

The interaction between the pulmonary and the nervous system (brain-lung cross talk) and the impact of coexisting pulmonary problems on perioperative outcomes in neurosurgical patients are shown in Fig. 1.

The common coexisting pulmonary problems in neurosurgical patients are discussed below:

Obstructive Lung Disease

Chronic obstructive pulmonary disease (COPD) has significantly higher incidence in surgical population (10–40%) compared to general population (5%). It is also the third leading cause of mortality. The presence of a coexisting disease adds to the severity and worsens prognosis in COPD patients. Recent studies have shown link between neurological outcome and COPD [4]. This points to commonality in risk factors for developing COPD and neurological diseases such as stroke and cognitive dysfunction. There is significant evidence toward interaction between the brain and the lung [5].

The modification of airway, progressive hypoxia, airflow limitation, and hyperinflated lung fields associated with COPD causes a state of chronic systemic inflammation. These changes

might cause endothelial dysfunction and impaired vascular reactivity. During surgery, this can lead to increased airway reactivity, increased airway pressures, and airway colonization with bacteria, increasing the risk for postoperative pulmonary complications (PPCs). Residual effects of anesthetic drugs and prolonged respiratory depression with opioids are also seen in COPD patients. There is also an increased propensity to develop pulmonary edema and thromboembolic complications due to the presence of coexisting cardiovascular disease.

Restrictive Lung Disease

Restrictive lung disease is characterized by decreased forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) with normal FEV_1/FVC ratio. Most of the restrictive disease pattern is seen with interstitial lung disease, neuromuscular disease, and lesions in the lung [6]. Vertebral deformity is also associated with pulmonary restriction. This causes hypoxemia, hypercapnia, cor pulmonale, and pulmonary arterial hypertension (PAH), which are potentially reversible with fusion surgery. These patients have higher risk for postoperative complications. Management of these cases poses a significant challenge to the anesthesiologist in the perioperative period. Following surgery, there could be extubation failure and need for prolonged ventilation [7].

Pulmonary Infection

Hospital-acquired pneumonia is the second most common nosocomial infection. Neurosurgical patients have more propensity to develop lung infection during hospital admission due to prolonged immobilization, aspiration, and intubation. Patients with intracranial lesions may present with seizure which also increases the risk for aspiration [8]. Posterior fossa lesions with brainstem involvement have poor airway reflexes and are prone to repeated silent regurgitations [9]. Cerebrovascular pathologies also increase the risk of pneumonia. Traumatic brain injury (TBI) can be associated with airway trauma and bleeding, lung contusion, neurogenic pulmonary edema (NPE), and aspiration pneumonitis.

Respiratory Dysfunction

Chronic hyperventilation patterns are observed in patients with raised intracranial pressure (ICP) resulting in respiratory alkalosis. This causes leftward shift of oxygen dissociation curve resulting in worsening of hypoxemia. In patients with TBI, hypoxemia is observed even after craniectomy and ICP control in the perioperative period. The causes of hypoxemia in TBI can be divided into central (head) trauma, drug overdose, peripheral (chest) trauma, coagulopathy, embolism, and aspiration [10]. Tube block and inadequate ventilation are also common in the postoperative period [11].

Cervical spine injury can lead to diaphragmatic dysfunction and reduced ability to cough and can cause respiratory compromise. At the level of thoracic spine, abdominal muscles are affected which leads to paradoxical breathing and reduction in functional residual capacity [8, 10].

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) has higher prevalence in surgical population and is characterized by increased daytime sleepiness, apnea, and airway abnormalities. These patients have additional risk factors (hypertension, diabetes, and obesity) which further add to the risk of perioperative complications [12]. Patients with OSA are more prone to develop cerebral and cardiac ischemic events. OSA is also seen in patients with acromegaly who have progressive somatic disfigurement. These patients have various systemic manifestations, and difficulty in airway management is frequently encountered. Obesity further

alters the respiratory mechanics restricting chest wall mobility which is worsened by supine or prone position. Patients with OSA are vulnerable to the depressive effects of anesthetic agents. There is blunted response to hypoxemia, hypercapnia, and increased risk for upper airway obstruction. These patients might be on continuous positive airway pressure (CPAP) therapy preoperatively which needs to be optimized before surgery. There is also risk of unplanned ventilation, reintubation, weaning failure, and prolonged hospital stay in these patients [13].

Pulmonary Complications Following Neurological Insult

Postoperative Pulmonary Complications

Neurosurgical procedures are recognized as high risk for the occurrence of PPCs such as pneumonia, atelectasis, acute lung injury (ALI), and pulmonary edema [14]. Craniotomy can cause a decrease in lung volume and respiratory pattern which increases the need for postoperative ventilation. Mechanical ventilation, increased ICP, and preexisting lung disease are risk factors for PPCs. The pulmonary changes following neurosurgery and respiratory depression caused by drugs also contribute to PPCs. PPCs are potentially preventable if recognized early and reversible if appropriate management is promptly instituted [8].

Neurogenic Pulmonary Edema

NPE is a diagnosis of exclusion and is typically seen within hours of neurological insult. This condition presents as acute onset tachypnea and hypoxemia preceded by a neurological insult. The incidence is 23% following subarachnoid hemorrhage (SAH) and 33% following status epilepticus. The etiology is linked to catecholamine surge and inflammatory response following brain insult. The diagnostic criteria include (1) bilateral infiltrates, (2) arterial oxygen tension to inspired oxygen fraction (PaO2/FiO2) ratio <200, (3) no evidence of left atrial hypertension, (4) presence of neurological injury with increased ICP, and (5) absence of other causes of acute respiratory distress syndrome (ARDS) [15].

Thromboembolic Complications

Pulmonary thromboembolism (PTE) is seen in about 0–25% of neurosurgical patients. The major risk factors include prolonged immobilization, hypercoagulable state, stroke, malignant tumors, and TBI [16]. TPE causes hypoxemia and significant morbidity and mortality.

Acute Respiratory Distress Syndrome

Brain-lung cross talk refers to several pathophysiological mechanisms occurring simultaneously between brain and lung and vice versa [17]. ARDS is defined as "acute onset, bilateral lung infiltrates with no evidence of elevated left atrial pressure and PaO2/FiO2 <200." A PaO2/FiO2 between 200 and 300 along with fulfillment of the rest of the criteria is called as ALI [18]. ARDS is not a disease per se; it can occur in the setting of aspiration, infection, and alveolar hemorrhage. This syndrome can occur in neurosurgical population due to NPE [8, 10].

ALI is associated with poor outcome and is seen in 20–25% of the patients with brain injury. Neuropsychological changes seen in patients recovering from ARDS implicate a close relationship between the brain and the lung. The two-hit hypothesis which describes the mechanism of ARDS in neurosurgical patients refers to catecholamine storm following brain injury which primes the normal lung (first hit), while the second hit may be an infection, transfusion, or inappropriate ventilator setting. This leads to alveolar inflammation resulting in ALI [19].

Fluid Management in Pulmonary Disease

Neurosurgical patients may have coexisting pulmonary problems which require careful titration and selection of fluids. Some drugs such as osmotic agents and diuretics used in the management of neurosurgical patients also influence fluid therapy including the type and volume administered. Often, fluid management strategies for management of brain pathology and coexisting pulmonary condition may be dissimilar requiring judicious fluid titration to achieve optimal outcomes. Here, we discuss individual pulmonary pathologies, factors influencing the selection of fluids, and appropriate fluid management strategies in this population based on the current understanding and evidence.

Fluid Management in Patients with Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) often occurs as a consequence of permeability or hydrostatic pulmonary edema. Increased alveolar fluid predisposes to bacterial colonization and pneumonia. Therefore, fluid management strategy aimed at optimizing the lung fluid balance can be beneficial. Studies have shown that a depletive fluid management strategy (fluid restriction to 1500 mL/d and diuretic when brain natriuretic peptide values are ≥200 pg/mL) results in reduction in the incidence of VAP [20].

Fluid Management in ARDS and Sepsis

Fluid management approach in patients with ARDS should aim to achieve optimal oxygen delivery without increased lung edema. Alteration in pulmonary permeability (leading to non-cardiogenic pulmonary edema) and circulatory failure are common but divergent manifestations necessitating balanced approach to fluid therapy. Fluid management strategy also depends on the stage of ARDS. Fluid administration in ARDS can increase preload, augment cardiac output (CO), support blood pressure (BP), and improve organ perfusion. However, inappropriate fluid administration can lead to alveolar flooding and venous congestion, worsen endothelial permeability, and exacerbate edema.

Positive fluid balance is associated with longer duration of mechanical ventilation, intensive care and hospital stay, and higher mortality. Hence, restrictive fluid management with monitoring of extravascular lung water, pulmonary capillary wedge or central venous pressure, and use of diuretics (after achieving hemodynamic stability) and albumin are suggested to improve outcomes. However, fluid responsiveness should be assessed since sepsis and ARDS can be associated with circulatory failure. Positive pressure ventilation results in positive fluid balance, so early withdrawal should be considered where possible [21].

Some studies have assessed the effect of type of fluid on outcomes in critically ill patients including those with ARDS. Currently, there is evidence to suggest no benefits of albumin and hydroxyethyl starch over crystalloids in improving outcomes. Rather, hydroxyethyl starch was associated with increased risk of mortality and acute kidney injury [22, 23].

Many patients with sepsis develop pulmonary dysfunction and require careful consideration with regard to fluid management. Beyond the early resuscitative phase, excessive fluid administration can result in edema and organ dysfunction. Dynamic variables can predict hemodynamic response to fluid administration and help guide titration of fluids. Colloids offer no advantage over crystalloids, and among the crystalloids, balanced salt solutions appear to be better than saline in this population [24].

Fluid Management in Obstructive Sleep Apnea

OSA is associated with airflow cessation during sleep with episodes of apnea and/or hypoapnea. OSA is common in obese individuals and in

patients with congestive cardiac failure and renal disease. Volume overload and nocturnal fluid shift contribute to OSA manifestation. Optimizing fluid management with fluid and salt restriction and the use of diuretics along with CPAP is suggested to minimize adverse respiratory manifestations in patients with OSA [25].

Fluid Management in Pulmonary Thromboembolism

Neurosurgical patients are vulnerable to development of PTE from non-ambulation, dehydration, brain pathology, etc. Fluid management in these patients requires careful consideration of the cardiopulmonary pathophysiology. Patients with PTE are likely to have a dilated right ventricle (RV) while also manifesting with hypotension. Fluid administration to improve BP can be hazardous as it can increase RV stress and may decrease CO and BP by affecting the left ventricle (LV). In such patients, judicious fluid and hemodynamic management becomes important. If RV size is less than LV size, fluid administration will be beneficial. If this does not improve BP or is contraindicated (RV size > LV size), vasopressor (norepinephrine) may help in improving the hemodynamic instability but can increase RV afterload. Inotrope (dobutamine) increases RV contraction, decreases pulmonary vascular resistance, and improves coronary perfusion and, hence, may be preferred in these situations [26].

Fluid Management in Patients with Pulmonary Arterial Hypertension

PAH often leads to right heart failure. These patients are vulnerable to fluid overload which can result in ascites and peripheral edema. Fluid and salt restriction, use of diuretics, and measures to reduce RV afterload, improve CO, and maintain BP are necessary in neurosurgical patients especially those with raised ICP. Restriction in sodium-containing fluids and corticosteroids may be necessary to maintain salt/fluid balance. However, this should be balanced with requirements of management of brain edema and reduction in ICP [27].

Fluid Management in Chronic Obstructive Pulmonary Disease

COPD often leads to cor pulmonale [RV failure from PAH] and peripheral edema. However, even when CO is normal, there is hypercapnia-related dilation of the precapillary sphincters causing decrease in peripheral vascular resistance and effective circulating volume (despite increased body water). This results in elevated levels of renin, aldosterone, arginine vasopressin, and atrial natriuretic peptide leading to retention of salt and water. Hypoxemia, which is common in advanced stages of COPD, causes decrease in glomerular filtration rate and reduction in sodium excretion. It also causes pulmonary vasoconstriction, PAH, and RV failure [28–30]. Fluid management becomes challenging in these conditions. Careful fluid management is imperative in the setting of hypotension and RV failure. Vasopressors and inotropes, rather than fluid administration, are necessary to improve CO and reduce RV ischemia.

Fluid Management in Neurosurgical Patients

This section of the chapter will deal with general principles of fluid therapy in the neurosurgical patients. Fluid management in specific neurosurgical conditions are dealt elsewhere in the textbook. Some of the considerations regarding fluid management in neurosurgical patients include:

1. Alteration in water and electrolyte homeostasis produced by brain injury itself or from drugs administered to reduce ICP (diuretics and steroids)
2. Need for fluids to maintain circulatory volume prone to alterations from vasodilatation produced by anesthetics and blood loss during neurosurgery

3. Potential for cerebral edema and consequent changes in cerebral blood flow (CBF) and oxygenation from overzealous fluid therapy

Goals of fluid management in neurosurgical patients include maintenance of intravascular volume, prevention of hemodynamic fluctuations and consequent cerebral edema and intracranial hypertension, and preservation of CBF and oxygenation to prevent occurrence of new or progression of preexisting neurological injury and poor neurological outcome [31].

Principles of Fluid Management

Osmolality/Osmolarity and Osmotic and Oncotic Pressure

The term "osmolarity" denotes the molar number of osmotically active particles per liter of the solution, whereas "osmolality" implies molar number of osmotically active particles per kilogram of solvent. Osmotic pressure is the hydrostatic force acting to equalize the concentration of water on both sides of the membrane that is impermeable to substances dissolved in that water. Osmotic pressure is generated by all osmotically active molecules in the solution which includes large and small molecules (ions). Colloid oncotic pressure (COP) is the osmotic pressure generated by large molecules (plasma proteins, synthetic colloids, etc.) [32].

Fluid Movement Across the Capillaries and Interstitium

Starling described factors that control the movement of fluids between intravascular and extravascular spaces which includes transcapillary hydrostatic gradient, osmotic and oncotic gradients, and permeability of the capillary membrane separating these spaces.

Starling equation is written as $Q_f = K_f S[(P_c - P_t)\text{-}\sigma(\pi_c - \pi_t)]$ [33]—Q_f, the net amount of fluid movement between capillaries and interstitial space; K_f, the filtration coefficient for the membrane; S, the surface area of the membrane; P_c, the hydrostatic pressure in the capillary lumen; P_t, the hydrostatic pressure in the interstitium; σ, the coefficient of reflection (ranges from 0 to 1 and is different in the brain and peripheral tissues); π_c, the oncotic pressure of the plasma; and π_t, the oncotic pressure in the interstitium.

The capillary endothelium of peripheral circulation has a pore size of 65A°, and permeability is more to small molecules and ions (Na^+, Cl^-) and almost nil to large molecules (proteins). Hence, in the periphery, the net water movement is determined by large molecules in the plasma (oncotic gradient), i.e., if COP reduces, there will be movement of fluid from vessels to the interstitium. However, the blood-brain barrier (BBB) separates the brain and spinal cord from the intravascular compartment. BBB consists of endothelial cells which form tight junctions in the capillaries and are surrounded by a layer of pericytes delineated by foot process of astrocytes. In patients with intact BBB, these tight junctions limit the diffusion of both large (proteins) and small molecules (ions) across the capillaries and brain interstitium. The effective pore size in brain capillaries is 7–9 A° [34]. Fluid movement across BBB is determined by the total osmotic gradient generated by both large and small molecules in contrast to those in peripheral tissues where it is determined by the COP produced by large molecules. This explains the fact that large volume administration of isotonic crystalloids and dilutional reduction of COP causes peripheral edema but does not increase brain water content provided the BBB is intact [35].

In patients with intact BBB, a decrease in plasma osmolarity results in movement of water into the brain interstitium. The opposite occurs when plasma osmolarity increases compared to the interstitium. This forms the basis of osmotherapy with hypertonic solutions to reduce ICP. However, if the BBB is damaged following neurological injury, this phenomenon ceases due to inability to establish the osmotic gradient [36].

Choice of Intravenous Fluids

The most important consideration regarding the choice of intravenous fluids includes osmolarity and COP. Isotonic crystalloids do not remain in the intravascular compartment for a long time especially following large volume administration due to their diluting effect on the COP resulting in interstitial edema. This was the physiological rationale behind advocating colloids to maintain the COP and prevent interstitial edema by various researchers for resuscitation earlier. The landmark SAFE trial comparing saline and albumin for resuscitation in intensive care proved otherwise [37]. Following SAFE trial, a post hoc analysis of 460 well-matched TBI patients from the trial showed that using albumin for resuscitation led to a significant increase in 2-year mortality compared to the saline group [38]. The possible explanation could be damage to BBB resulting in free movement of albumin into the brain interstitium and resulting in cerebral edema. Similarly, synthetic colloids have been found to be counterproductive in SAH [39]. Thus, it appears that colloids do not have superiority over crystalloids in neurosurgical patients and crystalloids are preferable for both maintenance and resuscitation.

Among the crystalloids too, the choice has been unclear. Even though saline is used as a preferred fluid in neurosurgical patients, large volume and prolonged administration has been found to be associated with acid-base and electrolyte abnormalities. A recent trial comparing saline and balanced salt solution in the management of SAH patients showed balanced solutions are associated with more stable electrolytes, acid-base profile, and less activation of stress hormones [40]. Balanced fluid administration resulted in reduced incidence of hyperchloremic acidosis and higher serum magnesium and calcium levels as compared to saline in TBI [41]. Though there are no clear guidelines prescribing the choice of crystalloids for fluid management in brain-injured patients, recent literature suggests preference toward balanced salt solutions by clinicians in view of favorable acid-base and electrolyte profile following large volume administration.

To Load or to Run Dry?

Optimal dosing of fluids plays an important role in preventing the progression of neurological injury especially secondary brain injury. Both over- and under-administration of fluids are deleterious. Traditionally, SAH patients were managed using HHH therapy to prevent vasospasm and delayed cerebral ischemia. However, positive fluid balance in SAH patients is associated with increased incidence of vasospasm, prolonged hospital stay, and poor neurological outcome [42, 43]. It is also associated with cardiovascular side effects and delayed neurological deficits [44, 45]. Conversely, overt hypovolemia should be avoided in SAH patients, especially in those with vasospasm [31]. Thus, euvolemia is most appropriate, and fluid overload is associated with intracranial and extracranial complications producing poor outcomes in SAH patients.

In patients with trauma, traditionally managed patients show more positive fluid balance than echocardiography-guided fluid resuscitation. This contributes to cardiovascular side effects, pulmonary edema, poor neurological outcome, and increased mortality [46]. Conversely, encouraging negative fluid balance was also found to be detrimental with increased mortality and poor neurological outcome in TBI patients [47]. Therefore, tailoring the fluid therapy to individual patient requirement should be the standard of care in neurosurgical patients.

Monitoring Circulatory Volume

Monitoring of intravascular volume status is necessary in the management of neurosurgical patients. Bedside volume assessment using BP and urine output is highly unreliable as it is affected by many confounding factors in neurosurgical population. Utilization of advanced hemodynamic monitoring is recommended to monitor the circulatory volume and guide fluid management.

CO monitoring is a feasible method of assessing the volume status and a reliable guide to fluid administration. Transpulmonary thermodilution

has been extensively studied in SAH patients [48, 49]. SAH patients were found to have lower global end-diastolic index (GEDI) but higher cardiac index immediately following SAH, due to the increased circulating catecholamines. This is different from the low CO and low GEDI occurring with hypovolemia. Acute brain injury patients have splanchnic vasoconstriction due to catecholamine surge resulting in fluid shifts causing NPE even with low CO. Overzealous fluid therapy in them can cause systemic and cerebral complications. Utilizing CO monitoring in SAH patients reduces the fluid intake and results in better outcomes [44].

Assessment of Fluid Responsiveness

Fluid responsiveness indicates increased CO in response to fluid challenge. This has been increasingly utilized to monitor and guide intravenous fluid administration in goal-directed fluid therapy. Fluid responsiveness can be assessed using static and dynamic parameters. Static parameters include central venous pressure, pulmonary artery occlusion pressure, and cardiac filling pressures (RV end-diastolic volume, LV end-diastolic area, etc.). Dynamic parameters include stroke volume variation, pulse pressure variation, systolic pressure variation, and inferior vena cava collapsibility. Static parameters may not be reliable in neurosurgical patients [50]. Dynamic parameters of fluid responsiveness are more reliable to assess volume status and guide fluid management [51]. Using fluid responsiveness to guide fluid management in acute brain injury improves cerebral oxygenation and perfusion. Additionally, using advanced hemodynamic parameters results in fewer complications and improved outcomes [52].

Fluid management in neurosurgical patients has bearing on clinical outcomes. Current evidence suggests that both hypovolemia and hypervolemia are undesirable and euvolemia with isotonic fluids is warranted. Monitoring of advanced hemodynamic parameters to assess fluid responsiveness and target fluid management has been found to be beneficial.

Conclusions

Coexisting pulmonary pathology in neurosurgical patients often necessitates modification in fluid management strategy. This is both in terms of volume administered and the type of fluids. Hypotonic fluids and hypervolemia or hypovolemia should be avoided. Understanding fluid physiology and pathophysiological changes in neurosurgical patients helps decide appropriate fluid strategy. Apart from pulmonary and neurological conditions, cardiac status also plays an important role in these patients, and this should be considered during fluid therapy. Competing interests, such as brain edema and cor pulmonale, often make decisions difficult, and individualized fluid management strategies become important. Finally, dynamic fluid assessment tools and laboratory parameters should be used to guide selection of volume and type of fluid during fluid management.

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Fluid Management in Neurosurgical Patients with Coexisting Renal Problems

Priya Gupta and Indranil Chakraborty

Abstract

Kidneys are the major organs regulating fluid and electrolyte homeostasis. The goals of fluid management in neurosurgical patients are to maintain normovolemia and avoid reduction of serum osmolarity. Fluid and electrolyte management in neurosurgical patients with renal impairment can be challenging. History and clinical examination often yield limited information. Diagnosis and severity are estimated by laboratory tests. Significant perioperative renal conditions commonly seen are acute renal failure (ARF), chronic renal failure (CRF), and end-stage renal disease. Perioperative management includes thorough preoperative evaluation and optimization, goal-directed premedication, and close intraoperative hemodynamic monitoring including invasive monitoring where appropriate. The goal is to maintain perioperative normovolemia using balanced salt crystalloids like plasmalyte or normal saline, colloids like 5% albumin, or blood and blood products. Close postoperative monitoring of such patients is often necessary.

P. Gupta · I. Chakraborty (✉)
Department of Anesthesiology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA
e-mail: chakrabortyindranil@uams.edu

Keywords

Fluid management · Renal disease · Neurosurgery

Introduction

The aims of fluid management in neurosurgical patients are to maintain normovolemia and avoid reduction of serum osmolarity [1]. The kidney is a major organ to maintain fluid homeostasis. Kidneys receive approximately 20–25% of total cardiac output via renal arteries. Most of this blood is received by the renal cortex and only 5% of cardiac output flows through the renal medulla. The renal blood flow is regulated by sympathetic tone and autoregulation. The renal autoregulation is maintained with mean arterial blood pressure between 50- and 150-mm Hg. Fall in mean arterial blood pressure below 50 mmHg results in decreased renal blood flow (RBF) and glomerular filtration rate (GFR).

Renal Function Evaluation

History and physical examination usually yield limited information about renal function status unless the disease is advanced. Diagnosis and estimation of severity is mostly by laboratory analysis including blood and urine tests.

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1. Urinalysis: Assays include urinary pH, specific gravity, protein, glucose, cell, and cast.
2. Blood urea nitrogen (BUN) (normal is 10–20 mg/dL): It is an unreliable measure of renal function due to influence by hydration, diet, and coexisting diseases.
3. Serum creatinine (normal is 0.6–1.3 mg/dL): It is influenced by skeletal muscle mass, evidenced by lower values in females. Serum creatinine is a reliable indicator of GFR in healthy people but not in the critically ill. Creatinine values are slow to respond to acute changes in GFR.
4. Creatinine clearance (normal is 110–140 mL/min): It is the most dependable measurement of GFR as it is not affected by age. The urine is collected over a period of 24 hour and is calculated using the formula:

$$\text{Creatinine clearance}\left(\text{mL}/\text{min}\right)=\left[U_{\text{cr}}\times U_{\text{Vol}}\right]/P_{\text{cr}}.$$

where U_{cr} is urinary creatinine concentration (mg/100 mL), U_{Vol} is urine volume (mL/min), and P_{cr} is plasma creatinine concentration (mg/100 mL).

5. Glomerular filtration rate (GFR) (normal is 125–140 mL/min): It is the best measure of renal function [2]. The glomeruli filter approximately 180 L/day (125 mL/min) of plasma. The normal GFR depends upon age, sex, and body size. GFR can be estimated from serum creatinine by following formula

   GFR (mL/min) = [(140 − Age in years) × Weight in Kg]/serum creatinine × 72

   Cystatin C, a nonglycosylated basic protein with a low molecular mass (13 kD) that is freely filtered by the glomerulus, has been used for estimating the GFR [3].

6. Fe_{Na} (fractional excretion of sodium): It is the percentage of filtered sodium that is excreted in urine. Its value can differentiate between prerenal ($Fe_{Na} < 1\%$) and renal ($Fe_{Na} > 2\%$) causes of azotemia. It is calculated using the formula

$$Fe_{Na}(\%) = [(P_{Cr} \times U_{Na})/P_{Na} \times U_{Cr})] \times 100$$

where P_{Cr} is plasma creatinine concentration, P_{Na} is plasma sodium concentration, U_{Na} is urine sodium concentration, and U_{Cr} is urine creatinine concentration.

Significant Perioperative Renal Conditions

1. Acute renal failure (ARF): It is defined as sudden but reversible renal dysfunction. The common causes are sepsis, drugs, antibiotics, trauma, and hypovolemia. The condition is diagnosed by kidney function test, electrolyte levels, and radiologic tests. The commonly seen perioperative complications include pulmonary edema, hyperkalemia, pericarditis, altered mental status, and metabolic acidosis. The management includes the following steps:
   (a) Eliminate or adjust potential renal insults by discontinuing nephrotoxic drugs, readjust the dose of antibiotics, avoid hypotension to maintain renal perfusion, and avoid contrast agents.
   (b) Manage intravascular volume by monitoring, assessment, and goal-directed therapy.
   (c) Manage electrolyte imbalances such as hyperkalemia, hyperphosphatemia, hypocalcemia, hypomagnesemia, and hyperuricemia by correcting acid–base imbalance such metabolic as acidosis.
   (d) Nutrition: by focusing on low salt diet and fluid restriction.
   (e) Hemodialysis. In certain conditions, dialysis may be necessary to optimize fluid, electrolyte, and metabolic imbalance.
2. Chronic renal failure (CRF): It is progressive and irreversible deterioration of renal function for at least 3 months because of systemic disorders like hypertension, diabetes, or kidney diseases like hereditary or obstructive diseases. It is defined as the presence of kidney damage (urinary albumin excretion of 30 mg/day or decreased GFR of less than 60 ml/min/1.73 m^2 for 3 months), irrespective of cause [4]. The severity of CRF is expressed by

the level of GFR and albuminuria [5–9]. Decrease in GFR increases the risk of infections, cognitive and physical dysfunction, acute myocardial infarction, heart failure, and sudden cardiac death, thereby increasing morbidity and mortality [10]. The management includes the following steps:

(a) Treat the reversible causes of kidney failure by improving perfusion, avoidance of nephrotoxic drugs, and treating the urinary tract obstruction.
(b) Progression of the condition rate can be slowed by treating underlying cause and renal protection strategies.
    (i) In diabetic and nondiabetic adults with CKD and urine albumin excretion of <30 mg/24 hours or equivalent, blood pressure goals are systolic ≤140 mmHg and diastolic ≤90 mmHg[10].
    (ii) In diabetic and nondiabetic adults with CKD and urine albumin excretion of >30 mg/24 hours or equivalent, blood pressure goals are systolic ≤130 mmHg and diastolic ≤80 mmHg[10].
    (iii) Angiotensin receptor blocker or angiotensin-converting enzyme (ACE) inhibitor should be used in patients with urine albumin excretion of more >300 mg/24 hours or equivalent [10].
    (iv) Lifestyle interventions, cessation of smoking, exercise, and diabetes control.
(c) Treat complications like volume overload, hyperkalemia, metabolic acidosis, and anemia.
(d) Hemodialysis, especially in the immediate perioperative period, can be useful to optimize metabolic, fluid, and electrolyte derangement. Post-dialysis monitoring of electrolyte levels is recommended.

3. End-stage renal disease (ESRD): Defined as GFR < 15 mL/min, it results in multi-organ derangement. The cardiovascular effects include hypertension (often refractory to therapy), progressive atherosclerotic disease, and fluid overload leading to anasarca, ascites, and pericardial effusion. Chronic metabolic acidosis results in myocardial dysfunction leading to arrhythmia and cardiomyopathy. Multiple electrolyte abnormalities are also seen. Hyperkalemia can result in cardiac arrhythmias. Decreased erythropoiesis leads to anemia (normocytic, normochromic). Uremia leads to deranged platelet function. Many patients are on hemodialysis or peritoneal dialysis. Immediate preoperative dialysis is recommended to optimize metabolic and fluid derangements. Monitoring post-dialysis electrolyte levels is necessary.

Anesthetic Considerations

1. Preanesthesia evaluation. In addition to routine evaluation, patients with coexisting renal problems should be evaluated for type, duration, severity, and presence of signs and symptoms of complications. If the patient is on dialysis, the type and last date of dialysis should be determined. The examination of the central nervous, pulmonary, and cardiac systems is done to rule out the signs and symptoms of uremia. The airway management can be difficult due to swelling and edema around the head and neck region because of chronic fluid overload and use of medications like steroids. The laboratory examination should include complete blood count (anemia, platelet dysfunction); metabolic profile with an emphasis on electrolytes (potassium and calcium), serum creatinine, and GFR; EKG to rule out arrhythmias; and chest x-ray if required.
2. Premedication. Aspiration prophylaxis should be considered in view of high incidence of gastroparesis. Dose of anxiolytics like midazolam should be reduced because of altered pharmacokinetics. Getting intravenous cannula access is often difficult due to coexisting chronic vascular diseases, history of multiple intravenous access leading to peripheral venous thrombosis, and generalized body swelling (anasarca). Presence of arteriove-

nous fistula in upper extremities may limit the availability of intravascular access as well as space for placement of blood pressure cuff.

3. Intraoperative management**.** Pharmacokinetic changes include disturbance in volume of distribution, protein binding, metabolism, and excretion/elimination of anesthetic drugs. Hypotension is common after induction with propofol. Therefore, dose should be reduced. If hyperkalemia is suspected or documented, avoid succinylcholine. Avoid or reduce dose of long-acting non-depolarizing muscle relaxants whose metabolism or excretion or both are renal function dependent. Use of cisatracurium is encouraged. Use of short-acting opioids like remifentanil or fentanyl is usually well tolerated. The dose of long-acting opioids like morphine or hydromorphone should be reduced due to metabolite accumulation.
4. Hemodynamic monitoring: Perioperative monitoring a patient with renal disease undergoing neurosurgery under general anesthesia can be difficult. Along with standard ASA monitors, invasive monitoring such as arterial line, central venous pressure, or pulmonary artery catheter may be needed. Less invasive and dynamic noninvasive monitoring of cardiovascular and volume status such as point-of-care ultrasonography (POCUS), transthoracic or transesophageal echocardiography, and cardiac output monitoring modalities could be used as alternatives. Urine output should be monitored if the patient produces urine.

Fluid Management

For neurosurgery cases, normovolemia should be maintained and hypovolemia or hypervolemia should be avoided. But in patients with coexisting renal disease, management of fluid administration during an anesthetic is challenging due to the following reasons.

(a) Difficulty in maintaining intravascular fluid and electrolyte balance due to deranged excretory and secretory functions.
(b) Poor end-organ reserves due to chronic disease and hypoperfusion.
(c) Difficulty in intraoperative monitoring of fluid and electrolyte balance such as unreliability of urine output as a guide; necessity of invasive/advanced/expensive/complicated monitoring modalities.

Hypervolemia may lead to pulmonary edema, while hypovolemia may cause hemodynamic instability and organ damage.

Crystalloids: Isotonic or slightly hypertonic balanced salt solutions such as plasmalyte or normal saline are suitable for most neurosurgical cases. Hyperkalemia and metabolic acidosis can develop in patients with end-stage kidney disease. Therefore, lactate containing fluids like Ringer's solution should be avoided. Hypotonic and glucose containing fluids should be avoided in cases of craniotomies and hyperglycemia. Administration of large volumes of normal saline may result in hyperchloremic metabolic acidosis. This can be avoided by using balanced salt solutions such as plasmalyte. Conversely, hyponatremia can occur with administration of large volumes of hypotonic solutions (i.e., solutions with lower sodium concentration than plasma).

Colloids: In patients who require immediate intraoperative volume expansion and where packed red blood cells (PRBCs) are either not immediately available or are contraindicated, 5% albumin can be administered. It should be titrated based on hemodynamic response in patients with poor urine output due to renal disease. In patients with renal disease who have adequate urine output, that can be used as an indicator for fluid therapy.

Blood: Perioperative blood transfusion should be given in patients with renal disease only if clinically indicated based on hemodynamic monitoring or end-organ dysfunction. In patients with ongoing surgical bleeding or a hemoglobin <7 g/dL, transfusion of RBCs is often clinically indicated. Potassium should be checked after transfusion since hyperkalemia may develop in an anuric patient.

Mannitol: It should be avoided in patients with renal disease. Mannitol can induce initial

(but transient) increase in plasma osmolality, which can cause hypervolemia and congestive heart failure in susceptible patients. It can also cause hyponatremia (dilutional) and hyperkalemia (transient) leading to worsening edema and changes due to hyperkalemia.

Summary

The aims of fluid management in neurosurgical patients should be to maintain normovolemia and avoid reduction of serum osmolarity. In patients with renal disease, detailed history and physical examination should be performed, and renal function evaluation done by laboratory blood and urine tests. Premedication with aspiration prophylaxis and reduced dose of anxiolytics may be used. Intravenous access can be difficult due to chronic vascular disease and presence of arteriovenous fistulas in the upper extremities. Pharmacokinetic changes due to renal disease may necessitate alteration in doses of aesthetic medications. Invasive and noninvasive cardiovascular intraoperative monitoring may be necessary. Perioperative normovolemia should be maintained and hypervolemia should be avoided. Isotonic or slightly hypertonic balanced salt solutions such as plasmalyte or normal saline are suitable. Lactate containing fluids like Ringer's solution should be avoided in patients with preexisting metabolic acidosis. Colloids like albumin and blood products may be used where clinically indicated.

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Fluid Management in Neurointensive Care

Gentle S. Shrestha and Ankit Rimal

Abstract

Fluid management in the neurocritically ill patient poses unique challenges for the critical care physicians. Apart from general fluid management of the critically ill, an injured brain is predisposed to secondary insults by the nature of the fluids used, the volume status, and hemodynamic fluctuations. Of central interest is the complex interplay between cerebral volumes in response to changes in osmolality in the context of fluid therapy in patients with disrupted blood-brain barrier (BBB). The chemical composition of fluids used in neurocritical care is of special relevance with this respect. Vital elements include the osmolality and the colloid osmotic pressure of the fluid in question. With patients being admitted for a myriad of medical and surgical reasons, generalizing fluid management would not be proper. This chapter aims to discuss the relevant physiology and give an overview of fluid management in neurocritical patients.

Keywords

Acute ischemic stroke · Blood-brain barrier · Colloids · Crystalloids · Fluids · Hyperosmolar therapy · Intracranial pressure · Neurocritical care · Subarachnoid hemorrhage

Background

Fluid management in neurointensive care has broad clinical implications. In addition to "general fluid management" to assure appropriate hemodynamics in these patients, equally important and of distinct clinical implication are the nature of the fluid being used and the nature of injury to the brain. Arguably, nowhere else in the human body would this be of so much importance.

While there is considerable disagreement among clinicians working in the neurointensive unit, with respect to best practices, one thing is certain: fluid management in the critically ill patient in a neurointensive unit is aimed at providing an optimal cerebral blood flow (CBF) in order to supply oxygen as required. Systemic and local factors that compromise this target need careful deliberation. Central to the variation in practices stem from a paucity of high-quality studies. Of note is an inability to incorporate sophisticated monitoring tools into clinical practice for various reasons.

G. S. Shrestha (✉) · A. Rimal
Department of Critical Care Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

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Pathophysiological Considerations

Blood-Brain Barrier

Although the Starling equation elaborates on the factors that govern movement of fluid between the intravascular and the extracellular space, the central nervous system is peculiar in that it is isolated from the intravascular compartment by the blood-brain barrier. With the size of pores in between the tight junctions in the blood-brain barrier limited to about 7–9 Å, movement is limited for most ions [1, 2]. On the contrary, movement of water across this barrier is free and is determined by the relative concentrations of solutes. An acute fall in plasma osmolality is therefore accompanied by a rapid and acute increase in the water content of the brain [3]. Compensation by neuronal cells, during such a physiological extreme, is achieved by a drop in their volume and is due to an active reduction of the intracellular osmoles, causing abundant water movement into the extracellular space. Conversely when plasma osmolality achieves normalcy, there is active internalization of osmoles, a process that is far less efficient than the process of reduction of osmoles and may even lead to demyelination in its most severe form [4].

In contrast to the peripheral tissue compartment where movement of water is governed by the oncotic gradient, it is the osmolar gradient that does so in the CNS. This phenomenon explains why administration of isotonic crystalloids results in peripheral edema due to a dilutional reduction of plasma proteins but not an increase in the intracranial pressure (ICP) due to brain edema. The use of hyperosmolar agents to increase plasma osmolarity to reduce the water content of the brain and the ICP is of great clinical significance.

The blood-brain barrier is expected to be compromised in most critically ill patients in the neurointensive care unit. Would the blood-brain barrier act more like peripheral capillaries if it were to be disrupted? There is no concrete experimental evidence in favor, but in an injury of sufficient magnitude resulting in leakage of plasma proteins into the interstitial space, no oncotic gradient can be expected to cause water movement since the proteins leak directly in the brain [5].

Cerebral Autoregulation

Autoregulation is the ability of the cerebral circulation to alter its resistance in order to maintain a constant CBF over a wide range of mean arterial pressure (MAP) [6]. An intact autoregulatory capacity is essential to increase the CBF and thus the oxygen delivery when there is systemic hypotension. Autoregulation is influenced by pathology and time course over which cerebral perfusion pressure (CPP) occur. A patient with a head injury or with preexisting hypertension may have a dysregulated response.

Neurocritically ill patients are bound to have autoregulatory failure. Although the precipitating factor maybe anywhere from acute ischemia to diabetes mellitus, the final common pathway for dysfunction is vasomotor paralysis. This vasomotor paralysis can take the form of hypoperfusion and ischemia or of hyperperfusion and circulatory breakthrough, both phenomena best avoided in a patient with a primary neurologic insult.

Cerebral Perfusion

Perfusion at the tissue level is determined by both the arterial pressure and the venous pressure with abnormal pressures at either ends leading to deleterious consequences. A lower arterial pressure will result in sluggish flow, while an elevated venous pressure can lead to brain edema. The central venous pressure is unlikely to affect the ICP since it is usually much lower than the latter but can theoretically do so [7]. If indeed that is the case, an elevated central venous pressure (CVP) may preclude venous outflow and contribute to increases in ICP.

It is not unusual for the critically ill brain-injured patient to suffer from central neuroendocrine abnormalities of sodium and water homeostasis. Early and precise diagnosis of diabetes insipidus (DI), syndrome of inappropriate

secretion of antidiuretic hormone (SIADH), and cerebral salt-wasting syndrome (CSWS) is of major importance, because the recommended fluid management is unique for these conditions.

Nature of Fluids

There is no evidence in favor or against a more beneficial effect of colloids over crystalloids in the injured brain. Studies in animal models aiming to substantiate the same have shown conflicting results with some speculating benefit of colloid solutions [8, 9] while others demonstrating the contrary [10, 11].

The useful effects of using hyperosmolar solutions in an injured brain seem reliant on the capacity of these agents to drag fluid out from areas of the brain with an intact blood-brain barrier [12].

Crystalloid Vs. Colloid

In a propensity matched analysis, administering colloids in patients with subarachnoid hemorrhage during the period at risk of delayed cerebral ischemia did not reduce delayed ischemic neurological deficits (DIND) or delayed infarcts [13]. Importantly, it was associated with poorer long-term outcomes.

In the same study, a negative fluid balance showed association with more infarcts in patients having severe angiographic vasospasm. Interestingly, instituting a positive fluid balance was correlated with worse outcomes and protracted intensive care stays in all grades of vasospasm.

The authors concluded that administration of colloids did not ensure a mean positive balance in patients as compared to those who did not. This supports the physiological perspective that administration of colloids in order to maintain intravascular volume may be unavailing and that it may actually lead to more harm.

Tseng et al. demonstrated poorer Glasgow Outcome Scores (GOS) at discharge and at 6 months with administration of colloids, calculated as cumulative daily doses, as compared to crystalloids, had better GOS [14]. Colloids are believed to exacerbate systemic inflammation and thus may contribute to these poorer scores.

Resuscitation Fluids

With respect to resuscitation fluids given to patients with severe traumatic brain injury (TBI), a double-blind RCT done in patients who were comatose in the prehospital setting, administration of hypertonic (7.5%) saline when compared to Ringer's lactate solution did not result in improved extended GOS or rate of favorable outcome at the end of 3 and 6 months of injury [15]. Similar results were seen when Baker et al. compared 7.5% saline/6% dextran with normal saline (NS) for resuscitation in another RCT [16]. Larger, multicenter studies need to be conducted before considering a definitive fluid for resuscitation in neurocritical patients.

Hypo-osmolar fluids and fluids containing glucose are avoided in the neurocritical care patient. A reduction in the plasma osmolality caused by administration of a hypo-osmolar agent can cause cerebral edema by driving water across the osmotic gradient and increasing ICP. After administration of glucose-containing fluids, once glucose is metabolized, only the free water remains, reducing plasma osmolality. Additionally, glucose administration increases neurologic damage and can worsen both local and global ischemia due to ischemic glucose metabolism and tissue acidosis. Commonly used crystalloids along with their composition are given in Table 1.

Albumin

Albumin is believed to have neuroprotective effects by lessening cerebral edema, reducing volume of infarcted brain, and ameliorating behavioral function. The same was established using high doses of 25% albumin in animals with acute ischemic stroke [17, 18]. However, in a randomized, multicenter, placebo-controlled

Table 1 Composition of commonly used IV solutions

Intravenous fluid	Osmolarity (mOsm/L)	Composition (mEq/L)						
		Na	Cl	K	Ca	Mg	Dextrose (g/L)	Lactate (g/L)
5% Dextrose in water (D5W)	278						50	
0.9% NaCl	308	154	154					
Lactated Ringer's solution	275	130	109	4	3			28
Plasmalyte	298	140	98	5		3		
3% NaCl	1026	513	513					
7.5% NaCl	2566	1283	1283					
20% Mannitol	1098							

trial in humans, albumin in high doses did not improve outcomes in patients with acute ischemic stroke [19].

The SAFE Study Investigators in their post hoc study concluded that in critically ill patients suffering from TBI, fluid resuscitation with 4% albumin resulted in higher mortality as compared to NS, strictly in severe TBI patients [20]. There is concern, however, regarding the nature of the colloid compared, which was found to be severely hypo-osmotic [21].

Dysnatremia

Dysnatremia is a common clinical entity causing morbidity in neurointensive care, with both extremes associated with sustained neurological deficits and increased mortality [22, 23]. Normal saline has traditionally seen exclusive use in the neurocritical patient for its tendency to reduce fluid shifts across a damaged blood-brain barrier and prevent cerebral edema. Normal saline, however, is far free from fallacies with large volume (>50 mL/kg) use associated with hyperchloremic metabolic acidosis [24]. Balanced salt solutions have been shown to prevent the development of hyperchloremic acidosis in elderly surgical patients [25]. A single-center RCT in subarachnoid hemorrhage (SAH) patients concluded that administration of balanced crystalloid solutions did result in more hyponatremia or hypo-osmolality when compared to saline-based fluids [26]. Another single-center RCT, although underpowered, did not show reduced incidence of hyperchloremic acidosis in patients with severe TBI and high-grade SAH [27]. What is evident is that there are insufficient studies to recommend regarding the preference for normal saline or buffered solutions in neurocritical patients.

Hyperosmolar Solutions to Reduce ICP

Common mechanisms to reduce ICP among hypertonic saline and mannitol include their ability to dehydrate the brain by creating an osmotic gradient and causing cerebral vasoconstriction by reducing the viscosity of blood. Hypertonic saline may however be advantageous in that it has a quicker onset of action and a more robust and prolonged reduction in ICP and may work in patient in whom mannitol has failed [28].

Two RCTs using equimolar concentrations of hypertonic saline and mannitol demonstrated that mannitol was effective as hypertonic saline (HTS) in decreasing ICP in patients with TBI [29, 30]. Although HTS was seen to rapidly reduce the ICP in response to a bolus dose and was associated with a lower in-hospital mortality, this did not translate into superior outcome at 6 months. HTS, however, did show superiority in maintaining cerebral perfusion in one study, which could of potential benefit in patients with cerebral ischemia [30].

The use of symptom-based bolus dosing of hypertonic saline has been recommended as opposed to sodium target-based dosing to reduce ICP in patients with SAH [31]. The guideline also fell short of recommending the use of hypertonic saline to improve neurological outcomes

since there was insufficient data regarding the same.

Mannitol administration increases the risk for developing acute renal injury, and the recommendation is to use the osmolar gap over serum osmolarity thresholds during treatment with mannitol to monitor the risk of acute kidney injury (AKI) [31]. Although the osmolar gap has not been proven to predict AKI during treatment with mannitol, the osmolar gap appears to correlate best with mannitol concentration which in turn is best associated with toxicity. However, there is not enough evidence to recommend a cut-off value for osmolar gap when evaluating the risk of AKI [31]. It is thus recommended that renal functions be measured closely in these patients [31].

Although a conditional recommendation with very low quality of evidence, it has been suggested to minimize severe hypernatremia to an upper serum sodium range of 155–160 mEq/L as well as hyperchloremia to a serum chloride range of 110–115 mEq/L in order to decrease the risk of AKI [31].

A Cochrane review has, in line with the majority of other recommendations, concluded that on the basis of the limited data available, there is weak evidence to suggest that HTS is no better than mannitol in the long-term management of acute traumatic brain injury [32].

The "triple-H" therapy of hypertension, hypervolemia, and hemodilution was accepted as a treatment measure for symptomatic delayed cerebral ischemia (DCI) in the 1980s [33]. This modality of hemodynamic augmentation has of late come into question since the hypervolemia component is likely of no use and might actually be detrimental [34]. Hypervolemic therapy aimed at maintaining an elevated central venous pressure did not prevent DCI and did not achieve the target of increasing cerebral blood flow [35]. Hypervolemia is detrimental in patients with diminished cardiac reserve, with increased risk of developing pulmonary edema. Current guidelines recommend the judicious use of isotonic solutions to correct hypovolemia in order to maintain a euvolemic state and avert fluid overload [36]. Specific to avoiding DCI, colloid administration and a positive fluid balance were associated with worse outcomes [13].

Hemodilution and Hematocrit

A consequence of fluid administration is a reduction in the hematocrit. This hemodilution is responsible for increasing the CBF and is a compensatory phenomenon to a reduction in the arterial oxygen content [37]. However, in the setting of a neurocritical patient, the normal physiologic response to hypoxia and hemodilution is attenuated and may, in fact, contribute to secondary brain injury. As a result, it seems beneficial to maintain the hematocrit at an optimal level of 30–33% to optimize both the oxygen-carrying capacity and the viscosity and help improve neurological outcomes [38].

Goals of Fluid Management in Neurointensive Care

The primary objective of fluid management in neurocritical care is achieving optimal cerebral oxygenation and perfusion while limiting secondary brain injury. Monitoring plays a crucial role in identifying these endpoints and can guide fluid therapy objectively. Clinical judgment along with monitoring can help guide fluid therapy across an array of clinical conditions.

Available Guidelines

Numerous guidelines and consensus statements are available for fluid management in the brain-injured patient [39–42].

Aneurysmal Subarachnoid Hemorrhage

Although only nimodipine has been established to improve outcome in this group of patients [43], the importance of fluid management cannot be sidelined as hyponatremia and hypovole-

mia, which are frequently encountered, are important causes of secondary brain injury. The incidence of cerebral infarcts in hypovolemic patients is increased, particularly when fluids are restricted [44].

Acute Ischemic Stroke

Hypoperfusion following acute ischemic stroke is common since inadequate intake is a major concern. These patients are susceptible to exacerbation of the ischemic brain insult as well as systemic complications such as renal impairment and thrombosis. On the other side, hypervolemia in these patients can worsen brain edema and stress the myocardium. While euvolemia is desired, patients with ailments such as renal failure and heart disease might benefit from vigilant volume resuscitation [41].

Cerebral and Cerebellar Infarction with Swelling

The use of isotonic saline and avoidance of hypo-osmolar fluids forms the mainstay of maintenance fluid management in this group of patients. As with all other cases, fluids with dextrose are avoided [42].

Acute Cerebral Edema

Guidelines from the Neurocritical Care Society for the treatment of acute cerebral edema have been summarized in Table 3.

As can be observed from Table 2, wide consensus is to avoid hypovolemia and hypervolemia and target euvolemia. Hypovolemia is a state of depleted intravascular volume that is inadequate to sustain minimally sufficient cerebral perfu-

Table 2 Excerpt of guideline/consensus conference statement on fluid management in neurocritically ill patients

Guideline	Management
AHA/ASA Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage [40]	• Maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI (Class I, Level of Evidence B) • Administration of large volumes of hypotonic fluids and intravascular volume contraction is not recommended after aSAH (Class III, Level of Evidence B) • Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended (Class III, Level of Evidence B)
AHA/ASA Guidelines for the Early Management of Patients with Acute Ischemic Stroke [41]	• Hypovolemia should be corrected with intravenous NS • Apart from unusual losses, daily fluid maintenance for adults can be estimated as 30 mL/kg of body weight • For patients who are hypovolemic at presentation, rapid replacement of the depleted intravascular volume followed by maintenance intravenous fluids is reasonable
AHA/ASA Recommendations for the Management of Cerebral and Cerebellar Infarction with Swelling [42]	• Use of adequate fluid administration with isotonic fluids might be considered (Class IIb, Level of Evidence C) • Hypotonic or hypo-osmolar fluids are not recommended (Class III, Level of Evidence C) • Use of prophylactic osmotic diuretics before apparent swelling is not recommended (Class III, Level of Evidence C)
Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference [39]	• Intravascular volume management should target euvolemia and avoid prophylactic hypervolemic therapy. In contrast, there is evidence for harm from aggressive administration of fluid aimed at achieving hypervolemia (high-quality evidence, strong recommendation) • Isotonic crystalloid is the preferred agent for volume replacement (moderate quality evidence, weak recommendation) • In patients with a persistent negative fluid balance, the use of fludrocortisone or hydrocortisone may be considered (moderate-quality evidence, weak recommendation)

Table 3 Guidelines for the acute treatment of cerebral edema in neurocritical care patients [31]

Cerebral edema in patients with subarachnoid hemorrhage • Using symptom-based bolus dosing of hypertonic sodium solutions rather than sodium target-based dosing for the management of ICP or cerebral edema in patients with SAH (conditional recommendation, very low-quality evidence) • Cannot recommend a specific dosing strategy for HTS to improve neurological outcomes in patients with SAH, due to insufficient evidence
Cerebral edema in patients with traumatic brain injury • Use hypertonic sodium solutions over mannitol for the initial management of elevated ICP or cerebral edema in patients with TBI (conditional recommendation, low-quality evidence) • Suggest that neither HTS nor mannitol be used with the expectation for improving neurological outcomes in patients with TBI (conditional recommendation, low-quality evidence) • Suggest that the use of mannitol is an effective alternative in patients with TBI unable to receive hypertonic sodium solutions (conditional recommendation, low-quality evidence) • Recommend against the use of hypertonic sodium solutions in the prehospital setting to specifically improve neurological outcomes for patients with TBI (strong recommendation, moderate-quality evidence) • Suggest against the use of mannitol in the prehospital setting to improve neurological outcomes for patients with TBI (conditional recommendation, very low-quality evidence)
Cerebral edema in patients with acute ischemic stroke • Suggest using either hypertonic sodium solutions or mannitol for the initial management of ICP or cerebral edema in patients with acute ischemic stroke (conditional recommendation, low-quality evidence) • Cannot recommend either hypertonic saline or mannitol for improving neurological outcomes in patients with acute ischemic stroke, due to insufficient evidence • Suggest clinicians consider administration of hypertonic sodium solutions for management of ICP or cerebral edema in patients with acute ischemic stroke who do not have an adequate response to mannitol (conditional recommendation, low-quality evidence) • Suggest against the use of prophylactic scheduled mannitol in acute ischemic stroke due to the potential for harm (conditional recommendation, low-quality evidence)
Cerebral edema in patients with intracerebral hemorrhage • Suggest using hypertonic sodium solutions over mannitol for the management of ICP or cerebral edema in patients with intracerebral hemorrhage (conditional recommendation, very low-quality evidence) • Suggest that either symptom-based bolus dosing or using a targeted sodium concentration is appropriate hypertonic sodium solution administration strategy for the management of elevated ICP or cerebral edema in patients with intracerebral hemorrhage (conditional recommendation, very low-quality evidence)
Cerebral edema in patients with bacterial meningitis • Insufficient evidence to determine whether hypertonic sodium solutions or mannitol is more effective to reduce ICP or cerebral edema in patients with community-acquired bacterial meningitis
Cerebral edema in patients with hepatic encephalopathy • Suggest using either hypertonic sodium solutions or mannitol for the management of ICP or cerebral edema in patients with hepatic encephalopathy (conditional recommendation, very low-quality evidence) • Insufficient evidence to determine whether either hyperosmolar therapy or ammonia-lowering therapy improves neurological outcomes in patients with hepatic encephalopathy

sion and oxygenation. Similarly, euvolemia is an intravascular volume that suffices the required cerebral perfusion to maintain adequate brain oxygenation [45]. Considering the available evidences and aiming to minimize secondary brain injury, judicious fluid management can be a cornerstone for improving outcome of patients in neurointensive care (Table 3).

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Fluid Management in Sepsis

Michaël Mekeirele, Domien Vanhonacker, and Manu L. N. G. Malbrain

Abstract

Adequate fluid management in sepsis requires a thoughtful approach. While early aggressive fluid therapy is generally required, one should also be aware of the risks of blind continued administration of large fluid volumes. In the first part of this chapter, we offer an in-depth literature overview on the available fluids in sepsis. In the second part, we stress the importance and prove the relevance of viewing fluids as drugs. Finally, we explain that sepsis can be divided into four temporally distinct phases each requiring a different fluid strategy: resuscitation, optimization, stabilization, and evacuation. We offer a phase-by-phase guidance using this ROSE conceptual model.

Keywords

Fluid management · Sepsis · Septic shock · Intensive care medicine · ICU

Introduction

The third international consensus definition for sepsis and septic shock stated the following: "Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection" [1]. Septic shock is a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are profound enough to substantially increase mortality [1]. In order to address the circulatory dysfunction, early aggressive fluid therapy has been one of the cornerstones in the treatment of septic shock using an early goal-directed therapy [2]. The revised surviving sepsis campaign guidelines advocate the start of 30 ml/kg of IV fluid within the first hour [3]. On the other hand, the body of evidence and awareness has grown that positive daily and cumulative fluid balances during ICU stay could increase mortality [4]. Furthermore, studies have shown that the type of IV fluid given during resuscitation also has an impact on the patients' outcome [5–7].

This led to two important concepts. The *first concept* is the fact that fluids should be considered as drugs. They come with indications, contraindications, and potential adverse effects.

M. Mekeirele
Vrije Universiteit Brussel (VUB), Universitair ziekenhuis Brussel (UZB), Department of Critical Care, Jette, Belgium

D. Vanhonacker
Vrije Universiteit Brussel (VUB), Universitair ziekenhuis Brussel (UZB), Department of Critical Care, Jette, Belgium

Vrije Universiteit Brussel (VUB), Universitair ziekenhuis Brussel (UZB), Department of Anesthesiology, Jette, Belgium

Manu L. N. G. Malbrain (✉)
International Fluid Academy, Lovenjoel, Belgium

First Department of Anaesthesiology and Intensive Therapy, Medical University of Lublin, Lublin, Poland

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Similar to antibiotic stewardship, a more thoughtful administration of fluids is necessary, hence giving birth to the concept fluid stewardship. This addresses the importance of choosing the right drug, applying the right dose, using it for the correct duration, and thinking timely about de-escalation. This concept is named the 4 Ds of fluid therapy referring to drug, dose, duration, and de-escalation [8].

Even more important, the *second concept* states that adequate fluid therapy during sepsis requires a different strategy depending on the phase of illness. The first phase is one of a more aggressive resuscitation to *rescue* the patient's life; second, we need to *optimize* organ perfusion by more diligently titrating fluids; in the third phase, we aim at *stabilizing* the fluid balance to a neutral daily fluid balance; and in the final phase, we try to *evacuate* the potentially accumulated fluids. Hence, the ROSE acronym has been proposed as a mnemonic for this conceptual model [8].

In this chapter, we will summarize the available literature on fluid therapy in sepsis using the abovementioned concepts of 4 Ds and ROSE as illustrated in Fig. 1 [8].

Key points that will be discussed:

- Fluids are drugs and should be treated accordingly with indications, contraindications, and adverse effects.
- One should consider the 4 Ds of fluid therapy: drug, dose, duration, and de-escalation.
- We need to consider the four dynamic phases of fluid therapy in sepsis applying the ROSE conceptual model: resuscitation, optimization, stabilization, and evacuation.

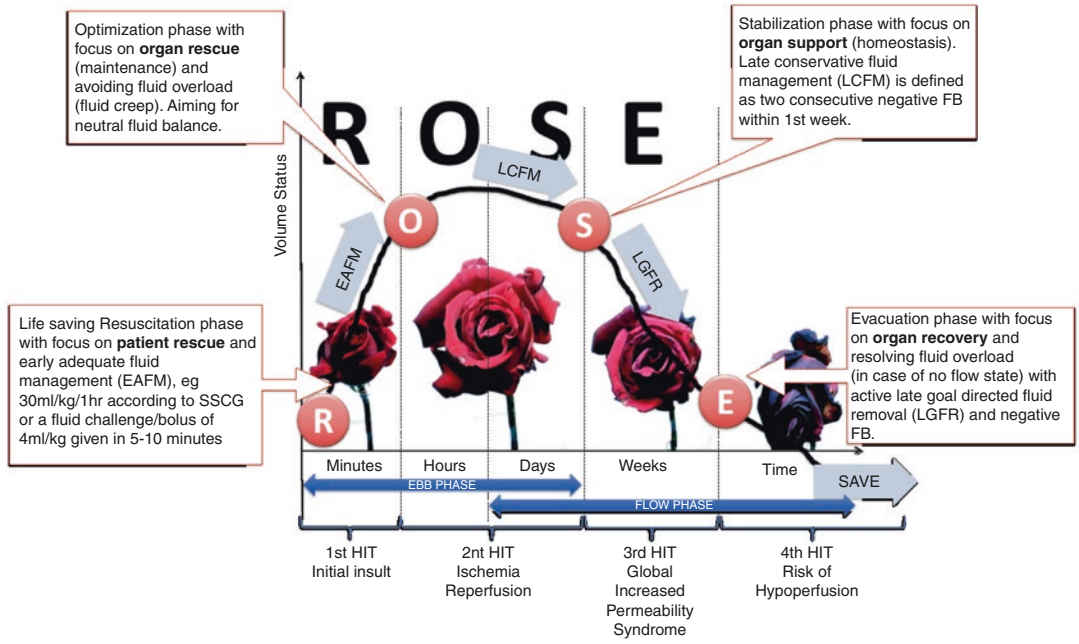

Fig. 1 Visualization of the ROSE conceptual model. Graph showing the four-hit model of shock with evolution of patients' cumulative fluid volume status over time during the five distinct phases of resuscitation: resuscitation (R), optimization (O), stabilization (S), and evacuation (E) (ROSE), followed by a possible risk of hypoperfusion in case of too aggressive deresuscitation. On admission patients are hypovolemic, followed by normovolemia after fluid resuscitation (EAFM, early adequate fluid management), and possible fluid overload, again followed by a phase going to normovolemia with late conservative fluid management (LCFM) and late goal-directed fluid removal (LGFR) or deresuscitation. In case of hypovolemia, O_2 cannot get into the tissue because of convective problems; in case of hypervolemia, O_2 cannot get into the tissue because of diffusion problems related to interstitial and pulmonary edema and gut edema (ileus and abdominal hypertension). Adapted according to the Open Access CC BY License 4.0 with permission from Malbrain et al. [8]

Drug

The available types of fluids have been extensively described in earlier chapters. In this section, we will take you through the available literature on the use of different types of fluid in sepsis.

Colloids

Background

Historically, synthetic colloids have been used in abundance in septic shock mainly because it was assumed that when using colloids less volume would be needed to expand the circulating blood volume in order to obtain hemodynamic stabilization. Traditionally, it was suggested that one would need to double the volume of crystalloids as compared to colloids to achieve the same increase in intravascular volume. However, recent data show that in reality this ratio may be closer to 1.3:1 or even 1:1 in cases of acute shock, after induction of anesthesia and during surgery where fluid distribution, elimination, and excretion are altered [9, 10].

Hydroxyethyl Starches (HES)

Over time, strong evidence grew regarding the negative effects of synthetic colloids. In the VISEP study, a two-by-two factorial randomized controlled clinical trial (RCCT) including 537 patients, administration of hydroxyethyl starch (HES, $n = 262$) was compared to using crystalloids, mainly Ringer's lactate ($n = 275$) [6]. A central venous pressure (CVP) of 8 mmHg was targeted. Administration of HES as opposed to crystalloids was associated with higher rates of acute renal failure and/or renal replacement therapy (RRT): 34.9% vs. 22.8% ($p = 0.002$) [6]. Acute kidney injury (AKI) was defined as a doubling of baseline creatinine values or requirement for renal replacement therapy. This complex study also compared intensive insulin therapy ($n = 247$) to conventional insulin therapy ($n = 290$). HES 10% was given at a maximum limit of 20 mL/kg/day; however, more than 10% of the patients exceeded this limit. More patients in the HES group had heart failure or received emergency surgery, and the study was stopped prematurely because of a higher incidence of hypoglycemia in the intensive insulin group.

The increased need for RRT in patients treated with synthetic colloids was later confirmed, albeit discussable, by the CHEST trial including 7000 patients, comparing administration of HES with saline [7]. In this pragmatic study, there was no difference in 90-day mortality nor in the incidence of AKI (according to RIFLE scoring). There was even a reduction in patients with RIFLE-R and RIFLE-I and similar RIFLE-F in patients administered 6% HES. The use of 6% HES did result in an increased urinary output and slight increase in serum creatinine. Only the (subjective) need for RRT was significantly different: 7.0% in the HES group vs 5.8% in the crystalloid group (RR 1.21; 95%CI 1–1.45; $p = 0.04$). Patients were randomized after an average of 11 ± 156 h pointing toward large differences between patients and non-Gaussian distribution. There has been a lot of criticism on the CHEST trial especially since the authors did not want to share the raw data [11, 12].

In a 2012 RCCT, the 6S study in 798 patients showed that administration of HES not only increased the need for RRT when compared to Ringer's acetate but also significantly increased mortality in patients treated with HES [5].

The defenders of the popular HES solutions were at first relieved when the results of the CRYSTMAS study were published. In this study, 196 patients were randomly resuscitated using either 6% HES 130/0.4 or NaCl 0.9%. The authors stated there was no difference in adverse events between both groups, while a lower volume of fluids was needed when using HES [13]. However, soon after, publication concerns arose about potential publication bias. When the full data set was reassessed, there appeared to be no volume-saving effect when using HES. The study was also proven to be underpowered to identify differences in the need for RRT. However, there was a trend against the use of HES regarding mortality and time to RRT with a doubling in the need for RRT in the patients treated with HES [14].

The CRISTAL study is another trial at first seemingly stating similar outcomes when administering crystalloids or colloids, this time in patients with hypovolemia. Over 9 years, 2847 patients were included. However, it was an open-label trial where mainly HES was used as a colloid besides gelatins and dextran, but also human albumin was administered. All these colloids were analyzed as one group. Although subgroup analyses were performed, these were underpowered to show significant differences in renal failure or mortality. It should also be noted that NaCl 0.9% was the main crystalloid used. As explained later, NaCl 0.9% is also associated with detrimental effects on renal function and an increased need for RRT [15].

Based on this evidence, the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA stated that starches mustn't be used anymore in patients with burn injuries, renal failure, sepsis, and septic shock [16].

Gelatins

Gelatins have always been less popular as a colloid. A recent systematic review stated that gelatins increase the risk of anaphylaxis and may increase mortality, renal failure, and bleeding due to extravascular uptake and coagulation impairment. The prospective GENIUS trial aiming at confirming or refuting this statement should be finalized in 2021. Given the cheaper and safer alternative fluids, we advise against the use of gelatins for the time being [17].

Dextran

Data on effectiveness and complications of dextran are scarce. A retrospective analysis of 332 patients stated that dextran 70 increased bleeding risk and need for blood products [18]. A more recent study propensity score matching 778 patients could not confirm these findings [19]. However, older data also showed tissue deposition of dextran after administrating this fluid in hemodialysis patients [20]. Given the absence of evidence favoring dextran and given the cheaper and proven safe alternatives, we do not recommend the use of dextran.

Human Albumin

Following the evidence on synthetic colloids, concerns arose about the use of albumin in ICU patients. The SAFE study was an RCCT comparing administration of fluid boluses of either albumin 4% or saline 0.9% in patients with sepsis. In this study, albumin appeared to be safe to administer [21]. A post hoc analysis in a subset of patients with severe sepsis showed that the use of albumin had an adjusted odds ratio for death of 0.71 (95% CI: 0.52–0.97; $p = 0.03$), suggesting a mortality benefit [22]. However, it should be noted that all patients already received initial fluid resuscitation before inclusion resulting in less administered fluid volumes during the intervention in both groups. As later explained, this implies that this trial is performed during the optimization phase rather than during the resuscitation phase.

In the ALBIOS trial, including patients with sepsis, simultaneous administration of crystalloids and albumin 20% ($n = 903$) to achieve and maintain a serum albumin of 30 g/L (with a normal range being 34 to 54 g/L) also appeared to be safe when compared to using only crystalloids ($n = 907$). Again, a post hoc analysis suggested a potential outcome benefit when using albumin in septic shock [23]. Given the broad use of NaCl 0.9% in both studies, the post hoc analysis should be critically appraised keeping in mind the available literature on balanced and unbalanced crystalloids that will be discussed later, disfavoring the use of NaCl 0.9%.

A third trial on albumin, the EARSS study by Charpentier and Mira in 2011, has only been published in abstract. In this multicenter prospective trial, early administration of 100-mL albumin 20% every 8 h was compared to sole application of saline 0.9%. The mortality, 24.1% in the albumin group and 26.3% in the saline group, was not significantly different [24].

While all individual trials merely show a trend toward mortality reduction, Wiedermann combined the data and showed that the pooled relative risk is 0.92 (CI: 0.84–1.00; $p = 0.046$) [24]. In our opinion, this implies that albumin 4% or 20% could be a viable option in a subset of

patients with severe sepsis or septic shock, respectively, in case of low serum albumin levels (<30 g/L).

A final large trial worth mentioning is the FEAST trial. This RCCT in African children with febrile illness and impaired perfusion compared administration of either albumin boluses, NaCl 0.9% boluses, or no boluses. The fluid administrated in the intervention groups was 20 mL/kg or 40 mL/kg over 1 h potentially followed by another 20 ml/kg or 40 ml/kg over 1 h. After inclusion of 3141 patients, this study was prematurely ended due to increased mortality in both groups treated with fluid boluses. While technically this is a study including albumin resuscitation, it should mainly warn against uncontrolled fixed administration of large fluid boluses [25].

Take-home messages on the use of colloids for resuscitation in sepsis:

- Based on the literature, synthetic colloids (especially HES solutions) mustn't be used in sepsis, burns, or patients with renal failure.
- Albumin 4% or 20% could be a viable option in a subset of patients with severe sepsis or septic shock, respectively, in case of low serum albumin levels (<3 g/dL).

Crystalloids

Crystalloids are less expensive than colloids. As they appear to be as effective as human albumin, they are more generally used in septic shock. However, the term crystalloid covers a lot of different fluid types with different properties. The tonicity of the fluid will determine its initial distribution volume. As such, *hypotonic* crystalloids have no place in fluid resuscitation during septic shock. However, in the absence of contraindications such as craniocerebral trauma or ischemic stroke, these are the maintenance fluids of choice. Maintenance fluids are given when daily fluid needs cannot be covered orally or in case of cellular dehydration [26–28]. Regarding resuscitation fluids, we will now first cover the hypertonic crystalloids followed by the unbalanced and balanced isotonic crystalloids.

Theoretically, administering a *hypertonic* fluid should increase the intravascular volume more than isotonic infusions due to the higher tonicity favoring a fluid flux toward the intravascular space. However, the recent HYPERS2S trial using hypertonic saline as a resuscitation fluid did not show reduced cumulative fluid administration nor positive outcome effects. Although there was an initial trend toward less fluid administration during resuscitation, this effect was nullified by supplementary fluid administration due to hypernatremia [29]. Similar results were found in the HERACLES trial examining the use of hypertonic saline for resuscitation in patients admitted to the ICU after cardiac surgery [30].

The detrimental effects of *isotonic* hyperchloremic fluids when compared to balanced solutions have been well established in preclinical studies. The use of (ab)normal saline 0.9% was consistently associated with metabolic acidosis, decreased renal perfusion, and increased AKI [31–38]. Two pilot studies SPLIT and SALT, while underpowered to show a significant difference, confirmed the feasibility of comparing balanced and unbalanced crystalloid solutions in the ICU [39, 40]. Two large randomized trials, SMART [40] in the ICU and SALT-ED [41] in the emergency department, showed that patients treated with balanced crystalloids had a significant reduction in MAKE 30 (*m*ajor *a*dverse *k*idney *e*vents within *30* days), a composite outcome for death, need for RRT, and persisting renal dysfunction. In these trials, the benefit of balanced crystalloids was greatest in the subgroup of patients admitted to the ICU with sepsis or septic shock. The number needed to treat to prevent one death, new RRT, or persisting renal dysfunction was around 20.

Take-home messages on crystalloids for resuscitation in sepsis:

- Based on the available data, isotonic balanced crystalloids (and not saline) should be the

resuscitation fluid of choice in patients with sepsis and septic shock.
- Overzealous administration of (ab)normal saline may contribute to hyperchloremic metabolic acidosis.

Blood Products

Blood products are not commonly administered as a resuscitation fluid in patients with septic shock. However, the concern of an adequate hemoglobin level as a means for oxygen transport has led Rivers and coworkers to implement transfusion triggers in their bundle of early goal-directed therapy [2]. During the last decade, evidence grew that a more restrictive transfusion strategy might be as good or even better than aiming for a higher hemoglobin level [42–44].

The first large RCCT suggesting the benefit of a lower transfusion threshold in ICU was the TRICC trial by Hébert et al. Contrary to previous beliefs and retrospective studies, they showed that maintaining a hemoglobin level between 7 g/dL and 9 g/dL resulted in a similar to better outcome than aiming for a hemoglobin level between 10 g/dL and 12 g/dL. There was a trend favoring overall survival and a significant lower in hospital mortality in the group treated with a restrictive transfusion strategy [43].

The TRISS trial, including nearly 1000 anemic patients with septic shock, proved that also in septic patients a hemoglobin transfusion threshold of 7 g/dL led to similar outcomes than aiming for a hemoglobin level above 9 g/dL. This was true for all age groups, for patients with cardiovascular comorbidities and who were independent of SAPS II score. Patients with an acute coronary syndrome, active bleed, or burns were excluded from this study [44]. On the other hand, a more recent RCT targeting 300 oncological septic patients reported a lower 90-day mortality in the group with the more liberal transfusion strategy [45].

It remains unclear whether blood product shelf life or the nonapplication of leucocyte depletion could be an explanation as to why adhering to a higher transfusion threshold leads to more unfavorable outcomes. While leucocyte reduction is common practice nowadays in Europe and Australia, its application in the beforementioned studies is unclear. In 2008, leucocyte depletion was proven to be associated with reduced frequency of non-hemolytic febrile transfusion reactions, reduced risk of CMV transmission, reduced risk of HLA alloimmunization and platelet refractoriness, as well as reduced mortality and organ dysfunction in cardiovascular surgery patients [46]. The impact of red blood cell shelf life remains unclear. The first concerns arose in 2008, after the publication of a retrospective study stating that transfusion of red blood cells after 14 days of storage was associated with a higher rate of postoperative complications and a reduction in short- and long-term survival. However, post hoc analysis showed that patients receiving these “older” red blood cells also received more units of red blood cells, possibly suggesting a selection bias toward more severely ill patients in the group treated with older blood products [47].

Take-home message on blood products in sepsis:

- Given the current evidence, we propose to adhere to a lower transfusion threshold of 7 g/dL, transfusion practice that can however be further tailored to the individual patient’s needs.

Duration

Murphy et al. showed that the more microcirculatory hypoperfusion and subsequent organ damage related to ischemia reperfusion occurs, the longer the delay in fluid administration in patients with septic shock [48]. They compared outcomes in sepsis when using a strategy of either early adequate or early conservative fluid therapy combined with either late conservative or late liberal fluid administration. They found that patients treated with a combination of early adequate and late conservative fluid management had the best outcomes [48]. Other studies suggest that especially the late conservative approach might have

the biggest impact on outcome [49–52]. One should not continue fluids to treat the numbers (e.g., to normalize a low urine output, central venous pressure, cardiac output, or blood pressure), but one should give fluids to treat shock and DO_2/VO_2 imbalance. Fluid therapy should be stopped when shock has resolved, or fluids are no longer needed.

Take-home messages on duration:

- Treating patients with a combination of early adequate and late conservative fluid management has the best outcome.
- Don't give fluids to treat the numbers but to treat shock and stop them when they are no longer needed.

Dose

As stated by Paracelsus, "all things are poison, and nothing is without poison; only the dose permits something not to be poisonous," and as described earlier, the detrimental effects of fluid overload are well established. Dosing should be adjusted to both pharmacokinetics and pharmacodynamics.

Pharmacokinetics describes how the body interacts with a drug. In fluid therapy, different types of fluids remain intravascular for a different percentage and for a different time period, favoring fluids with higher tonicity. It is well established that during vasoplegic shock these characteristics can be altered [9, 10].

Pharmacodynamics describes the interaction of a drug to its specific effect. Here, the Frank-Starling relationship between cardiac preload and cardiac output correlates to the dose effect curve as can be seen for other drugs. Due to the shape of the Frank-Starling curve, the effect of fluids on cardiac output is not constant. Determining an individual patient's position on the Frank-Starling curve and subsequently predicting the effect of fluid administration are the arts of prescribing adequate fluid therapy [53].

Given the evolving pharmacokinetic and pharmacodynamic properties of fluid therapy, the adequate dose of fluid therapy is dependent on individual factors as well as the timing of fluid administration. We will dig deeper into these characteristics when describing the four dynamic phases of fluid therapy.

Dynamic tests for assessing fluid responsiveness and tailoring fluid therapy according to patient needs, such as the passive leg raising test, are described elsewhere [8]. We would however like to point out that it is a misconception that all fluid-responsive critically ill patients should receive fluids. Resuscitation fluids can be stopped safely once the initial signs and symptoms of hypovolemia and shock have resolved and should not be continued to treat numbers.

Administration of a fluid bolus or even better a (mini-)fluid challenge is the preferred way of fluid administration during resuscitation. It is a quick infusion of a small amount of fluids within a short period of time (5–10 min). The volume administered with a fluid bolus is highly clinician-dependent varying between 500 mL (over 10 min) and 1000 mL (over 15–20 min) [54]. However, the smaller, the better, and the minimal fluid volume required to increase venous return is around 4 mL/kg/5 min [55]. We would advocate using smaller volumes when appropriate in combination with clinical evaluation of the hemodynamic effect after administration.

Take-home messages on dose:

- Given the evolving pharmacokinetic and pharmacodynamic properties of fluid therapy, the adequate dose of fluid therapy is dependent on both individual factors and the timing of fluid administration.
- We propose using fluid challenges of 4 mL/kg/5 min combined with clinical evaluation of the effect after administration.

De-escalation

As stated in the ROSE conceptual model, which will be discussed later, we must be aware when to stop administering resuscitation fluids and when to start fluid evacuation in case of accumulation. This is essential to prevent fluid overloading and the herewith associated increase in adverse

events. Fluid overload is defined as a 10% increase in fluid accumulation from baseline body weight.

The approach of restricted fluid therapy after initial resuscitation as well as application of diuretic therapy after stabilization is supported by the FACTT trial. In this trial, patients treated with a restrictive fluid management after initial resuscitation and diuretic therapy after stabilization had a reduced number of ventilator-dependent days [56].

The retrospective RADAR-trial including 400 patients also identified that a negative fluid balance on day three, achieved by active evacuation of accumulated fluid, is associated with an improved outcome. Limiting the intake of maintenance fluids and drug diluents and active fluid evacuation are essential steps toward achieving this goal [57].

The CLASSIC trial tries to evaluate the impact of early de-escalation: a fluid restrictive fluid resuscitation. While the CLASSIC trial was only a feasibility trial, it did show a trend toward benefit with a fluid restriction strategy. The results of the larger CLASSIC-2 trial are eagerly awaited [51].

In contrast to these results, the RELIEF trial, conducted in patients undergoing major abdominal surgery, showed that a restrictive fluid regimen was associated with increased AKI. There was no difference in mortality or disability between the two strategies. In our opinion, this study warns against blind fluid removal potentially leading to hypovolemia, while it should not necessarily refute controlled active fluid removal [58].

Take-home messages on de-escalation:

- Restrictive fluid management and diuretic therapy after stabilization can reduce the number of ventilatory-dependent days.
- During de-escalation, one should avoid hypovolemia.

The Four Phases of Fluid Resuscitation: The ROSE Principle

When managing fluid therapy during sepsis, one should mind not only the fluid but also the fluid-patient interaction as well as the phase of illness. Malbrain et al. proposed the mnemonic ROSE in 2014 after an initial publication describing four distinct phases in septic patients by Vincent in 2013 [8, 59]. This concept is summarized in Table 1.

During the initial phase, aggressive yet adequate fluid administration should be applied to rescue the patient. Following initial *resuscitation*, a more careful titration of fluids ought to be applied to *optimize* the circulation. This aims at counteracting organ damage while avoiding fluid overload. Neutral fluid balances should be targeted a few days after the initial septic shock to avoid the detrimental effects of positive fluid balances as described by the SOAP trial [4]. This phase is called the *stabilization* phase. The fourth and more heavily debated phase is the active *evacuation* phase to remove accumulated fluids. The recently published FACTT trial supports this active approach of fluid elimination [56].

Resuscitation Phase

When administering fluids during the resuscitation phase, we aim at restoring the intravascular volume to increase and maintain cardiac output. In this way, we try to increase oxygen delivery and restore tissue oxygenation.

As suggested by Rivers et al., the sepsis guidelines still favor the liberal use of resuscitation fluids, proposing 30 mL/kg of fluid therapy started in the first hour after presentation with septic shock [2, 3]. The blind adherence to these protocols does however not improve the outcome of patients with sepsis as was clearly shown by the PROCESS, PROMISE, ARISE, and SEPSISPAM studies [61–64] that have been discussed in previous chapters. Growing evidence from cohort studies and smaller trials support a more restrictive resuscitation strategy in septic shock [51, 58, 65]. In children and adults from low-income countries, early aggressive fluid therapy was even associated with increased mortality [25, 66]. Although these results might be related to the lack of access to mechanical ventilation or patient- and disease-specific parameters, other studies in high-income countries such as the SOAP and VASST trials also identified a

Table 1 The ROSE conceptual model avoiding fluid overload (adapted from Malbrain et al. with permission) [60]

	Resuscitation	**O**ptimization	**S**tabilization	**E**vacuation
Hit sequence	First hit	Second hit	Second hit	Third hit
Time frame	Minutes	Hours	Days	Days to weeks
Underlying mechanism	Inflammatory insult	Ischemia and reperfusion	Ischemia and reperfusion	Global increased permeability syndrome
Clinical presentation	Severe shock	Unstable shock	Absence of shock or threat of shock	Recovery from shock, possible global increased permeability syndrome
Goal	Early adequate goal-directed fluid management	Focus on organ support and maintaining tissue perfusion	Late conservative fluid management	Late goal-directed fluid removal (deresuscitation)
Fluid therapy	Early administration with fluid boluses, guided by indices of fluid responsiveness	Fluid boluses guided by fluid responsiveness indices and indices of the risk of fluid administration	Only for normal maintenance and replacement	Reversal of the positive fluid balance, either spontaneous or active
Fluid balance	Positive	Neutral	Neutral to negative	Negative
Primary result of treatment	Salvage or patient rescue	Organ rescue	Organ support (homeostasis)	Organ recovery
Main risk	Insufficient resuscitation	Insufficient resuscitation and fluid overload (e.g., pulmonary edema, intra-abdominal hypertension)	Fluid overload (e.g., pulmonary edema, intra-abdominal hypertension)	Excessive fluid removal, possibly inducing hypotension, hypoperfusion, and a "fourth hit"

relationship between positive fluid balances and increased mortality rates [4, 67].

Septic shock is a state of imbalance between oxygen supply (DO_2) and demand (VO_2) due to an effective or functional state of hypovolemia. Interest for the early introduction of vasopressors to reduce the functional hypovolemia and increase venous return by recruiting fluids from the splanchnic bed was sparked by the vasoplegic nature of septic shock [68]. Up to this day, no hard evidence supports this physiological plausible strategy. We are eagerly awaiting the results of the CLOVER trial, aimed at providing evidence on this topic. Inclusions should finish in the summer of 2021.

Summarizing the results from the literature, rapid fluid administration to achieve hemodynamic goals remains important. Rather than administering a fixed dose of fluids (one size fits all), an individualized approach, keeping the patient's premorbid conditions in mind, seems more appropriate [69–71]. The lower autoregulation threshold of the most vulnerable organs (brain and kidneys) should be reached [72]. To achieve this, it is key to obtain a correct assessment of fluid status as well as fluid responsiveness. The most adequate method is assessing functional hemodynamic parameters such as stroke volume and pulse pressure variation and tests such as end-expiratory occlusion or passive leg raising. The passive leg raising test is particularly interesting since it perfectly mimics fluid administration without giving a single drop of fluid. It is well studied and is recommended by the surviving sepsis campaign [73, 74]. Even more important than predicting fluid responsiveness is the repeated evaluation of the patient both before and after fluid administration in order to guide further fluid therapy.

Take-home messages on resuscitation phase:

- Rapid fluid administration to achieve hemodynamic goals remains important while keeping in mind the patient's premorbid conditions.
- The passive leg raising test is the preferred test to assess fluid responsiveness.
- Assessment of changes in functional hemodynamic parameters before and after fluid administration should be used to guide further individualized fluid therapy.

Optimization Phase

Within hours of initial resuscitation, a second hit occurs due to the reperfusion of previously ischemic cells. While fluid administration is evident during the initial resuscitation phase, a more cautious approach is warranted during optimization using the previously described dynamic tests for fluid responsiveness. In this phase, the risks of fluid overload should be monitored closely when deciding to administer extra fluids. Especially the evolution of lung impairment should warn against overaggressive fluid therapy at this stage. When in doubt, advanced hemodynamic monitoring can be of additional value. These techniques are described in previous chapters as well as in dedicated articles [75, 76].

Take-home messages on optimization phase:

- During optimization, a more diligent application of fluids is warranted.
- Invasive hemodynamic monitoring can help to optimize fluid therapy during this phase.

Stabilization Phase

A stabilization phase is usually obtained within a few days. This phase is characterized by the absence of shock or impending deterioration. During this phase, there should be no need for additional fluid boluses. In case the patients cannot have oral intake, hypotonic maintenance fluids should be given to cover the daily fluid needs (1 mL/kg/h), sodium (1–1.5 mmol/kg/day), potassium (0.5–1 mmol/kg/day), and glucose (1–1.5 g/kg/day) [28].

The focus should be on awareness of the total volume of fluids administered, including maintenance fluids, replacement fluids for ongoing losses, feeding fluids, as well as fluids administered along with medication. The recent retrospective RADAR study showed that these fluids contribute more to fluid input than resuscitation fluids [57]. The quantitative relevance of fluids administered as drug diluents and fluids to guarantee catheter patency, the so-called fluid creep, has been stressed by Van Regenmortel et al. [77]. It is important to take all these administered fluids into account when assessing the needs of a patient in order to prevent the detrimental effects of fluid overload [4, 57]. More often than not, this implies cessation of maintenance fluids due to an already sufficient administration.

Take-home messages on stabilization phase:

- During stabilization phase, one should aim for a neutral to negative fluid balance.
- All fluids, including drug diluents, should be taken into account when assessing the daily fluid needs of a patient.

Evacuation Phase

After the second hit due to ischemia reperfusion, patients can either start spontaneous evacuation of the accumulated fluids in the second and third space or remain in a "no flow state" retaining all administered fluids. This last scenario (or the global increased permeability syndrome) can result in a third hit due to impaired oxygen diffusion and nutrient absorption [78]. Conservative fluid administration or even active goal-directed fluid removal is advised during this late phase of illness. Late conservative fluid administration is defined by Murphy et al. as 2 consecutive days with a negative fluid balance during the first week of ICU stay [48]. Late goal-directed fluid removal implies the aggressive use of diuretics or renal replacement therapy with net ultrafiltration to actively remove the accumulated fluids. In order to achieve negative fluid balances with this strat-

egy, it is mandatory to minimize fluid administration to basic needs [50].

Recent literature supports this strategy by showing an independent survival benefit when obtaining 2 consecutive days with a negative fluid balance within the first week of admission or by attaining negative fluid balances by day three [48, 57]. Further confirmation from prospective randomized controlled trials such as the RADAR-2 and CLASSIC-2 studies is eagerly awaited since the current retrospective literature may only indicate that positive fluid balances are merely a biomarker for severity of illness [79]. The main risk to consider is being too aggressive while removing fluids, causing hypovolemia and hypoperfusion. Close monitoring is of paramount importance to avoid this fourth hit. Given its restoring effect on permeability of the glycocalyx, albumin might be the fluid of choice at this stage to facilitate fluid migration and removal from the second and third space.

Take-home messages on evacuation phase:

- While awaiting further studies, we would suggest aiming for 2 consecutive days with a negative fluid balance within the first week of admission and attaining negative fluid balances by day three.
- When evacuating accumulated fluids, one must avoid inducing hypovolemia.

Conclusion

Fluids administered during sepsis should be as meticulously selected as antibiotic therapy, and clinicians are to consider the drug choice, dose, preferred duration, and timely de-escalation. Balanced crystalloids are a good first choice and synthetic colloids should be avoided. Whenever prescribing fluid therapy for septic patients, one should be aware of the different dynamic phases during the course of illness. While early aggressive therapy is generally required during the initial resuscitation phase, continuous reassessment of fluid status and fluid responsiveness is mandatory. During the optimization phase following resuscitation, this becomes even more important, and advanced hemodynamic monitoring can be a useful aid for tailoring fluid therapy. Once the initial shock phase has resolved during stabilization, a restrictive fluid approach is warranted, aiming for neutral to negative fluid balances by taking into account all administered fluids and avoiding fluid creep. Finally, the accumulated fluids should be evacuated with diuretics or renal replacement therapy with net ultrafiltration Avoiding a third hit caused by decreased diffusion of oxygen and absorption of nutrients due to second and third space fluid accumulation as well as a fourth hit caused by hypovolemia and tissue hypoperfusion is quintessential.

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Part V

Fluids: Complications

Acid-Base Imbalance

Sujoy Banik

Abstract

The most commonly encountered problems with blood transfusion are associated with acid-base imbalance. In this chapter, we will learn:

1. Concepts for acid-base imbalances—Henderson-Hasselbalch equation, Boston system, Copenhagen system, and Fencl-Stewart system.
2. What kind of imbalances is seen after blood transfusion?
3. Management of complications/specific electrolyte imbalances after blood transfusion.
4. Choice of fluids.

Acid-base abnormalities rarely occur in isolation in the human body. They are very much interrelated and can be expressed as a function of changes in SID, A_{TOT}, and $PaCO_2$ by the Stewart-Fencl system. One must understand the various implications of the underlying causes while treating the metabolic abnormality and strive to treat the patient holistically in a better manner.

Keywords

Acid-base disorders · Electrolyte imbalance

Introduction

Acids and bases are like the yin and yang of the homeostatic mechanism of the human body. Made of almost 60% water, the electrolyte alterations in the intracellular and extracellular compartments of the body are tightly controlled to maintain homeostasis. Changes in carbon dioxide (CO_2) and electrolytes' relative concentrations change the ability of water to autoionize into hydrogen (H^+) and hydroxyl (OH^-) ions [1]. Changes in the composition of gases, water, and electrolytes in these fluid compartments present as differences in body water and acid-base balance, respectively. The pH of the solution is depicted as the negative logarithmic (base 10) value of the hydrogen ion (H^+) concentration. Changes in extracellular pH around the resting value of 7.4 are associated with acute and critical illnesses [2]. Such changes are called "acid-base abnormalities" [2].

Henderson-Hasselbalch Equation

Henderson and Hasselbalch defined "acid-base" balance by carbonic acid equilibrium [3–5]:

S. Banik (✉)
Department of Anesthesia and Perioperative Medicine, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada
e-mail: sbanik5@uwo.ca

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$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

The Henderson-Hasselbalch equation is:

$$pH = pKa + \log_{10}\left[HCO_3^-\right] / \left[H_2CO_3\right]$$

[Total CO_2] = [HCO_3^-] + [Dissolved CO_2] + [Carbamino CO_2] + [H_2CO_3] ≈ $PCO_2 \times 0$ .03 mmol CO2/L/mmHg, deriving further:

$$pH = 6.1 + \log\left[HCO_3^-\right] / PCO_2 \times 0.03$$

The concentrations of the [OH^-] and [H^+] ions are equal in distilled water at 25 °C, at $1.0 \times 10 - 7$ mmol/L. When the concentration of hydrogen ions exceeds that of hydroxyl ions ([H^+] > $1.0 \times 10 - 7$ mmol/L, [OH^-] < $1.0 \times 10 - 7$ mmol/L), the resulting solution is deemed an acid [5]. If the hydroxyl ion concentration is greater than the hydrogen ion concentration, then the solution is considered alkaline [5].

Since the product of the concentrations of hydroxyl and hydrogen remains constant, it follows that if an increase in the concentration of hydrogen ions occurs, there would be a conjugate reduction in the concentration of hydroxyl ions, and vice versa.

In the early twentieth century, Arrhenius defined an acid as any substance that delivers a hydrogen ion into the solution [6, 7]. A base is any substance that delivers a hydroxyl ion into the solution [6]. Because of its high dielectric constant, water is a highly ionizing solution [6]. Any compound with polar bonds will dissociate into their component parts (i.e., dissolve) in water [6]. Brønsted and Lowry (BL) further delineated that an acid is a proton donor and a base a proton acceptor [6]. Water is considered as amphoteric and can act either as an acid or as a base, depending on the reaction involved [6, 7].

The degree of dissociation of substances in water underlines the behavior of the substance [1, 2]. Therefore, they may act as strong/weak acids or strong/weak bases [2]. Lactic acid, whose pKa is 3.4, is completely dissociated at physiologic pH and behaves like a strong acid [8]. However, with a pKa of 6.4, carbonic acid is considered as a weak acid because it is incompletely dissociated [2]. Similarly, ions such as sodium (Na^+), potassium (K^+), and chloride (Cl^-), which do not easily bind other molecules, are considered strong ions—they exist free in solution [1]. As each Na^+ delivers a hydroxyl ion into extracellular fluid (ECF), it is functionally a base, as are all cations. As each Cl^- delivers a hydrogen ion into the ECF, it is functionally an acid, as are all anions [1].

Because all acid-base reactions are based on the principles of physical chemistry, three simple rules must be followed [1, 2]:

1. Electrical neutrality: The total positively charged ions must equal to the total negatively charged ions in aqueous solutions, in any compartment [1].
2. Dissociation equilibria: The dissociation equilibria of all incompletely dissociated substances, as derived from the law of mass action, must always be satisfied [1].
3. Mass conservation: The amount of any substance in each compartment remains constant unless it is added, removed, generated, or destroyed. Therefore, the total concentration of any incompletely dissociated substance is expressed as the sum of the concentrations of its undissociated and dissociated forms [1].

Understanding Acid-Base Abnormalities

Conventionally, acid-base disturbances have been classified as resulting from either alterations in arterial carbon dioxide ($PaCO_2$) tension (respiratory acidosis or alkalosis) or alterations in blood chemistry (metabolic acidosis or alkalosis). This is still a useful classification to understand acid-base chemistry (the CO_2-bicarbonate Boston approach or the base-excess Copenhagen approach [7–14]). However, it should be known that most respiratory or metabolic abnormalities rarely occur independently. The physical chemistry ("Stewart") approach allows the use of a simple model for understanding acid-base disturbances, as all abnormalities can be explained in terms of SID, ATOT, or PCO_2 [2, 7–14].

The CO_2-Bicarbonate Boston Approach

Investigators at Boston utilized the Siggaard-Andersen nomogram for CO_2, HCO_3^-, H^+, and pH relationships to describe acid-base abnormalities in the human body by describing the changes in terms of the bicarbonate concentration and the partial pressure of CO_2 [10–12]. This is still the most commonly used approach in North America, and it does provide a base level of familiarity and understanding of the basics of acid-base chemistry at a clinical and simplified biochemical level [12].

Acute respiratory alkalosis is characterized by a pH > 7.45, a low $PaCO_2$, and a low HCO_3^-.

In acute respiratory acidosis, a rise in $PaCO_2$ by 10 mmHg (1.3 kPa) causes HCO_3^- to increase by 1 mmol/L (1 mEq/L).

In chronic respiratory acidosis, ΔH^+ (nEq/L) = 0.8 (ΔPCO_2), arise in $PaCO_2$ by 10 mmHg (1.3 kPa) will cause plasma [HCO3$^-$] to increase by 3 mmol/L (3 mEq/L).

The Copenhagen Base Excess Approach

Better CO_2-tension measurement electrodes were developed in Copenhagen in the early 1950s [13]. Astrup and Jorgensen developed the standard bicarbonate—the actual bicarbonate concentration at 37 °C and at a $PaCO_2$ of 40 mmHg (5.3 kPa) [13]. They recognized that PCO_2 and [HCO_3^-] were not independent variables. As a result, they derived the BE as a measure that could differentiate respiratory from metabolic acid-base disturbances. As defined, the BE is the amount of strong acid (strong anion) or base (strong cation) required to return the pH to 7.4, assuming that PCO_2 is constant at 40 mmHg (5.3 kPa) and that the temperature is 37 °C [13–15]. They developed an alignment nomogram that allowed for the determination of BE from a single measurement of pH, PaCO2, and Hb concentration at 37 °C. Current algorithms for computing the BE are derived from the Van Slyke equation (1977) [13–15]:

$$BE = \left(HCO_3^-\right) - 24.4 + \left[2.3 \times Hb + 7.7\right] \times \left[pH - 7.4\right] \times \left(1 - 0.023 \times Hb\right)$$

The most commonly used estimation of BE uses just the bicarbonate and pH by the following equation:

$$BE = 0.93 \times \left(\left[HCO_3^-\right] - 24.4 + 14.83 \times \left[pH - 7.4\right]\right)$$

The Fencl-Stewart Approach

This approach assumes that the independent predictors of acid-base abnormalities, especially H^+ concentration, are the $PaCO_2$, the SID, and the A_{TOT} [16, 17]. The interplay between most other variables has been factored into this physical chemistry approach, and it is able to describe most complex clinical scenarios.

Strong Ions

Strong ions, like Na^+ and Cl^-, dissociate completely [1, 17]. The most common strong ions in the ECF are Na^+ and Cl^- [17]. Other strong ions include K^+, magnesium (Mg^{2+}), calcium (Ca^{2+}), and sulfate (SO_4^{2-}) [16–18].

Therefore, in any solution, the cumulation of the charges imparted by strong cations minus the

charges from strong anions will represent the SID [16]. SID independently influences hydrogen ion concentration [17]. In human ECF, SID is always positive [16]:

$$\mathrm{SID} = \left(\left[\mathrm{Na}^+\right] + \left[\mathrm{K}^+\right] + \left[\mathrm{Ca}^{2+}\right] + \left[\mathrm{Mg}^{2+}\right]\right) - \left(\left[\mathrm{Cl}^-\right] + \left[\mathrm{A}^-\right]\right) = 40 - 44\,\mathrm{mEq/L}$$

Hydroxyl ions almost always exceed hydrogen ions quantitatively in solution [16]. The relationship between SID and $[H^+]$ is nonlinear in these conditions [18]. Any change in SID will change both $[H^+]$ and $[OH^-]$ concentrations [18].

Weak Acid "Buffer" Solutions

The degree to which water dissociates and ionization to H^+ and OH^- may be also affected by weak acids. Weak acids are substances which are partially dissociated, the degree of which is dependent on present pH and temperature [1]. The predominant molecules in this group are albumin and phosphate [16, 19]. Stewart used the term A_{TOT} to depict the total concentration of weak anions or acids that impact acid-base balance [1].

The acid HA partly dissociates, represented by the equilibrium:

$$\left[\mathrm{H}^+\right] \times \left[\mathrm{A}^-\right] = \mathrm{KA} \times \left[\mathrm{HA}\right]$$

KA is the weak acid pKa. If it is presumed that HA and A^- have no further role in this reaction (the law of mass conservation) [1], the amount of A^- present in the solution must equal to the amount initially present, so:

$$\left[\mathrm{HA}\right] + \left[\mathrm{A}^-\right] = \left[\mathrm{ATOT}\right]$$

where [ATOT] is the total weak acid concentration [1, 16].

In other words, $[H^+]$ is a function of pCO_2, A_{TOT}, SID, and several constants [16, 17]. All other variables, especially $[H^+]$, $[OH^-]$, and $[HCO_3^-]$, are codependent and cannot independently impact acid-base balance [16–18].

Respiratory Acid-Base Abnormalities

Respiratory Alkalosis

The normal $PaCO_2$ is 40 mmHg (5.3 kPa). Respiratory alkalosis happens with decreasing $PaCO_2$, with the most common cause being hyperventilation.

A simple general rule for this reaction is as follows:

Acute respiratory alkalosis: $\Delta HCO_3^- = 0.2\ \Delta PaCO_2$

Hypocapnia usually presents as lightheadedness, visual disturbances, dizziness, and hypocalcemia. The hypocalcemia is caused by rise in negatively charged albumin in alkaline solutions. Acute hypocalcemia presents with paresthesia and tetany [1, 2, 20]. In the OR, patients may hyperventilate preoperatively due to anxiety and postoperatively secondary to pain, agitation, or a full bladder or poor mechanical ventilation strategy and may result in significant systemic and, in particular, cerebral vasoconstriction. Prolonged hyperventilation should not be used to treat intracranial hypertension due to significant cerebral hypoperfusion and ischemia [19].

Respiratory Acidosis

Respiratory acidosis is seen with acutely increased $PaCO_2$. This is generally associated with respiratory failure. This may result from problems with:

- Ventilation-perfusion mismatch—may be seen with atelectasis, pneumonia, pulmonary edema, pneumothorax, or pleural effusion [15]

- Peripheral neuromuscular pathology—such as poliomyelitis, myasthenia gravis, polymyopathies, or neuromuscular blockade [15, 16]
- Central neurogenic pathology—CNS depressants (like benzodiazepines, opioids, anesthetics,) stroke, spinal cord injury [15–17]

Clinically, patients have classic signs of CO_2 retention: cyanosis, vasodilatation, and narcosis.

$[H^+]$ increases but renal compensation is slow to respond, causing rise of bicarbonate to be tardy. This process also requires increased urinary excretion of Cl^-, and therefore pH falls fast [8, 11, 12].

Metabolic Acid-Base Disturbances

Metabolic acid-base disturbances reflect changes in serum protein and electrolyte composition and are usually caused by changes in the SID or A_{TOT} or both. Rising values of SID causes alkalosis; a fall in the SID causes acidosis [13].

These alterations may be caused by a change in the total or relative concentration of strong ions. For example, a decrease in the SID (i.e., more anions relative to cations) causes acidosis; this may occur because of a net rise in anions: mineral acids, like chloride, or organic acids present in the body like lactate or ketones (most organic acids can be metabolized). In addition, SID could decrease with an increase in the volume of distribution of the same quantity of ions [21–25].

A general rule to remember is that for every 1 mEq/L fall in the SID, there is a 1 mEq/L fall in the $[HCO_3^-]$ from the baseline.

Similarly, for every 1 mEq/L increase in the SID, there is a 1 mEq/L increase in the $[HCO_3^-]$ from the baseline—and this approach is widely used to characterize metabolic alkalosis.

Metabolic acidosis is important to treat from two stand points; the underlying cause of the acidosis must be treated, and the effects of the acidosis may be strong enough to deflect attention from the cause, which then creates a self-perpetuating vicious cycle. Metabolic acidosis is associated with changes in transcellular ion pumps and increase in the values of ionized calcium [16]. The clinical picture, therefore, presents as vasodilation, diminished muscular performance (especially myocardial depression), and various arrhythmias. Quick onset metabolic acidosis is usually associated with severe hypotension, cardiac arrhythmias, and death [17]. The oxyhemoglobin dissociation curve shifts rightward to increase oxygen offloading into the tissues as a result of ischemia [26]. Lactic acidosis caused by circulatory shock is much worse than hyperchloremic acidosis [22, 27]. Increasing $[H^+]$ in the cerebrospinal fluid (CSF) stimulates respiration through the activation of the respiratory center. Minute ventilation increases, reducing arterial CO_2 content, hence reducing the total body $[H^+]$ [22]. HCO_3^- concentration falls, due to buffering activity, and with the reduction in total CO_2. As a result, the blood pH falls less in metabolic acidosis compared with respiratory acidosis [23–25, 28–32].

Metabolic alkalosis is not commonly seen acutely. Symptoms and signs of metabolic alkalosis include lightheadedness, tetany, generalized vasoconstriction, and paresthesias. Usually the body responds to metabolic alkalosis by reducing ventilation to increase CO_2. This may cause slower weaning off of mechanical ventilation in critically ill ICU patients [24, 25, 28]. Therefore, establishing cause and effect may be useful to trigger appropriate treatment.

In normal ECF, the SID is 40–44 mEq/L, this positive charge being balanced mainly by weak acids (if this would not be balanced, the resultant pH of blood would be the alarming value of 11.9!). If the SID increases, there will be a concomitant increase in the relative concentration of cations to anions and alkalinize the solution. If the SID reduces, there would be a similar decrease in the relative concentration of cations to anions, and this acidifies the solution.

The SID of "normal saline" (NaCl, 0.9% NS), which consists of 154 mEq each of sodium and chloride, is zero. Since each bag of NS delivers relatively more chloride than sodium, hyperchloremia ensues, reducing the SID, causing "hyperchloremic acidosis" [30].

If free water is lost from the ECF, like high evaporative losses, ionic concentrations change,

and this concentration effects more commonly present ions and compounds (sodium rather than chloride) [31]. The SID rises, and the patient develops a so-called contraction alkalosis, usually seen after loop diuretics are administered [30, 33]. Loop diuretics like furosemide cause increased excretion of water than the electrolytes themselves [33].

If there is any event that removes chloride without sodium, like vomiting or pyloric stenosis, the resulting drop in chloride ions causes metabolic alkalosis (hypochloremic alkalosis) due to rise in SID [28]. Severe untreated diarrhea usually causes a generalized loss of both sodium and potassium, decreases the SID, and is usually seen with metabolic acidosis [29]. The most significant form of metabolic acidosis is associated with a net gain of "unmeasured" (organic acids that are not usually measured) anions and therefore a reduced SID [33–35]:

1. Increased lactate production: Hypoxia, liver dysfunction, and severe stress.
2. Decreased excretion: In severe renal failure, Cl^-, SO_4^{2-}, PO_4^{3-} ("fixed renal acids"), and various other metabolic intermediaries are not excreted.
3. Other acid production: β-hydroxybutyrate and acetoacetate are produced, for instance, diabetic ketoacidosis, starvation, or liver disease.

The total weak acid pool, mainly phosphate and albumin, is also a crucial variable in acid-base regulation [32]. Renal failure causes acidosis that is associated with hyperphosphatemia [33]. Hypoalbuminemia is common in the intensive care unit (ICU) [33]. Hypoalbuminemia decreases ATOT and is related to alkalosis [33–36]. There's a robust association between hypoalbuminemia and critical illness severity [37]. Albumin deficits are caused by breakdown of preexisting albumin to use the amino acids for protein synthesis, production of acute phase reactants and limiting albumin synthesis in the liver capillary leak with interstitial albumin loss, and plasma replacement with protein-free fluids [38].

Regulation of Acid-Base Balance

Extracellular H^+ is tightly regulated for homeostasis [17]. The tight control is actually needed for the prevention of change in transcellular ion pumps by regulating extracellular electrochemical balance to keep slower changes in ion flux rather than abrupt increases or decreases. Intracellular and extracellular buffers are present in the body to regulate ion balance [20]. A buffer may be a solution of two or more chemicals that minimizes changes in pH in response to the addition of an acid or base [20]. The ideal buffer would usually have a pKa between 6.8 and 7.2 [20].

Usually, weak acids behave as body buffers. CO2 serves as the primary source of body acid, requiring almost 12,500 mEq of H^+ daily for homeostasis, mostly excreted by the lungs, with kidney being a minor player in this regulation [19]. Hemoglobin (Hb) is the main buffer for CO_2 [20, 26]. Hb needs to bind the CO_2 to prevent any major rise in pH of the blood, as deoxygenated Hb is a strong base [20]. CO_2 easily diffuses across cell membranes [20].

Within the red blood cell, CO_2 dissolves in water and, in the presence of carbonic anhydrase enzyme, creates H_2CO_3, which then converts to hydrogen and bicarbonate by electrical ionization [21]. H^+ combines with histidine on deoxyhemoglobin (the "Haldane" effect) [15], and bicarbonate is actively pumped out of the cell. Chloride moves in to preserve electrical neutrality (the chloride shift) and to maintain the continued production of acid [23]. CO_2 is also buffered directly by Hb (carbaminohemoglobin) and by plasma proteins (carbamino proteins) [22]. Venous blood contains 0.68 mmol/L extra CO_2 over arterial blood: 27% as carbaminohemoglobin (CO_2 bound to Hb), 8% dissolved, and 65% as HCO_3^- ions [24]. The principal CO_2 buffering system, Hb, is overloaded in acute respiratory failure causing acidosis. In response, the kidney excretes an increased chloride load, using NH_4^+, a weak cation, to again preserve electrochemical balance [39]. This is how ECF osmolality is maintained [39]. This process is conventionally referred to as "metabolic compensation" [40]. An increase in

total body CO_2 content, mainly with increase in serum bicarbonate, is seen with chronic respiratory acidosis [1, 2, 35–45].

Hypercarbia compensation requires decrease in CSF chloride [25] and a rise in CSF SID [30–32]. This is thought to be related to active transport mechanisms across the blood-brain barrier or at choroid plexus, which is a target for blockage by acetazolamide and furosemide [33–36]. This causes a rightward shift within the PCO_2 response curve: hypercarbia triggers a compensatory increase of the respiratory drive at a higher PCO_2 level than under normal conditions [36]. Bicarbonate acts like a dependent variable that increases or decreases with PCO_2 [37]. The rate of conversion of CO_2 to HCO_3^- is dependent on carbonic anhydrase activity and occurs slowly [38]. This makes it easier to tell if the change is acute or chronic. Metabolic acid is buffered principally by increased alveolar ventilation, producing alkalosis, with compensatory extracellular weak acids. These weak acids include plasma proteins, phosphate, and bicarbonate. The bicarbonate buffering system (92% of plasma buffering and 13% overall) is probably the most important extracellular buffer [46]. The pKa of bicarbonate is relatively low (6.1), but the system derives its importance from the enormous quantity of CO_2 present in the body [47]. The coupling of bicarbonate and H_2O produces CO_2, which is then excreted through the lungs, increasing alveolar ventilation [48].

Acid-Base Imbalance After Blood Transfusion

Blood transfusion is commonly required for treatment of anemia and hypovolemic shock after major polytrauma. Massive transfusion has its own accompanying problems, like hemolysis, and electrolyte abnormalities, like hyperkalemia and hypocalcemia. Along with replacing the components of blood, albumin may also need to be replaced in massive blood loss. In recent times, intravenous albumin has also been used intraoperatively as a colloid to mitigate blood transfusion.

The impact of hypoalbuminemia on acid-base equilibrium has been grossly underestimated. Fencl and Figge modified Stewart's theory [16]. The concentration of albumin in the body acts as the main positive charge balancing the negative charge of the SID [24]. As a result, acidosis may go undetected in the presence of hypoalbuminemia [25] which may be primarily caused by unmeasured anions (UMA), when the Boston/Copenhagen models are used to interpret the blood gases: pH, bicarbonate, base deficit, and the anion gap (AG) [25]. In fact, hypoalbuminiemia may be associated with adverse outcomes, among other major issues [31–34].

This compensatory mechanism must be known to caregivers. For example, anesthetized or critically ill patients on controlled mechanical ventilation are unable to control their pCO_2 [45]. A massive reduction in pH may ensue from acute metabolic and respiratory acidosis together [39]. The kidney takes care of sodium and chloride excretion maintaining balance of these crucial ions in the body [49].Usually, the kidney excretes a net chloride load, using NH_4^+, a weak cation, to neutralize urinary chloride ions [39]. During the presence of metabolic acidosis, the kidneys remove chloride predominantly. In metabolic alkalosis, sodium and potassium are excreted while chloride is retained [50]. Urinary bicarbonate is present to preserve electrical neutrality. Abnormalities in the renal chloride excretion may be responsible for many inherited acid-base disturbances. In renal tubular acidosis, the kidney is unable to excrete Cl^- in tandem with Na^+ [41]. The use of parenteral nutrition (other gastrointestinal (GI) losses from small bowel, diarrhea, or pancreatic losses), the heavy use of "normal" saline (with high chloride concentration), and the use of carbonic anhydrase inhibitors like acetazolamide are responsible for hyperchloremic metabolic acidosis [39, 41].

Choice of Fluids

The choice of fluid for various situations has always been a controversial topic. The requirements for electrolyte replacement in various situ-

ations are usually different, and therefore fluid management must be almost always customized for the individual patient. 0.9% NS and Ringer's lactate, which are classified as crystalloids, are used initially for most clinical situations for resuscitation and maintenance [40]. The problems with the so-called "normal" saline have been outlined above. Ringer's lactate is also slightly hypotonic in vivo, and the lactate component may depend on liver function for metabolism. Balanced crystalloids have been developed with non-lactate containing electrolyte solutions, with acetate and gluconate in varying concentrations to replace lactate [40, 46–56]. This has the purported advantage of entering the Krebs cycle directly bypassing the lactate-pyruvate cycle, and therefore may not depend on liver function for metabolism.

Colloids like starch and gelatin have been used to augment intravascular volume. These have been noted to have significant side effects as allergic reactions (to gelatin mostly) and platelet dysfunction causing bleeding tendency (in starch-based colloid solutions).

Concentrated NS solutions like 3% NS, 7.5% NS, and 23.4% NS have been used variously to treat hypovolemic shock and raised intracranial pressure (3% NS especially for this purpose, replacing mannitol in many centers for this purpose) [19, 20, 36, 51, 53, 54]. These tend to behave as colloids initially, augmenting intravascular volume significantly for few hours before being metabolized as other crystalloids due to their underlying NaCl makeup.

Conclusion

Acid-base abnormalities rarely occur in isolation in the human body. They are very much interrelated and can be expressed as an amalgamation of changes in SID, A_{TOT}, and $PaCO_2$ by the Stewart-Fencl system. The underlying changes (acidosis/alkalosis) may be respiratory or metabolic or, more commonly, a combination of both, as compensatory mechanisms work toward homeostasis. One must understand the various implications of the underlying causes while treating the metabolic abnormality and strive to treat the patient holistically in a better manner.

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Coagulation Abnormalities

Rajeeb Kumar Mishra

Abstract

Hemostasis is a complex physiological process resulting from a delicate balance between procoagulant and anticoagulant pathways. This intricate process, if disturbed either in the form of inherited or acquired causes, can lead to various abnormalities in coagulation. In patients of different neurological etiologies, often an associated coagulopathy is observed, resulting in a poor outcome. This chapter deals with the various abnormalities observed in coagulation and the implications in various neurological etiologies.

Keywords

Von Willebrand disease · Hemophilia · Factor V Leiden mutation · Antiphospholipid syndrome · Traumatic brain injury · Brain tumors · Drug-induced coagulopathy

Introduction

Hemostasis is a complex process of maintaining circulatory integrity, which involves various biochemical and cellular events [1]. This physiologic process is a delicate balance between the procoagulant and anticoagulant pathways, limiting exsanguination caused by a trivial injury and simultaneously maintaining the intravascular blood circulation, preventing systemic coagulation [2]. The whole process of hemostasis involves interactions between the vascular endothelium, plasma proteins, and thrombocytes. Abnormalities in coagulation are often encountered in various neurological etiologies as a result of altered hemostatic mechanisms [2–6]. In this chapter, the clinical implications of various coagulation abnormalities associated with different conditions will be discussed.

Overview of Normal Coagulation

Primary hemostasis involves platelet plug formation at the injured endothelium, followed by the process of secondary hemostasis, which involves more complex interactions between endothelium, platelets, and circulating coagulation factors [1, 7]. Vascular endothelium maintains the fluidity of blood by inhibiting unprovoked thrombogenesis. Uninjured vascular endothelium possesses both antiplatelet activity and anticoagulation properties. Prostacyclin and nitric oxide released from the healthy endothelium prevent platelet adhesion. The vascular endothelium plays a significant role in the activation of various proteins, which are antico-

R. K. Mishra (✉)
Department of Neuroanesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, India
e-mail: drrajeeb@nimhans.ac.in

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agulants. It also produces tissue factor pathway inhibitor (TFPI), which can inhibit factor Xa and tissue factor (TF)-factor VIIa complex. Apart from this, endothelial heparan sulfate accelerates antithrombin (AT) mediated degradation of factors IXa, Xa, and thrombin. On the other end, loss of vascular endothelial integrity exposes the underlying extracellular matrix, von Willebrand factor (vWF), which shifts the balance toward plasma-mediated coagulation to generate thrombin. Platelets are critical to hemostasis. They adhere to the damaged endothelium, subsequently get activated, and aggregate to form a stabilized platelet plug by fibrin cross-links. Platelet glycoprotein receptors such as Ib and IIb/IIIb play vital roles in adhesion and fibrin cross-link formation.

Once the plasma proteins are exposed to TF, they are activated, leading to a cascade of reactions that culminate in fibrin generation. Thrombin, the critical element, generates fibrin from fibrinogen and activates platelets as well. The plasma-mediated coagulation cascade is described as extrinsic and intrinsic pathways, which converge to a common pathway leading to insoluble fibrin formation. Finally, the fibrin forms a cross-link with factor XIIIa, and cross-linked fibrin gives the clot stability [8].

Fibrinolysis [7]

The whole process of coagulation is not considered to be finished until the fibrinolysis occurs. The process of fibrinolysis begins once the hemostatic plug stops the bleeding. The endothelium releases tissue plasminogen activator (tPA), which activates plasminogen to plasmin leading to clot lysis [7]. The whole fibrinolytic process is governed by inhibitors of tPA and plasmin (α_2-antiplasmin) [7]. Deficiency of these inhibitors can cause excessive fibrinolysis, which in turn can lead to excessive bleeding. Apart from that, exogenously administered drugs like streptokinase and urokinase can cause fibrinolysis, and if in excess, they can result in bleeding diathesis. The interesting aspect of the excessive fibrinolytic activity is the generation of the end product of fibrinolysis. These end products are generally referred to as fibrin-degraded products (FDP) and play a significant role in coagulation abnormalities. In fact, the FDPs are anticoagulants and can inhibit thrombin activity, which in turn prevents fibrin generation from fibrinogen [9]. D-dimer, an FDP produced by the degradation of cross-linked fibrin clots, are usually elevated in DIC [10].

Endogenous Anticoagulation

The intrinsic anticoagulation system plays a vital role in maintaining the delicate balance of hemostasis [11]. Various substances such as endothelium-derived TFPI, AT, and hepatically synthesized proteins C and S are essential determinants of endogenous anticoagulation.

Monitoring of Coagulation

Perioperative coagulation monitoring aims to identify patients at risk of bleeding. Traditionally, coagulation monitoring is accomplished by doing laboratory-based conventional coagulation tests (CCT), which include prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR). These assays have a longer waiting time. More so, CCT could lead to a diagnostic dilemma about the underlying coagulation abnormalities leading to a delay in the decision-making. The use of point-of-care (POC) tests, namely, activated clotting time (ACT); thromboelastography (TEG); rotational thromboelastometry (ROTEM); sonoclot, which evaluates the viscoelastic properties of blood; and activated clotting time (ACT), has addressed many of the shortfalls of CCT. However, in a recent trial involving traumatic brain injury (TBI) patients, the authors did not observe any difference in overall outcome in CCT or viscoelastic hemostatic assays (VHA)-based management [12].

Conventional Coagulation Tests

The PT evaluates the functioning of plasma-based coagulation, especially the extrinsic and common pathways. INR is a way of normalizing the PT results among various laboratories, which is a ratio of PT of the patient to control PT raising to the power of the International Sensitivity Index (ISI) [13]. These tests are sensitive for factors VII and X as compared to fibrinogen. Any prolongation in PT indicates either factor deficiency or the presence of inhibitors of coagulation (antiphospholipid, fibrin degradation products) [13]. The aPTT evaluates the intrinsic and common pathways, and prolongation in aPTT denotes deficiencies in factors VIII and IX [9]. Platelet count more than 100,000 μL is associated with optimal hemostasis [1]. Bleeding time is traditionally used to evaluate the platelet-mediated hemostasis. Most recently, the anti-Xa factor activity assay is used to evaluate patients on drugs inhibiting factor Xa such as unfractionated heparin (UFH), low molecular weight heparin (LMWH), and fondaparinux.

Point-of-Care Coagulation Tests

Laboratory-based CCTs are the common and mainstay of perioperative coagulation testing. However, the increasing availability of various POC modalities provides opportunities to assess the process of coagulation in detail. ACT is one such modality that measures clot formation by the intrinsic and common pathways. The usual range of ACT is 107 ± 13 s. It is commonly employed in the neurointerventional suite to measure the heparin activity. Viscoelastic coagulation measures gained acceptance at various levels, attributed to their ability to monitor the complete spectrum of coagulation. The TEG (TEG 5000 Thrombelastograph Hemostasis Analyzer System, Haemoscope, Braintree, MA) [14] uses a rotating cup that holds the blood, into which the pin is suspended to measure the impedance generated by the evolving clot in the cup and is transferred electronically to form a graphical output [14]. Although the ROTEM (TEM Systems, Durham, NC) functions analogously, technology seems to be different as compared to TEG. In ROTEM, the motion is generated from the pin, and optical detectors carry out the signal transmission, not by torsion wires [14]. Various times and measurements of angulations, measured from the graphical tracings, provide information on different parts of the whole coagulation process, including platelet function. Sonoclot (Sonoclot Analyzer, Sienco Inc., Arvada, CO) produces characteristic clot signatures by measuring the impedance to a vibrating sensor in the blood sample. The use of ROTEM in different neurological illness has been proven to be a valuable tool in identifying associated coagulopathy [3–5, 15].

Platelet Function Assays

The viscoelastic hemostatic analyzers can measure platelet dysfunction, but the sensitivity and specificity are limited; hence, the platelet function analyzers are incorporated into clinical practice. Platelet aggregometry is one such tool that measures the platelet function in various conditions and can aid in assessing coagulopathy. In a retrospective analysis in TBI patients, the use of platelet aggregometry was found to be useful in identifying the presence of platelet dysfunction. The study aimed at measuring the activation of platelets by the arachidonic acid receptor pathway (ASPI). However, the researcher could not find an independent association of platelet aggregometry values with clinical outcome following TBI [16]. Apart from platelet aggregometry, several other point-of-care platelet function analyzers such as Platelet Function Analyzer-100, VerifyNow, Multiplate Analyzer, and Vasodilator-Stimulated Phosphoprotein Phosphorylation Assay (VASP assay) are available [17].

Abnormalities in Coagulation

Coagulation disorders can be broadly divided into conditions that cause excessive bleeding and conditions which result in excess thrombogen-

esis. Further bleeding diathesis can be subclassified as inherited and acquired bleeding disorders.

Bleeding Disorders

Inherited Bleeding Disorders

The inherited form of bleeding disorders either involves platelet or coagulation pathways. Von Willebrand disease (vWD) is the most common form of inherited bleeding disorder [1]. The deficiency in vWF both in quantity and quality has resulted in poor platelet adhesion leading to weak platelet aggregation [1]. CCT in this disorder will remain normal, while specific assays such as vWF and factor VIII measurement remain the cornerstone of diagnosis in suspected individuals. Hemophilia is an X-linked form of an inherited bleeding disorder, which results from factor VIII deficiency (hemophilia A) or factor IX deficiency (hemophilia B). Abnormality in aPTT is often noticed in CCT; specific factor analysis and factor activity confirm hemophilia diagnosis. Milder presentation of vWD often responds to desmopressin; however, vWF and factor VIII concentrates are usually necessary to prevent and treat associated life-threatening complications [18, 19]. In hemophilias, administration of specific recombinant factors to prevent and treat perioperative bleeding diathesis often remains the cornerstone of management [20]. However, recombinant factor VII concentrates [21] and prothrombin concentrates are also utilized where factor VIII therapy fails [1]. Apart from these entities, several other factor deficiencies such as factor XIII are described, manifesting in life-threatening intracranial hemorrhage (ICH). The incidence of ICH in factor XIII deficiencies is 30% [22].

Acquired Bleeding Disorders

The acquired form of bleeding disorders of hemostasis is mostly attributed to medications, diseases involving the liver and kidney, and numerous underlying diseases, leading to disseminated intravascular coagulopathy (DIC). Systemic diseases such as liver dysfunction can lead to deficiencies of factors II, V, VII, and IX–XII and protein C and S. Moreover, in liver dysfunction, the defective removal of sialic acid moiety from fibrinogen results in dysfibrinogenemia [23]. Renal dysfunction and uremia can cause decreased platelet adhesion [24]. Many patients of chronic renal failure and uremia present to the neurocritical care with intracranial bleeding [25]. At the same time, DIC as a manifestation of underlying disorders such as malignancy, sepsis, and trauma can cause upregulation of TF leading to activation of coagulation cascade resulting in widespread microthrombosis [23]. In DIC, CCTs show thrombocytopenia, increased PT, aPTT, hypofibrinogenemia, and elevated markers of fibrinolysis, e.g., D-dimers [23]. Management of DIC is essentially treating the underlying cause with supportive treatment with platelets, fibrinogen, and fresh frozen plasma (FFP) [23]. However, antifibrinolytics is contraindicated in DIC as the fibrinolytic system is required in dissolving the widespread fibrin [23].

Various medications such as antiplatelets, anticoagulants, and the increased usage of direct oral anticoagulants (DOACs) can lead to various coagulation abnormalities. Many patients on these medications seek neurological services for the associated neurological conditions or intracranial complications related to the pharmacologic agents. In patients of spontaneous ICH, 27% patients were found to be on antiplatelet agents [17].

Antiplatelets drug are increasingly used for various underlying thrombophilic conditions. These agents can alter coagulation by affecting platelet activation, aggregation, and adhesion. TBI patients who are on antiplatelets can have poor outcomes because of more propensity of intracranial bleeding [26]. For patients who are on aspirin, a cycloxygenase inhibitor, platelet transfusion can reverse the effects of aspirin, while for those who are on clopidogrel, a P2Y12 inhibitor, platelet transfusions might not be beneficial as the active metabolite can inhibit the newly transfused platelets [17]. Some authors

also suggest that desmopressin 0.4 mcg/kg can also be considered in patients with antiplatelet drugs [27].

Vitamin K antagonist such as warfarin inhibits the γ-carboxylation of vitamin K-dependent clotting factors, namely, factors II, VII, IX, and X, leading to reduced activity. In a retrospective analysis of traumatic ICH with patients on different anticoagulants, authors concluded that DOACs are safer alternatives to warfarin [28]. In this study, the rates of hematoma expansion, morbidity, and mortalities were compared between DOACs and warfarin. The patients who were on DOACs had lesser hematoma expansion and greater median discharge Glasgow Outcome Scale (GOS) and good outcome [28]. Vitamin K antagonists such as warfarin activity should be reversed with administration of intravenous vitamin K and three or four-factor prothrombin complex concentrates (PCC), rather than FFP [27].

Patients on oral Xa inhibitors can receive four-factor PCC for reversal if ICH occurs within 3–5 $t_{1/2}$ of the agent [27]. Apart from this, a new approach to effectively reverse the activity of factor Xa activity is the use of recombinant inactivated human factor Xa (andexanet alfa). By reducing the anti-Xa activity in patients of major intracranial and gastrointestinal bleeding, andexanet alfa is an efficacious hemostatic agent in patients on Xa inhibitors [29], whereas reversal of direct thrombin inhibitors such as dabigatran can be achieved with idarucizumab [27]. PCC can also be used if idarucizumab is not available.

Unfractionated heparin (UFH) and low molecular heparin (LMWH) inhibit factors IIa and Xa via antithrombin. LMWH has more predictable pharmacokinetics as compared to UFH. Presence of heparin is assessed by increased aPTT and prolonged ACT. Heparin can be reversed by protamine sulfate (1 mg for 100 units of heparin). Protamine reversal is also recommended for LMWH. Recombinant factor VIIa (rFVIIa) is also recommended if protamine is contraindicated [27].

The use of thrombolytics can cause plasmin activation and lead to degradation of the fibrinogen and fibrin, which can have the potential to cause coagulation abnormality. Although the evidence is of low quality, cryoprecipitate and alternatively tranexamic acid can be used to treat an ICH occurring due to a thrombolytic agent [27].

Prothrombotic Disorders

Like bleeding disorders, prothrombotic disorders can also be classified as inherited and acquired prothrombotic disorders. Many prothrombotic states have a propensity to cause thrombotic events and can involve both venous and arterial systems.

Inherited Thrombotic Conditions

The most common of these include a single-point mutation in factor V (factor V Leiden). Another mutation affecting prothrombin can also lead to thrombophilia. Factor V Leiden mutation makes the factor resistant to degradation by activated protein C, while in the mutation of the prothrombin gene, increased thrombin concentrations in plasma lead to a hypercoagulable state. In a series of cranial dural arteriovenous fistula patients, authors found a mutation involving the prothrombin gene was higher than the average population [30]. In general, factor V Leiden mutation leads to venous strokes as compared to arterial strokes; the incidence of this mutation is observed in 20% in deep venous thrombosis (DVT) and up to 60% in recurrent DVT [31].

Acquired Thrombotic Conditions

Autoantibodies against phospholipid-binding proteins can result in antiphospholipid syndrome (APS), characterized by venous or arterial thrombosis, often associated with certain autoimmune conditions. Patients in APS commonly manifest DVT, recurrent thrombosis, and recurrent pregnancy loss. They are often positive for lupus anticoagulant. In patients diagnosed with APS, cerebrovascular events are described as 3–20% [32]. Most neurological manifestations are due to

microthrombosis and large vessel thrombosis leading to headache, seizures, cognitive dysfunction, movement disorders, and often ischemic stroke [32, 33].

Another acquired condition that merits discussion is heparin-induced thrombocytopenia (HIT). HIT is two types (types I and II), which often occurs after exposure to heparin, and resultant antibodies are formed against heparin-platelet factor 4 (PF-4) (HIT antibodies). This immune complex then binds s to platelets and activates them, which lead to a prothrombotic state [34]. HIT type II is immunogenic, whereas type I is a non-immunogenic reaction to heparin. HIT, especially type II, can lead to widespread arterial and venous thrombosis. The occurrence of cerebral venous thrombosis (CVT) is a fatal manifestation of HIT [35]. Often, the condition is diagnosed by an absolute or relative decrease in platelet count more than 50% after exposure to heparin administration and confirmed by demonstrating HIT antibodies [1]. Once diagnosed, any form of heparin should be discontinued, and platelet transfusion should not be done unless <20,000 per cmm [1]. Direct thrombin inhibitors such as lepirudin should be used instead of heparin [1].

The use of procoagulant medications also alters the process of coagulation. Antifirniolytics, and specific procoagulant factor concentrates are reserved for use in hypocaogulable states. The use of tranexamic acid has been beneficial in reducing perioperative bleeding [36]. Tranexamic acid competitively inhibits the plasminogen activation, thus impairing fibrinolysis. The early use of tranexamic acid in TBI patients has been proven to be beneficial [37]. However, the downside of tranexamic acid use could be the prothrombotic state leading to stroke, DVT, myocardial infarction, and pulmonary embolism. However, the exact effect of tranexamic acid on these thrombotic complications remains inconclusive.

The use of specific factors in factor-depleted patients can also cause disturbances in coagulation. The use of rFVIIa is associated with reports of thrombotic events involving both arterial and venous systems. The higher dose of rFVIIa is associated with arterial rather than venous thrombosis [38]. The PCC used for different conditions can also be associated with significant thrombogenic risk. Heparin, proteins C and S, and AT are added to the PCC to reduce the thrombogenic potential of PCC [1, 39].

Abnormalities Related to Neurological Conditions

Traumatic Brain Injury

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity, and the coagulation abnormalities associated with TBI could result in secondary insult to the brain, which can translate to poor clinical outcome [40]. Depending on the definition of coagulopathy, the incidence of TBI induced coagulopathy span between 10 and 97.3% [6]. The incidence remains higher in severe TBI as compared to moderate degree of TBI [6]. In one study, authors reported that deranged INR at admission and prothrombin time index (PTI) at 24 h after hospital admission were highly predictive of mortality in TBI patients [6]. Despite the advancements, the pathogenesis of such a condition is poorly recognized. One theory suggests the systemic dissemination of brain-derived substances post-disruption of the blood-brain barrier results in widespread systemic coagulopathy [41]. Within minutes of injury, fibrinogen degradation products are detected in the circulation. TBI-induced coagulopathy is multifactorial, caused by depleted coagulation factors and platelets due to blood loss and ongoing DIC [42]. The presence of hypothermia, dilution, and acidosis further augments the coagulopathy [42]. In TBI, excessive TF after injury leads to activation of the extrinsic pathway of coagulation [42], and the counterregulatory mechanisms to limit the coagulation process are mostly inadequate. Traumatic endotheliopathy leading to damage to the endothelium and glycocalyx layers might contribute to coagulopathy associated with TBI. In a study in isolated severe TBI patients, researchers found out the association of coagulopathy (defined by INR > 1.27) with plasma syndecan-1 shedding as

a marker of glycocalyx damage [43]. Severe tissue damage is associated with hyperfibrinolysis with elevated D-dimer and fibrin-degraded products [44]. In a large cohort of adult TBI patients, researchers found out that early administration of antifibrinolytics such as tranexamic acid in a dose of 1 g bolus dose over 10 min, followed by 1 g over 8 h infusion (within 3 h of injury), resulted in reduced mortality related to TBI as compared to placebo [37].

Brain Tumor

Brain tumors, especially glioblastoma multiforme (GBM), can cause heightened procoagulant activity attributed mostly to two significant factors. Firstly, the brain's milieu is a rich source of TF, which is present on astrocytes' surface [45]. Secondly, important factor is the inherent molecular traits of tumor cells, which lead to activation of procoagulant pathways [45]. These not only cause localized microthrombosis but also cause systemic procoagulant activity. An example of this is central nervous system (CNS) lymphoma, which shows more thrombogenic potential than extracranial lymphoma [46]. The occurrence of systemic thrombosis such as venous thromboembolism (VTE) in high-grade GBM patients is 1.5–2% VTE per month survival and 17% at 6 months [45, 47]. One study in malignant glioma patients found out that treatment with subcutaneous dalteparin 5000 units daily can reduce VTE incidence at 6 months and modest survival benefit at 12 months; however, the major intracranial bleed was more in the dalteparin group as compared to the placebo group [47].

Neurovascular Pathologies

After spontaneous rupture of aneurysmal subarachnoid hemorrhage (aSAH), patients remain in a hypercoagulable state up to the initial 24 h, as evidenced by ROTEM [3]. In a comparative analysis with healthy controls, aSAH patients had more clot firmness, platelet maximum clot elasticity, and thrombin generation [3]. The presence of early platelet activation detected by the maximum amplitude of clot assessed by ROTEM is associated with poor outcome and delayed cerebral ischemia following aSAH [48].

In a TEG-based study, authors found out faster clotting is observed as an immediate response to ICH substantiated by baseline shorter R time and higher maximum amplitude at 36 h after ICH [49]. However, presence of hypocoagulability in TEG at admission is associated with the sign of poor outcome [50]. Furthermore, it is found out that deep ICH required longer clot formation times (indicated by R times in TEG) as compared to lobar ICH [15].

Acute Stroke

The abnormalities of coagulation are often implicated in venous strokes such as CVT. Thrombotic occlusion of vessels can occur due to abnormalities in platelets or inherited coagulation disorders. Many prothrombotic states such as factor V Leiden mutation and mutation of prothrombin are implicated in venous strokes [30]. Deficiency of proteins C and S and AT, which are thrombin antagonists, can lead to acute ischemic thrombosis. Apart from these, APS and HIT are acquired conditions associated with recurrent arterial thrombosis. There is a formidable association of cerebral arterial thrombosis with the presence of lupus anticoagulant [51]. The presence of serum D-dimer is associated with the severity of the stroke and also can predict the outcome [52].

Intraoperative Blood Loss and Coagulopathy

Often neurosurgical procedures are associated with a significant intraoperative blood loss and fluid shift, which disturbs the hemostatic mechanism, often leading to a hypocoagulable state in the postoperative period. Perioperative blood loss-induced acquired abnormalities of coagulation occur secondary to the exsanguination, hemodilution, and consumption of coagulation

factors [53]. Large volume resuscitation in ongoing blood loss leads to dilutional coagulopathy, with reduced plasma concentrations of most coagulation factors. It has been observed that after blood loss of 200% of circulating blood volume (CBV), levels of coagulation factors and platelets reach critical levels [54]. Besides blood loss, associated hypothermia and acidosis depress the enzymatic function and reduce thrombin generation [54]. Patient blood management (PBM) according to the ROTEM-based algorithms in major bleeding has been shown to be effective in reducing blood loss, transfusion requirements, and therefore associated complications [55]. Several ROTEM-based thresholds for transfusion of blood components as plasma, fibrinogen, platelets, and antifibrinolytics are defined, serving as a guide to management in patients at risk of significant blood loss in trauma patients [56].

Conclusion

The process of coagulation is influenced by numerous factors. Neurological illnesses themselves can lead to disturbed coagulation disturbances. The use of different drugs also manipulates the coagulation to various degrees. Having in-depth knowledge about the different coagulation abnormalities, especially in the backdrop of neurological illnesses, help the anesthesiologists to manage perioperative coagulation efficiently.

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Adverse Effects of Fluid Administration

Isabel Belda, Tomeu Ramis, Ana Fervienza, Neus Fàbregas, and Ricard Valero

Abstract

Fluid therapy in acute brain injury patients is a part of the basic or maintenance care.

Adverse effects of fluid administration incidence and severity depend on the infused volume, the composition and tonicity of the fluids, and the chronic and acute pre-existing conditions of the patient.

Whereas hypovolaemia could worsen secondary cerebral lesions, recent data suggests that cerebral or systemic fluid overload could also exacerbate it through their effects on the lungs and the heart and their interactions with the brain.

Ionic and osmolarity disturbances are relatively frequent in neurologic patients. Their consequences can be devastating if there is a disruption of the blood-brain barrier.

Glucose-containing solutions have been associated with a worsening of acute cerebral lesions.

Keywords

Fluid therapy · Brain injury · Adverse effects · Cerebral oedema · Osmolality · Osmotherapy Fluid overload

Introduction

Fluid therapy is an essential component of the management of neurological or neurocritical patients. It has general indications (resuscitation and volume maintenance) as well as neuro-specific ones (controlling intracranial pressure, management of delayed cerebral ischaemia).

Available evidence is consistent with the consideration of fluid management as 'basic or maintenance care' having an impact on outcome for patients having sustained head trauma or subarachnoid haemorrhage [1, 2].

Central nervous system (CNS) vascular physiology is distinct from the rest of the body. It is a crucial aspect that the healthy blood-brain barrier (BBB) is impermeable to unregulated solute diffusion as it has tight intercellular junctions [3].

Movement of fluid through the BBB is thus governed by Starling's equation and results from the balance of forces 'pushing' water out of the capillaries (mostly hydrostatic pressure) and those 'pulling back'. As in other tissues, this force depends on the concentration of molecules

I. Belda · T. Ramis · A. Fervienza · N. Fàbregas
R. Valero (✉)
Neuroanaesthesiology Section, Department of Anaesthesiology, Hospital Clínic de Barcelona, Barcelona, Spain
e-mail: rvalero@clinic.cat

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which are unable to cross the semipermeable membrane. In contrast with other tissues and as a result of the tight junctions being impermeable to virtually all ions, the force balancing hydrostatic pressure is osmotic pressure (about 5545 mmHg, with sodium and its associated anions as main contributors) in lieu of oncotic pressure (which is about 30 mmHg and is exerted by big molecules, specially albumin). Hence, when the BBB is intact, administration of substantial volumes of isotonic fluid, which would likely lead to peripheral and/or pulmonary oedema as it is distributed throughout the extracellular compartment, will not cause cerebral oedema nor increase intracranial pressure (ICP) [4].

There is an important variability in the fluid regimens administered to these patients. It is likely that these differences in clinical practice stem from a lack of robust scientific evidence in the published guidelines. Some of the terms used on them (such as 'euvolaemia') may be interpreted subjectively [5].

The main objectives of fluid therapy in these patients are reverting hypovolaemia quickly by restoring intravascular volume, avoiding hypotension in order to ensure a constant cerebral blood flow (CBF), and limiting cerebral ischaemia and hypoxia. This has to be done while averting intracranial hypertension, which could otherwise cause cerebral hypoxia and ischaemia, as well as other complications.

This treatment is not, however, devoid of risks and potential complications (Table 1): an excessively liberal fluid therapy might cause or worsen cerebral oedema and increase ICP, particularly in patients with increased risk of oedema (those with inadequate secretion of antidiuretic hormone syndrome or kidney injury) or BBB disruption (head trauma, postoperative) [18].

In the following sections, different adverse effects of fluid administration in neurologic and neurocritical patients will be discussed (Fig. 1). They have been classified as derived from hypovolaemia; from volume overload; from hypoosmolarity; from ionic, osmolar, or oncotic overload; from glycaemia alterations; and allergic reactions.

Table 1 Main adverse effects according to the fluid

Fluid type	Major adverse effects
Crystalloids	
Crystalloids (in general)	• Osmotic changes [6] • Hyponatraemia, cerebral oedema [7] • Dilution acidosis, hyperchloraemic acidosis [8]
Glucose-containing solutions	• Cerebral oedema [9] • Tissue acidosis [10]
Hyperosmolar solutions	• Rebound ICHT [11]
– Mannitol	• Hydroelectrolytic disbalance • Fluid overload: pulmonary oedema, hypertension, congestive heart failure • Acute kidney failure (high dosages) [12] • Dermic necrosis (extravasation) • Polyuria leading to hypovolaemia [11]
– HSS	• Hypernatraemia [13]
Colloids	
Dextrans	• Haemostasia impairment (↓VW factor, ↓VIIIc factor, ↓platelet aggregation) • Kidney function impairment [14]
Gelatines	• Anaphylactic reactions (often mild) [15]
HES	• Kidney injury [16]
Albumin	• Microorganism transmission • Cerebral oedema increase (possible) [17]

Hypovolaemia Effects

For a long time, restrictive fluid management has been the preferred approach for patients with intracranial pathology, due to fears of liquids increasing cerebral oedema [19].

Nonetheless, a disproportionately restrictive fluid administration strategy might lead to hypovolaemia and a reduction of CBF in patients with increased fluid losses (those bleeding or suffering from *diabetes insipidus*) [20]. Hypotension episodes can also increase ICP and result in a reduction of cerebral perfusion pressure. The consequences of this situation might be devastating [21]. Volume depletion has been reported in up to 50% of patients with subarachnoid haemor-

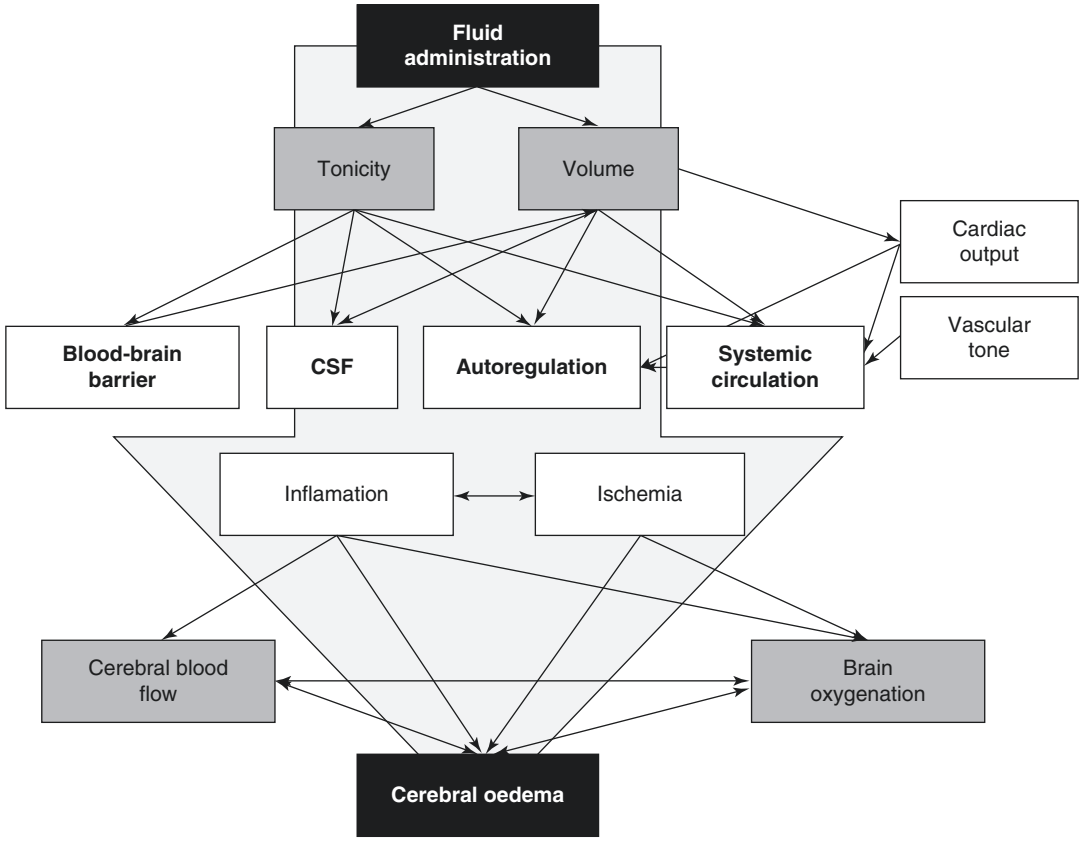

Fig. 1 Fluid administration physiological effects added to inflammation and ischaemia favour cerebral oedema (modified from van der Jagt [5])

rhage (SAH). When they develop angiographic vasospasm, volume depletion is associated with delayed neurologic impairment [22].

Recently, there has been a lively debate regarding the concept of 'normovolaemia' in patients with SAH and how to monitor their volume state exactly, as hypervolaemia may also make delayed neurologic impairment (or delayed cerebral ischaemia) more severe [23].

Volume Overload Effects

Frequently, adverse effects of fluid administration are caused by the infusion of an excessive volume. The main affected organs then are the lungs and heart. Most fluids will distribute extensively through the extravascular compartment (depending on their effective osmolarity and other factors). Hypertonic solutions such as mannitol and, remarkably, hypertonic saline solution (HSS) increase cardiac output [11].

The most important systemic complications of volume overload are vascular endothelial dysfunction, tissue oxygenation impairment, heart failure, pulmonary oedema, and haematologic alterations. These complications may affect the CNS in a direct or indirect manner [24]. However, research on consequences of fluid overload is seriously hampered by a lack of uniform definitions and the fact that cerebral oedema is difficult to routinely assess [3].

Vascular Endothelium Alterations

The endothelial glycocalyx is a thin sugar-based lining on the apical surface of endothelial cells and has been found to be damaged in critical illness and after acute care surgery. It has been linked to several important physiological functions of the microcirculation: mechano-transduction, blood coagulation, immunity, antioxidation, and interaction with serum proteins and sodium. When the endothelial glycocalyx is disrupted, the resulting extravascular fluid leak may promote oedema formation with all of its consequences, so avoiding fluid overload is recommended [25].

Tissue Oxygenation Alterations

Volume overload causes capillary and lymphatic vessels to be obstructed, which impairs tissue oxygenation. This impairment might lead to organ dysfunction if it persists. There are plenty of observational studies which show an association between volume overload and mortality in the critically ill. An overloaded patient might present with acute respiratory distress syndrome (ARDS), acute kidney injury, or sepsis [26].

In the clinical setting, volume overload effects are seen primarily in capsule-contained organs such as the kidney and liver [7], but they can also be seen in other organs. Volume overload is associated with worsened scar tissue formation, intestinal malabsorption, or the ileum. In the most severe cases, mesenteric ischaemia can appear [27].

The increase in CBF caused by haemodilution is an active compensatory response to a decrease in arterial oxygen content in normal brains. This response is analogous to that seen in hypoxia. Nevertheless, when there is cerebral lesion, normal response of CBF to hypoxia or haemodilution might be attenuated, and this alteration could therefore lead to secondary tissue damage [28].

Heart Failure and Pulmonary Oedema

There are not many tools that allow us to measure the effects of fluids on cerebral oedema on the bedside. Specific neuromonitoring (CBF, ICP, tissular oxygenation) is not always available, which makes its management harder [29].

When a significant amount of fluids is administered, intracardiac pressures and myocardial work are increased. This increased strain put on the cardiovascular system might develop into acute heart failure which can lead to pulmonary oedema. These effects are more severe in patients with a previously abnormal cardiovascular function. Severe pulmonary oedema might in its turn develop into ARDS, which has a significant morbimortality [30].

Haemodynamic and oxygenation changes cause significant alterations on CNS physiology. Evidence shows that an alteration in cardiac output, whether it is acute or chronic, leads to changes in CBF independently from other parameters which also play a significant role in determining it, such as $PaCO_2$ and blood pressure [31].

Patients with an acute brain injury (ABI) are more prone to lung damage than the rest of critical care patients. There is close relation between the damaged brain and lung, which is bidirectional (brain-lung and lung-brain) (Fig. 2). This is summed up in a hypothesis dubbed ‘the double-hit model’. The ‘first hit’ consists of a massive catecholamine and proinflammatory cytokine liberation from the injured brain onto the systemic circulation through the BBB. This proinflammatory state increases lung susceptibility to stressors such as mechanical ventilation or infection, which then act as the ‘second hit’.

In the other direction, a primary lung alteration such as ARDS or complications of mechanical ventilation (mostly, mechanical ventilation-associated pneumonia) can worsen the patients’ neurologic state. These detrimental effects are caused by a systemic humoral inflammatory response, the mediators of which go through a disrupted BBB and exacerbate ABI. As a consequence, mechanical ventilation strategies can affect the lungs and aggravate a pre-existing cerebral lesion, which can in its turn feedback into the lung lesion [32].

Furthermore, all surgical, trauma, or septic patients develop lung vascular lesions to some extent. These lesions increase capillary permeability and therefore oedema. They might be prone

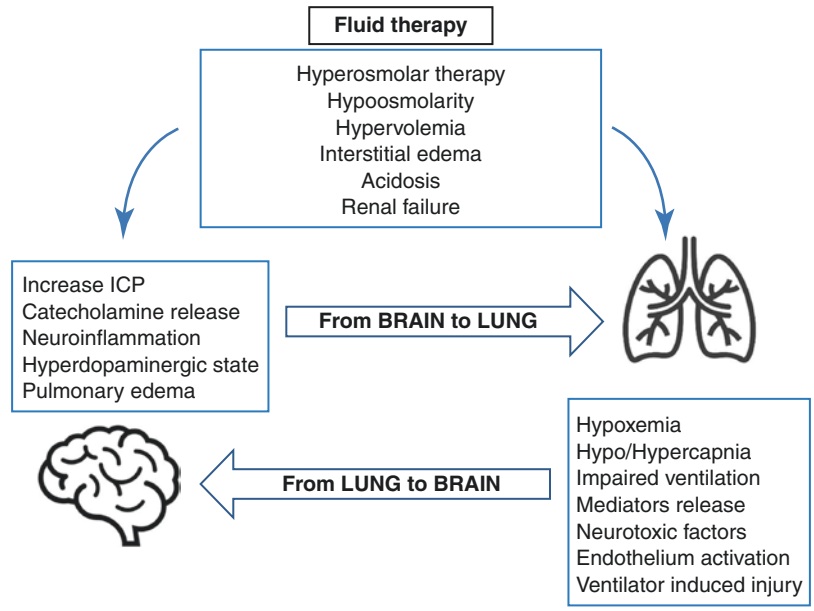

Fig. 2 Fluid therapy effects on 'brain-lung' and 'lung-brain' crosstalk. Attribution text: lungs by Karina from the Noun Project and the brain by Meaghan Hendricks from the Noun Project

to suffer from pulmonary congestion even with mildly elevated capillary wedge pressures. Thus, a persisting positive fluid balance can be associated with a longer mechanical ventilation and difficult weaning. Positive fluid balance is also associated with a higher incidence of sepsis, length of stay, and in-hospital mortality [33].

Haematologic Alterations

Indiscriminate fluid administration leads to haemodilution and dilutional anaemia. This results in a decrease in oxygen delivery to the brain. This is a potentially risky situation for all patients, but expressly so for patients with a coexisting cerebral lesion.

Excessive dilution of coagulation factors is also frequent, and it impairs correct haemostatic function [34]. This increases the risk of cerebral haemorrhage, which can even appear spontaneously in these patients.

Dextran use has been associated with an inhibition of platelet aggregation and a decrease in Von Willebrand and VIIIc clotting factors, as well as alterations in kidney function [14].

It seems that third-generation hydroxyethyl starch (HES) solutions (as 6% HES 130/0.4 or 130/0.42) cause haemodilution but do not have any other deleterious effects on homeostasis. However, there is not enough evidence from wide-scope studies to adequately assess their safety and effectiveness in patients with severe haemorrhagic shock [28].

Hypoosmolarity Effects, Hyponatraemia, and Cerebral Oedema

Many CNS conditions present with hyponatraemia frequently. Some of them are traumatic brain injury, CNS infections, CNS tumours, and acute neurovascular lesions. Hyponatraemia and its management are crucial in patients with SAH because its presence has a negative prognostic value. It is associated with higher risk of death, vegetative status, and cerebral ischaemia [35].

Inadequate antidiuretic hormone (ADH) secretion syndrome and cerebral salt-wasting syndrome are the most frequent neurologic hyponatraemia causes [36]. The brain is the main target organ of hyponatraemia. Even a small decrease in plasma osmolality (<5%) can increase cerebral water content [37]. While most organs can withstand an increase in their volume, the

brain cannot as it is encased in the cranium, which is an almost completely rigid compartment. Therefore, an increase of the cerebral volume of 8–10% can cause intracranial hypertension which sequentially develops into transtentorial herniation, comma, and death [38].

Hyponatraemia encephalopathy clinical manifestations depend on its depth, the speed of its onset, and patient-specific factors and can be widely variable. Epileptic crises and myoclonus are frequent. Commonplace clinic manifestations of hyponatraemia (headache, apathy, cramps, nausea, and vomiting that develop into confusion, disorientation, agitation, sleepiness, and comma) coexist with the initial conditions of the patient with ABI, and this can worsen neurologic outcomes. It is important, then, not to exacerbate a potential pre-existing hyponatraemia with administered fluid therapy in neurologic and neurocritical patients. Hence, frequent monitoring of plasma sodium and osmolality is recommended.

Fluid osmolarity is much more important than its oncotic pressure in the pathogenesis of cerebral oedema. When treating a neurocritical patient, avoiding hypoosmolar crystalloid solutions is adequate to prevent their passage into the cerebral interstitium. Any administered fluid which has a sodium and potassium tonicity lower than that of plasma's aqueous phase (154 mEq L^{-1}) is to be considered hypotonic. Hypotonic fluids can cause hyponatraemia on their own, or they can worsen that caused by the underlying neurologic condition [39].

Lactated Ringer's solution has a calculated osmolarity of 275 mOsm L^{-1} but a measured osmolality of 254 mOsm kg^{-1}, which shows an incomplete dissociation. Infusing important quantities of this solution (>3 L) might reduce plasma osmolarity and increase cerebral water content and ICP. This is because about 114 mL of free water are given with each litre of lactated Ringer's solution [6]. Furthermore, in patients in septic shock or other liver hypoperfusion situations, lactated Ringer's solution has been associated with an exacerbation of lactic acidosis. This effect is thought to be due to a decrease in its clearance.

Even 0.9% saline can potentially cause hyponatraemia, when there is an excess of ADH if urinary osmolality is over 500 mOsm kg^{-1}. It can also cause acute kidney failure. These effects are particularly concerning in patients with CNS lesions. These patients may have abnormally high levels of ADH and urinary osmolality, and small changes in plasmatic sodium concentrations might worsen their pre-existing neurologic impairment [40].

Glucose-containing solutions, especially 5% glucose (also known as 5% dextrose or 5% dextrose in water), are hypotonic regardless of their calculated osmolarity. While glucose is quickly transported into the intracellular compartment and metabolised, free water remains in the intravascular component. This causes a decrease in plasma osmolarity and induces cerebral oedema. Thus, salt-devoid glucose-containing fluids should be avoided in patients with CNS pathology [41].

Routine administration of hypotonic fluids should be avoided in most patients undergoing intracranial procedures as cerebral oedema may be exacerbated [7].

Oncotic, Osmotic, or Ionic Overload

Hyperchloremic Acidosis

All available NaCl-containing fluids (0.9%, 0.45%) are acidic, their pH is about 5, and they may cause dilutional acidosis when administered quickly. This acidic pH is not attributable to Cl, as 0.9% NaCl's pH glass-bottled presentations have a pH of 7. It is, however, due to a reaction between the solution and the plastic bag (usually made out of polyvinyl chloride or PVC). These plastic bags are permeable to CO_2, so there are no $NaHCO_3$ plastic-stored presentations (as it would dissociate and dissipate).

Hyperchloremic acidosis is a complication of the administration of significant volumes of 0.9% saline solution. This is due to its high concentration of chlorine relative to plasma and its lower pH. The incidence of this complication is directly related to the administered amount of chlorine [8].

Hypernatraemia and Central Pontine Myelinolysis

Recent studies suggest HSS as the best osmotic treatment to decrease ICP because it also increases blood pressure and tissue oxygen pressure (PtiO2) in patients with severe traumatic head injury [42] or undergoing elective craniotomy [43]. HSS has a smaller diuretic effect than mannitol [44]. Increases in natraemia are milder than what may be expected after infusing sizable volumes of HSS, and its magnitude seems to be unrelated to HSS dosage or its osmotic charge. It also seems patients are usually able to tolerate acute sodium overloads up to 155–160 mEq L^{-1} without significant harm.

Nevertheless, it has to be noted that particularly rare adverse events, such as central pontine myelinolysis, which primarily occur after the rapid correction of severe hyponatraemia, are unlikely to be observed in small sample size RCTs [13].

HSS is unable to cross the intact BBB (so it stays in the intravascular compartment and out of the brain tissue). There have not been many complications to the use of HSS to decrease ICP. An abrupt increase in plasma osmolarity, however, is supposed to potentially cause a BBB disruption [45].

There are hyperosmolar colloid solutions available (6% HES 200/0.5 or dextran), which are dissolved in HSS (7.2–7.5%). These solutions combine characteristics of colloids and hyperosmolar crystalloid solutions. Their high sodium content amounts to an osmolarity of about 2500 mOsm L^{-1}. This hyperosmolarity causes water redistribution to the extracellular (intravascular) bodily compartment, so their plasma expansion effect is greater than that of an equal volume of isoosmolar fluid. An initial hypotensive response to their administration, caused by reflex vasodilation, has been reported [46].

Tissue Perfusion Alterations and Ischaemia

As stated previously, osmotic therapy forces water into the extracellular compartment (including the intravascular compartment). It also causes direct peripheral vasodilation. These two factors lead to an increase in cardiac output [47]. This effect is swiftly followed with a profuse urinary output with mannitol, which may lead to or worsen hypovolaemia, whereas diuretic response to HSS is smaller [11].

The effects of mannitol and SSH were investigated in patients scheduled to undergo elective supratentorial craniotomy for mass resection. Mannitol was associated with a significant increase in serum lactate concentration and SSH with a significant decrease in pulse pressure variation. These findings suggest that compared with SSH, mannitol likely results in a more significant decrease in intravascular volume, which could cause tissue hypoperfusion [48]. However, in a recently published trial on patients undergoing intracranial tumour surgery, mannitol administration was not associated with increased rates of lactic acidaemia [49].

Acute Kidney Failure

Impairment of kidney function has been reported occasionally in patients who received mannitol. Most of them were on high dosages and had a pre-existing kidney lesion. Excessive or repeated doses might produce detrimental hyperosmolarity [43].

Oh et al. [12] retrospectively studied patients undergoing craniotomy for primary brain tumour resection to identify factors associated with postoperative acute kidney injury, with an incidence of 5.4%. Factors found to be independently associated with acute kidney injury were the use of nephrotoxic drugs, excessive balanced crystalloid solution administration, preoperative anaemia, and increased serum chloride concentration.

Nowadays, HES solutions were the most frequently used synthetic colloids in Europe. They have classically been associated with kidney dysfunction due to their high molecular weight and long half-life. Recently, several studies have put HES solutions' safety into question. An increase in rates of acute kidney injury has been reported in patients with sepsis or septic shock resuscitated with these solutions. HES solutions are not

recommended in patients with ABI after the discouraging results of the SAFE trial [16] and others [50]. HES solutions are, in fact, associated with higher rates of kidney replacement therapies and other adverse events in critical care patients.

Hyperosmolarity and Cerebral Oedema

Both mannitol and HSS can potentially cause rebound intracranial hypertension, as other osmotically active drugs do [11]. Furthermore, with repeated doses, mannitol progressively accumulates in the interstitium. This accumulation can exacerbate cerebral oedema due to an increase in cerebral interstitium osmolarity [51]. When plasma osmolarity returns to basal levels, the osmotic gradient could be inverted which, in turn, could worsen cerebral oedema [52].

Mortality Increase

Albumin solutions contain human plasmatic protein, usually in suspension in 0.9% saline with a 4% concentration. Albumin is regarded as a very safe colloid solution, and the incidence of adverse effects after its administration is much lower than that of semisynthetic colloids. The main potential adverse effect is microorganism transmission. It is worth noting that the cost of human albumin solutions is considerably higher than the cost of other colloids.

In the last few years, findings discouraging its use in neurocritical patients have been published [17]. In a physiologic model of the vascular system, iso-oncotic colloid solutions stay within the intravascular space as they can't cross the endothelial membrane [53]. A significant increase in 2-year mortality was seen in patients resuscitated with 4% albumin when compared to those resuscitated with 0.9% saline [16]. The authors reporting this argue that, in patients with an altered BBB, there could be albumin passage to the cerebral interstitium which would in turn increase cerebral oedema, intracranial hypertension, and mortality.

Albumin usage was also associated with a greater number of interventions to lower ICP and to maintain cerebral perfusion pressure being needed. It is not clear whether ICP increase was due to albumin extravasation through a disrupted BBB or if it was instead related to the 4% albumin used in the SAFE trial [16] being lightly hypoosmotic and hypotonic [54].

Glycaemia Alteration Effects

Glucose solutions might cause hyperglycaemia, which is associated with a more severe neurologic injury and a worse prognosis [9]. Specifically, it may lead to an increased focal and global cerebral ischaemia. This is likely due to tissue acidosis in ischaemic areas where there is anaerobic glucose metabolism. Strict glycaemic control is hence recommended for all patients with ABI [10].

Keeping glycaemia around 110 mg dL^{-1} is recommended by some authors, but if this is the target, it is necessary to have a protocol to prevent hypoglycaemia. In recent years, glucose and insulin administration ('GIN therapy') to keep normoglycaemia in critically ill patients has become commonplace [55]. However, the ideal limits within which to keep glucose levels without causing hypoglycaemia are still hotly debated. There seems to be a stronger agreement regarding the avoidance of hyperglycaemia, as it is associated with a worsened neurologic prognosis and mortality. In the most recent available evidence, it is stated that a glycaemic target between 80 and 100 mg dL^{-1} cannot be recommended, as there is a great risk of hypoglycaemia. They seem to consider best practice to keep glycaemia under 140 mg dL^{-1} [56].

Allergic Reactions

After mannitol infusion, skin necrosis can occur if the solution gets out of the blood vessels. Anaphylaxis is rarely reported. Gelatines have a small plasma expanding effect and have been associated with anaphylactic reactions [15]. These reactions are often mild.

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Part VI

Blood and Blood Products: Basic Consideration

Composition of Blood

Thassayu Yuyen

Abstract

Blood is a fluid connective tissue circulating through blood vessels. There are two components in the blood, fluid component (plasma) and cellular elements (red blood cells, white blood cells, and platelets). Each of the components plays different roles which in summation provide various functions of the blood including transportation of gases, nutrients, wastes, hormones, etc., defense against invading microorganisms, maintenance of homeostasis, and distribution of heat. This article gives basic information about the component of blood and how to estimate blood volume. The various functions of blood are also described. Understanding this knowledge is helpful for physicians in order to offer a safe and effective care to the patients.

Keywords

Component of blood · Plasma · Red blood cells · White blood cells · Platelets · Function of blood · Blood volume

T. Yuyen (✉)
Department of Anesthesiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
e-mail: Thassayu.yuy@mahidol.ac.th

Introduction

Blood is a fluid connective tissue circulating through blood vessels, carrying elements such as nutrients, waste, heat, oxygen, and carbon dioxide from one location in the body to another. Blood is composed of fluid (plasma) which is about 55% of blood volume, and the remaining 45% is cellular elements (red blood cells, white blood cells, and platelets) [1] (Figs. 1 and 2).

Blood Volume

Blood volume refers to the total amount of fluid circulating in the whole blood vessels including arteries, veins, and capillaries and in the heart chambers at any time. The blood volume of the human adult is about 4–5 l depending on the individual's height and weight. In general, men have a greater blood volume than women; however, during pregnancy, a woman's blood volume may increase by 50% [2].

There are two equations used for estimation of blood volume. The Nadler equation developed by Dr. Nadler in 1962 based on gender, height, and weight in the calculation [3]. Another equation was developed in 2006 by Dr. Lemmens, Dr. Bernstein, and Dr. Brodsky. This equation allows physicians to predict blood volume over the wide range of body weights and body mass indices (BMI) in patients who are not stressed by acute trauma or critical illness [4] (Table 1).

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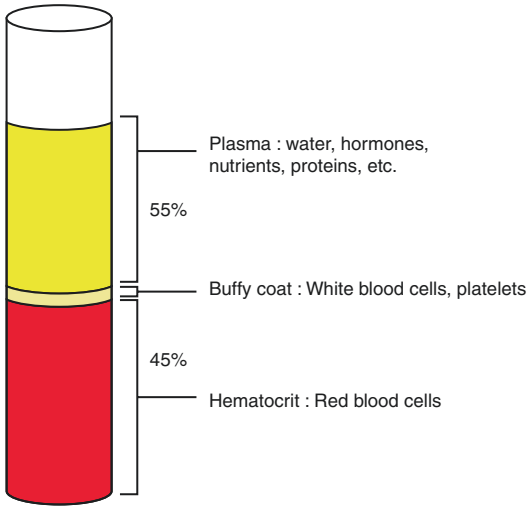

Fig. 1 Composition of blood: when spinning a blood sample in the specialized centrifuge. The three zones are separated. The bottom is the zone of red blood cells, called *hematocrit*. Located above the RBCs is *buffy coat*, the pale thin layer composed of white blood cells and platelets. Above the buffy coat is the *plasma*, the straw-colored fluid consists of water, hormones, nutrients, proteins, etc.

Plasma

The light yellow (straw-colored) fluid makes up to 55% of blood volume. More than 90% of plasma is water, and less than 10% are dissolved and suspended substances including proteins, electrolytes, vitamins, glucose, and amino acids [5]. Plasma proteins play an important role in regulating fluid exchange between body fluid compartments. The three major groups of plasma proteins are albumin, globulins, and fibrinogen.

Albumin is the majority of plasma proteins (54–60%), 3.5–5.0 g/dL of blood. It is produced by the liver with the synthesis rate of about 10.5 g/day and then circulated in the plasma with half-life of 25 days [6]. It is the most significant contributor to the oncotic pressure of blood which is essential in holding the water inside intravascular compartment and also drawing water from interstitial compartment into blood vessels. Moreover, albumin molecules serve as binding proteins which bind to electrolytes, fatty

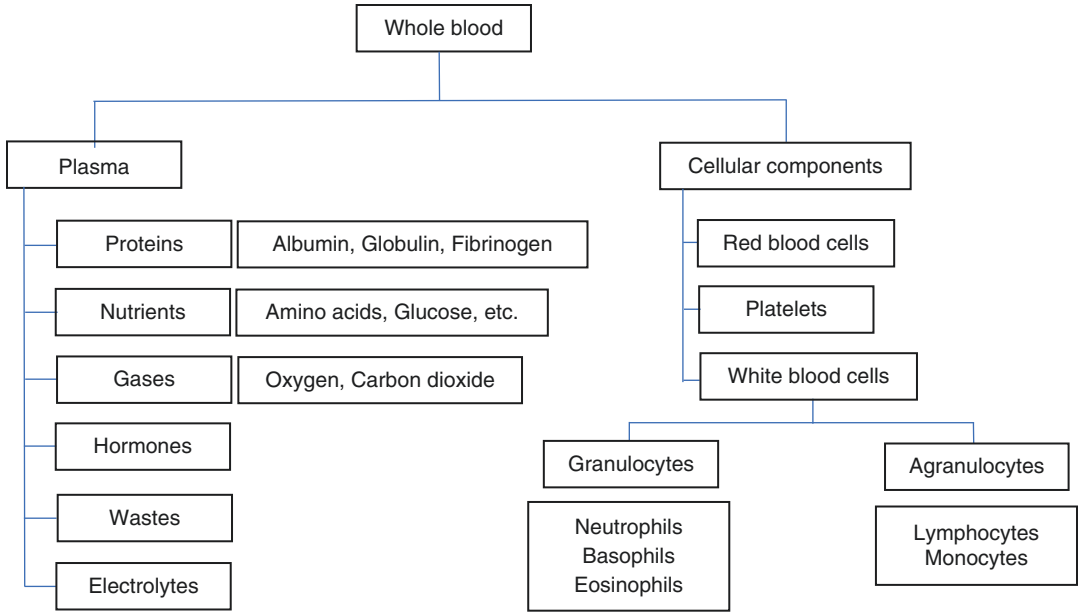

Fig. 2 The overview of components of blood

Table 1 Estimation of blood volume

Equation	Calculation
Nadler	Blood volume (liter) Men = [0.3669 × height(meters)^3] + [0.03219 × weight (kg)] + 0.6041women = [0.3561 × height(meters)^3] + [0.03308 × weight (kg)] + 0.1833
Lemmens-Bernstein-Brodsky	Blood volume (ml/kg) = 70 / square root (BMI/22)

acids, some medications, and steroid hormones. In general, lipids are water-insoluble molecules but binding to albumin enables their transport in watery plasma.

Globulins are the second most common plasma proteins (35–38%), 1.0–1.5 g/dL of blood. There are three main subgroups known as alpha, beta, and gamma globulins. The alpha and beta globulins are produced by the liver and circulate in the plasma transporting iron, lipids, and the fat-soluble vitamins A, D, E, and K to the cells. They also contribute to plasma oncotic pressure similar to albumin. The gamma globulins are produced by plasma cells, the specialized leukocytes. Their functions are involved in immunity generally known as antibodies or immunoglobulins.

Fibrinogen is the least abundant plasma protein (5–7%), 0.2–0.45 g/dL of blood. It is produced by the liver. It has an essential role in clot formation. Fibrinogen is converted by factor IIa (thrombin) to be fibrin and then combined with platelets forming a stable fibrin clot.

Other than proteins, plasma contains various substances including electrolytes (sodium, potassium, calcium ions), dissolved gases (oxygen, carbon dioxide, nitrogen), nutrients (vitamins, lipids, glucose, amino acids), and metabolic wastes. All of these non-protein solutes account for only 1% of the total plasma volume.

Red Blood Cells

Red blood cells (RBCs), or erythrocytes, are the most abundant cells of the cellular elements of blood. RBCs are approximately 7.8 μm in diameter. The morphology of RBCs is bi-concave disc [7], a shape that provides a large surface-to-volume ratio, maintained by a network of proteins that allow the RBCs to change their shape when passing through the various sizes of blood vessels. Immature RBCs contain nucleus, but when developed to be mature RBCs, the nucleus is disappeared. This change results in increasing the oxygen-carrying capacity of the mature RBCs. Since an absence of nucleus, RBCs are unable to divide, reproduce, and be repaired.

The red blood cell count is the number of RBCs per cubic millimeter of blood which is generally more than 4–5 million cells [1]. In cytoplasm of RBCs, there is hemoglobin (Hb), an oxygen-carrying protein, which is responsible for the carriage of oxygen transported in the blood. Hemoglobin contains four polypeptide chains; each chain comprises more than 140 amino acids [8]. There are also four heme groups for each hemoglobin. Heme is composed of porphyrin which binds to an iron atom, an important atom that reversibly binds oxygen as the blood circulates from the lung to the peripheral tissue. Accordingly, each molecule of hemoglobin can bind four atoms of oxygen. Oxygenated RBCs have red color so make the blood appear to be red when drawing out from an artery. When oxygenated RBCs reach the tissue through capillaries, they give the oxygen up and then carry up carbon dioxide. The carbon dioxide is then transported back to the lungs. The partially deoxygenated blood from a vein is darker red than that from an artery. The life span of RBCs is about 120 days [9]. When they are expired, they are eliminated by macrophages of the reticuloendothelial system that is part of the spleen, liver, bone marrow, and lymph nodes. The iron in the hemoglobin is recycled and reused at a later period.

White Blood Cells

The white blood cells (WBCs), or leucocytes, are fewer than RBCs. The normal WBC count is between 4000 and 11,000 per cubic millimeter of blood [1]. However, the WBC count is fluctuating during the day: lower value during rest and higher value during exercise. The WBCs are larger in size compare to RBCs, and they have a nucleus. There are five types of WBCs. Neutrophils, eosinophils, and basophils contain granules in the cells, so-called granulocytes, while monocytes and lymphocytes are absent of granules, so-called agranulocytes. Each of them has a role in the immune system. As a group they are involved in the body's defense mechanism against infection and unfamiliar particle invading the body.

Neutrophils

The neutrophils are 12–15 μm in diameter. The number of neutrophils is 2000–7500 per cubic millimeter [1]. The nucleus consists of 2–5 lobes joined together by hairlike filaments. Neutrophils are able to move by amoeboid motion. They extend the pseudopodium and follow by the contraction of filaments in the cytoplasm which make the cell move toward that direction. The neutrophils migrate to areas of infection or tissue injury induced by substances liberated at sites of tissue damage: the process called chemotaxis [10]. Half of the total neutrophils circulating outside the bone marrow are in the tissue, and the other half are in the blood vessels. Of those in the blood vessels, some are within the mainstream of circulating blood, and some move slowly along the inner walls of the blood vessels, ready to enter the damaged tissue.

The mechanism of neutrophils using to eliminate the invading organism is phagocytosis. Bacteria, microorganisms, and microscopic particles are engulfed by neutrophils and then encased in a vacuole. The granules of the neutrophil consist of enzymes which are able to digest many types of cellular materials. These enzymes are discharged into the vacuole containing the organisms. Hydrogen peroxide and active form of oxygen, superoxide, produced by a metabolic process within the granules then destroy the ingested organisms [11].

Eosinophils

The eosinophils have the same size as neutrophils. The number of eosinophils is 40–400 per cubic millimeter [1]. The granules are larger than the neutrophils', and the nucleus is generally divided to two nonsegmental lobes. After releasing from bone marrow, eosinophils circulate in the bloodstream just a few hours and then migrate into the tissue through the lymphatic channels. The common sites for migration are lung, skin, and respiratory tract. Like neutrophils, eosinophils respond to chemotactic signals released by the destructive cells and also have the phagocytic activity. Eosinophils specifically defense against parasites and play a role in hypersensitivity and allergic reactions [12].

Basophils

The basophils are also similar to neutrophils and eosinophils in terms of size. The number of basophils is 0–100 per cubic millimeter [1], the least abundant of the granulocytes. They contain the large dense granules which obscure the double-lobed nucleus. After releasing from bone marrow, basophils circulate in the bloodstream just a few hours and then migrate into the barrier tissues such as skin and mucosa. Basophils release histamine and leukotrienes, inflammatory cytokines, which cause bronchoconstriction during a hypersensitivity reaction. They are also involved in anaphylactic and inflammatory reactions [13].

Monocytes

The monocytes are the largest WBCs with the size of 15–18 μm in diameter. The number of monocytes is 200–800 per cubic millimeter [1]. They have a big folded nucleus and numerous fine granules in the cytoplasm especially near the

cell membrane. Monocytes are actively motile and have the phagocytic activity. After releasing from bone marrow, they circulate in the bloodstream about 10–12 h. Then, they enter the tissues and develop into macrophages, the tissue phagocyte that constitutes the reticuloendothelial system. Macrophages are found in almost all tissues of the body. They are called differently at various sites of the body such as Kupffer cells in the liver and Langerhans cells in the skin. Monocyte usually migrates into the inflamed tissue later than the granulocytes. They are generally involved in the site of chronic infections [14]. Moreover, macrophages play a key role in immunity by ingesting antigens and processing them so that lymphocytes are able to recognize as foreign particles.

Lymphocytes

The lymphocytes are quite smaller than granulocytes and slightly larger than erythrocytes. The nucleus of lymphocyte occupies most of the cell. The number of lymphocytes is 1300–4000 per cubic millimeter [1]. Lymphocytes are slowly motile. They are found in a large amount in the lymph nodes, spleen, thymus gland, tonsils, and lymphoid tissue of the gastrointestinal tract. They enter the bloodstream via lymphatic system by the thoracic duct draining into the venous system. Some lymphocytes may leave and reenter the circulation and can survive for more than a year. The lymphocytes are involved in the acquired immunity to foreign cells and antigens. They provide immunologic reactions to invading organisms, foreign cells, foreign proteins, and other antigens. There are two classes of lymphocytes classified by their type of immune response [15]. The B lymphocytes are involved in humoral immunity. They differentiate to plasma cells, which secrete immunoglobulin (antibodies) in order to response to antigens. Another class of lymphocyte is T lymphocytes, which are involved in regulating the antibody-forming function of B lymphocytes. They have a role in cell-mediated immune response. The T lymphocytes are also involved in the transplanted tissue rejection and in some types of allergic reaction. The essential function of lymphocytes is to defense against foreign organism. This task is accomplished by both T lymphocytes and B lymphocytes, usually acting together in sequential steps.

Platelets

Platelets, so-called thrombocytes, are the smallest cellular elements of blood, averaging 2–4 μm in diameter [16]. The platelet count is 150,000–440,000 per cubic milliliter [1]. Although much more numerous than WBCs, they occupy only small fraction of the volume of the blood due to their relatively tiny size. The morphology of platelets is oval, non-nucleated structure that contains vital elements such as potassium, calcium, clotting factors, and enzymes. Platelets can survive for 8–12 days [17] and then are destroyed by the spleen.

Function of Blood

There are various components of the blood. Each of these components plays different roles in maintaining the well-being of human life including transportation of nutrients, wastes, hormones, and gases around the body, immunological functions, and homeostatic regulation of pH and temperature.

Functions of Plasma

There are several vital functions of blood plasma [18].

1. The main function is transportation. Since plasma is composed of water for more than 90%, it is a good medium for transportation of a number of agents. Nutrients such as glucose, amino acids, and vitamins are absorbed from the GI tract into bloodstream and then are transported to the tissues. Some parts of oxygen received from the lung are dissolved in plasma and then carried to the peripheral tis-

sue. Carbon dioxide, an end product of aerobic respiration produced by the cells, are diffused from the tissues into bloodstream. Some part of carbon dioxide dissolved in plasma and then circulated back to the lung to exhale out to the atmosphere. Hormones from all endocrine glands of the body are transported to the target organ by plasma. Waste products from cellular metabolism are carried within the plasma and excreted by kidneys, lung, and skin.

2. Plasma contains various coagulation factors and fibrinogens which are essential in hemostasis.
3. Immunoglobulins (antibodies) in the plasma play an important role in the immune defense mechanism of the body.
4. Albumin, the most abundant proteins in plasma, contributes to the plasma oncotic pressure which is vital for controlling the movement of water between intravascular and interstitial compartment.
5. Plasma proteins are one of the buffer systems helping in controlling the acid-base balance of the blood.

Function of Red Blood Cells

Red blood cells contain hemoglobin which has an affinity with oxygen. The majority of oxygen content in the blood is attached to hemoglobin, called oxyhemoglobin (HbO2, [19]), and circulated to peripheral tissue by the cardiac output. At the tissue sites, carbon dioxide diffused from the cells to bloodstream. A part of carbon dioxide is also attached to hemoglobin, called carbaminohemoglobin (HbCO2), and carried to the lungs [20].

Function of White Blood Cells

There are five types of WBCs. All of them work together in order to defense against invading organisms and foreign particles. The granulocytes (neutrophils, basophils, eosinophils) have the phagocytic activities. Neutrophils are the major pathogen-fighting immune cells that migrate to sites of infection and then identify and kill microorganisms. They also send signals to alert other immune cells [21]. Monocytes play a role in cleaning dead cells and tissue regeneration [14]. Eosinophils deal with invading bacteria and parasites. Basophils are involved in allergic reaction. They stimulate histamine release, resulting in inflammation and bronchoconstriction especially in asthma [12]. Lymphocytes produce antibodies that give immunity to the body when faced with the previously infected organisms. T lymphocytes are involved in cell-mediated immunity; meanwhile, B lymphocytes are involved in humoral immunity.

Function of Platelets

The function of the platelets is involved in hemostasis [22], the prevention and control of bleeding. When a blood vessel is injured, an enormous number of platelets rapidly attach to the injured surface (platelet adhesion) and then become activated and recruit additional platelets to the injured site (platelet activation). After that, fibrinogen circulating in plasma forms bridges between activated platelets to form the platelet plug. This initial process is called primary hemostasis. However, the platelet plug is not stable enough to control the major bleeding, so requiring further secondary hemostasis from the various coagulation factors in plasma. If platelets are inadequate, in terms of either number or function, there will be defect in the control of minor bleeding presenting with clinical manifestation of epistaxis, petechiae, and gingival bleeding. The laboratory test results in prolonged bleeding time [23].

Conclusion

Blood is the fluid connective tissue, circulating through blood vessels carrying nutrients, hormones, gases, and waste products from one location to the other site in the body. Blood is composed of plasma and cellular elements. Its function includes transportation, balancing acid-base status, hemostasis, and immune function.

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The Coagulation Cascade

Siddharth Venkat Ramanan, Jayanth Rajan, and Shobana Rajan

Abstract

Hemostasis is an orchestrated and tightly regulated process. Damaged endothelium interacts with VWF and platelets to form a platelet plug. Coagulation factors are then activated on the surface of injured endothelium and platelets and create a fibrin mesh. Fibrinolysis is activated to dissolve the platelet plug and return the endothelium to its typical structure.

Keywords

Primary hemostasis · Secondary hemostasis · Von Willebrand factor · Coagulation cascade

Background

Blood is a transport system and must be in fluid state to function as one, but to prevent excessive blood loss, it must form a clot at the site of vascular injury – a process called hemostasis.

Hemostasis may be described as occurring in the following phases:

a. Endothelial injury
b. Primary hemostasis – formation of the platelet plug
c. Secondary hemostasis
d. Fibrinolysis

The following discussion on hemostasis is predicated on several key principles:

a. There is a natural balance between pro-coagulant and anti-coagulant forces, and this balance is mediated primarily by the endothelium [1].
   i. Clot formation involves a shift to favor the pro-coagulant state [1].
   ii. Clot dissolution involves a shift to favor the anti-coagulant state [1].
b. Primary hemostasis refers to the formation of the platelet plug following an injury to the vascular endothelium.
c. Secondary hemostasis refers to the coagulation cascade that produces a fibrin clot.
d. Secondary hemostatic reactions involve the activation of plasma zymogen clotting factors [2].
e. Secondary hemostatic reactions require calcium and membrane phospholipids.
f. Vitamin K-dependent factors include factors II, VII, IX, X, protein C, and protein S.
g. Deficiency/dysregulation/dysfunction of clotting components may result in bleeding or thrombotic disorders.

S. V. Ramanan
Internal Medicine, University of Conneticut, Storrs, CT, USA

J. Rajan
Lake Erie College of Osteopathic Medicine, Erie, PA, USA

S. Rajan (✉)
University of Texas, Houston, TX, USA

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Components of the hemostatic process are:

a. Platelets
b. Plasma proteins – coagulation factors, fibrinolytic factors, and inhibitors
c. Vessel wall and endothelial cells

Platelets are the main effectors of the initial hemostatic plug and play an important role in secondary hemostasis. They are produced in the bone marrow through a process called thrombopoiesis. Thrombopoietin, the primary regulator of thrombopoiesis, is continuously produced by the liver and renal tubular epithelial cells and cleared by platelets and megakaryocytes. In thrombocytopenic states, it stimulates megakaryocytes to increase platelet production. Interleukin 6 increases thrombopoietin levels in proinflammatory situations causing reactive thrombocytosis [3]. Platelets are anucleate and discoid in shape, measure 2–4 μm in diameter, and have a mean cell volume of 6–10 fl. They contain at least three major types of granules (Table 1): α-granules, dense granules, and lysosomes.

Normal platelet count is 150,000–450,000/μL of blood, and their average life span is approximately 7–10 days, following which they are eliminated in the spleen and liver. About 30% of platelets produced in the bone marrow are sequestered in the spleen, and this number increases with an increase in splenic size

Von Willebrand factor (vWF): vWF, a large multimeric glycoprotein, is synthesized in endothelial cells and megakaryocytes and stored in Weibel-Palade bodies and alpha granules, respectively. VWF functions as a bridging molecule between platelets and subendothelial collagen. It helps maintain normal plasma levels of factor VIII by acting as its carrier protein and decreasing its clearance. Estrogen and thyroid hormone increase VWF production in endothelial cells. Endothelial VWF secretion occurs in a variety of ways. Stimulated secretion of ultra-large and large multimers from Weibel-Palade bodies is mediated by alpha-adrenergic agonists, fibrin, histamine, thrombin, and vasopressin analog (DDAVP). Non-stimulated basal secretion also from Weibel Palade bodies through the apical membrane contributes to the circulating VWF [4]. Non-stimulated, constitutive secretion of dimers and small multimers through the basolateral membrane contributes to the collagen-bound subendothelial VWF. ADAMTS13 is a metalloprotease secreted by endothelial cells, platelets, and hepatic stellate cells. It cleaves large and ultra-large multimers of VWF to smaller-sized multimers. Reduction in ADAMTS 13 activity would lead to piling up of ultra-large VWF multimers on endothelial surfaces upon which platelets can attach and accumulate.

Table 1 Contents in various platelet granules

Granules	Contents
α-Granules	P-selectin, fibrinogen, fibronectin, von Willebrand factor, thrombospondin, platelet-derived growth factor, platelet factor-4, and P-selectin
Dense granules	ADP, ATP, ionized calcium, histamine, epinephrine, and serotonin
Lysosomes	Cathepsins, β-galactosidase, β-glucuronidase, acid phosphatase, hexosaminidase, arylsulfatase

Tissue factor (TF): TF, also known as thromboplastin, is a 46 kDa membrane glycoprotein expressed in subendothelial smooth muscle cells, fibroblasts, and macrophages. It functions as the principal trigger for hemostasis in vivo. It is not generally expressed on endothelial cells and is exposed to blood flow only following endothelial damage and exposure of subendothelial matrix.

Coagulation factors and inhibitors: Most coagulation factors and inhibitors are produced in the liver as zymogens (inactive precursors). Additionally, factor VIII is also produced by lymphatics and renal glomeruli. Protein C, protein S, and coagulation factors II, VII, IX, X require vitamin K for posttranslational modification. Table 2 lists the various coagulation factors.

Vasoconstriction and Primary Hemostasis

Vasoconstriction

Disruption of vascular integrity results in immediate constriction of the injured segment (medi-

Table 2 Coagulation factors

Factor	Name
I	Fibrinogen
II	Prothrombin
III	Thromboplastin, tissue factor, CD142
IV	Calcium
V	Proaccelerin, labile factor, accelerator globulin
VII	Proconvertin, stable factor
VIII	Antihemophilic factor, antihemophilic factor A, antihemophilic globulin
IX	Christmas factor, plasma thromboplastincomponent, antihemophilic factor B
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin stabilizing factor, Laki-Lorand factor
Pre-Ka	Prekallikrein, Fletcher factor
HMW-K	High-molecular-weight kininogen, Fitzgerald factor
Ka	Kallikrein
PL	Platelet phospholipid

ated by reflex neurogenic mechanisms) and release of endothelium-derived factors like endothelin and thromboxane A2 (TxA2). The initial extravasation of blood into the surrounding tissues causes external compression of the vessels and contributes to stemming further bleeding.

Platelet Adhesion and Activation

Healthy vascular endothelium expresses substances like nitric oxide (NO), prostacyclin, heparans, and endothelial ADPase, which prevent adhesion of platelets to the vessel wall. However, endothelial disruption exposes the subendothelial layer, which contains collagen and VWF. Platelets bind to VWF via glycoprotein Ib (GpIb) receptor, and thus VWF functions to anchor platelets to the site of endothelial injury.

Platelets also directly bind to collagen through the GpIa/IIa receptor [5]. Platelet interaction with VWF and subendothelial collagen leads to its activation.

Platelet activation promotes clot formation by several mechanisms [1]:

- Activation alters the morphology of platelets and increases platelet surface area.
- TxA2 production further promotes platelet activation.
- Conformational shift in GpIIb/IIIa receptors supports platelet-platelet and platelet-fibrinogen interactions [6].
- Phosphatidylserine translocation allows for association with Ca^{2+} and secondary hemostasis.
- Release of granule contents (e.g., ADP) further promotes platelet aggregation.

Thrombin-mediated activation is via G-protein-coupled protease-activated receptors (PARs), specifically PAR-1 and PAR-4. ADP binds to G-protein-coupled purinergic receptors, P2Y1 and P2Y12. ADP is released from platelets upon platelet activation and functions in a paracrine/autocrine fashion to recruit additional platelets and amplify platelet aggregation.

These mechanisms are depicted below in Fig. 1.

Secondary Hemostasis: Coagulation Cascade

First described in the 1960s, the original "cascade model" postulated that coagulation was triggered by either the "extrinsic" or the "intrinsic" pathway, and they functioned independent of one another [7, 8]. However, recent studies have demonstrated that these pathways do not work as discrete tracks but are intertwined in the process of hemostasis [9]. The extrinsic pathway is activated upon exposure of plasma to TF, and the intrinsic pathway is activated by exposure of plasma to negatively charged surfaces like ellagic acid, celite, kaolin, or silica. Once coagulation is triggered by one of these pathways, clotting factors are sequentially activated in an amplification cascade, ultimately leading to clot formation. The original cascade model remains relevant in interpreting activated partial thromboplastin and prothrombin times in clinical practice. Also, there is a growing body of evidence

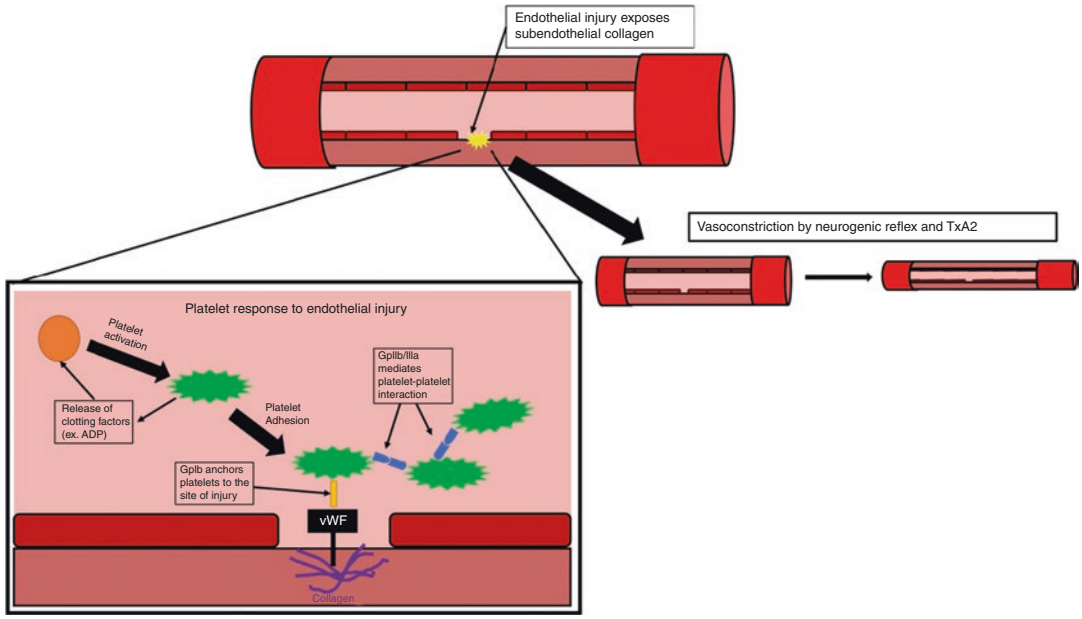

Fig. 1 Mechanisms of primary hemostasis and vasoconstriction

suggesting that intrinsic pathway activation may not play a significant role in in vivo (physiological) hemostasis [10].

In vivo, coagulation can be described as occurring in two phases: *initiation*, which occurs on tissue factor-expressing cells and produces 3% to 5% of the total thrombin generated, and *propagation*, occurring on platelets, which produces 95% or more of the total thrombin.

Initiation: Upon endothelial breech, activated factor VII (VIIa) in the plasma binds to the exposed TF. Usually, about 1% to 2% of factor VII is present in blood in the activated form (VIIa). The TF-VIIa complex activates factor X (Xa) (extrinsic tenase complex, ETC). Xa combines with activated factor V (Va) and substrate prothrombin to form the prothrombinase complex. Prothrombinase complex converts prothrombin to thrombin. In the initiation phase, only a limited amount of thrombin is produced before the extrinsic tenase complex is inactivated by the tissue factor pathway inhibitor (TFPI).

The processes in the initiation phase, including thrombin generation, are localized to surfaces of TF expressing cells in the subendothelium. The thrombin so produced then moves to the activated platelets in the platelet plug, which provide the surface for further assembly of multicomponent complexes. Thrombin activates platelets, factor V (released from alpha granules), and factor VIII (causing it to dissociate from VWF). Va and VIIIa bound to platelet membranes function as receptors for Xa and IXa, respectively.

Propagation: Thrombin from the initiation phase facilitates the conversion of factor XI to its active form (XIa), which activates factor IX (IXa); notably, the TF-VIIa complex can also directly activate factor IX [1]. IXa combines with activated factor VIII (VIIIa) and prothrombin to form the intrinsic tenase complex (ITC). ITC increases Xa production by 50–100-fold generating large amounts of thrombin. This positive feedback loop greatly amplifies thrombin production to sufficient quantities to convert soluble fibrinogen to insoluble fibrin. Fibrin then polymerizes to form a clot. Thrombin also activates factor XIII (XIIIa) to stabilize the clot by cross-linking overlapping fibrin strands. It, along with fibrinogen, also regulates clot size by controlling the volume of red blood cells trapped within the thrombus; in the absence of XIIIa, clots tend to be smaller.

The coagulation cascade is depicted below in Fig. 2.

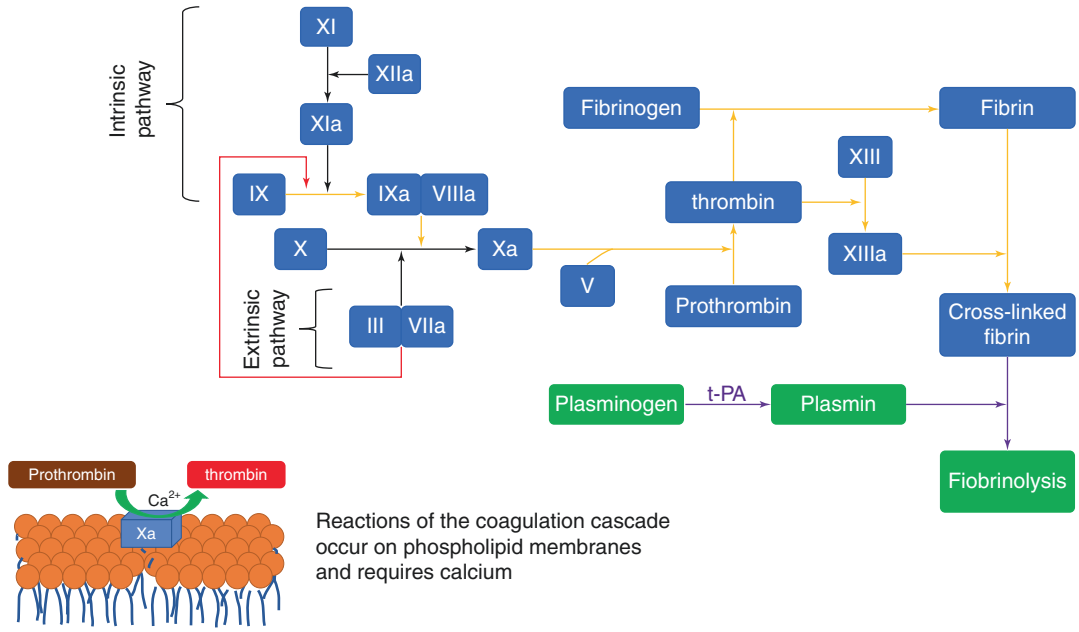

Fig. 2 Extrinsic and intrinsic pathways of secondary hemostasis; black arrows, pathways involved in in vitro coagulation; red arrows, pathways involved in in vivo coagulation; orange arrows, pathways involved in both in vitro and in vivo coagulation; purple arrows, pathways involved in fibrinolysis

Fibrinolysis

Tissue-type plasminogen activator (tPA) and the urokinase-type plasminogen activator (uPA) convert plasminogen, a zymogen secreted by the liver, to plasmin, a serine protease and a key enzyme in the fibrinolytic system. tPA is produced and secreted by endothelial cells, monocytes, and macrophages, while uPA is secreted by urinary epithelium. Both activators have a short half-life in circulation, 4–8 min, due to high concentrations of specific inhibitors. Plasmin cleaves fibrinogen and fibrin at multiple sites and releases fibrin degradation products (FDP) into the circulation; D-dimer is a particular FDP formed only upon degradation of cross-linked fibrin, and elevated levels imply ongoing intravascular coagulation and fibrinolysis [11, 12].

Fibrinolysis is regulated at multiple levels. Three serine protease inhibitors important in the inhibition of fibrinolysis are plasminogen activator inhibitor-1 (PAI-1), plasminogen activator inhibitor-2 (PAI-2), and α2-antiplasmin (α2AP). Platelets and endothelial cells synthesize PAI-1. PAI-2 is synthesized by white blood cells and the placenta; its levels significantly increase during pregnancy. PAI- 1 and 2 inhibit uPA and tPA [13, 14]. α2AP is secreted by the liver and is also contained within platelets. It rapidly inactivates plasmin by forming 1:1 stoichiometric covalent plasmin-α2AP complexes. XIIIa cross-links α2AP to the fibrin clot, making the clot significantly more resistant to digestion by plasmin [15, 16]. Thrombin-activatable fibrinolysis inhibitor, aka Carboxypeptidase B2, is a non-serine protease inhibitor of fibrinolysis. It is activated by thrombin-thrombomodulin complex and functions by cleaving the C-terminal lysine residues on fibrin (fibrin C-terminal lysine residues facilitate plasmin activity) [17].

Regulation of hemostasis and fibrinolysis:

Thrombosis is regulated at several different levels to prevent inappropriate clot formation. The systems involved in regulating thrombosis include [1]:

- Fibrinolysis: Conversion of plasminogen to plasmin by tissue type-plasminogen activator (t-PA) produced by endothelial cells or factor XII solubilizes fibrin clots. In turn, the activity of tPA is regulated by α_2-antiplasmin and plasminogen activator inhibitor.

- Blood flow: The flow of blood shears clotting factors away from the site of injury.
- TFPI: As noted earlier, inhibition of the TF-VIIa complex by TFPI complexed along with protein S decreases the rate of thrombin synthesis by the extrinsic pathway [18].
- Thrombin: Thrombin demonstrates pro-coagulant activity at the site of injury and anti-coagulant activity away from the injury site. As previously discussed, pro-coagulant effects of thrombin include conversion of fibrinogen to fibrin; activation of factor XIII; feedback activation of factors V, VIII, and XI; and platelet activation via the PAR-1/4 receptors. Thrombin also promotes inflammation, angiogenesis, and repair pathways in vascular endothelium via the PAR-1 receptor. Anti-coagulant functions of thrombin occur in healthy endothelium. Thrombomodulin, expressed in healthy endothelium, binds protein C and thrombin; thrombin activates protein C, which, using protein S as a cofactor, cleaves and inhibits factors Va and VIIIa [19].
- Heparin-like molecules: Antithrombin III is a plasma serine protease inhibitor. Serine protease inhibitors are irreversible suicide inhibitors and work by forming complexes with target enzymes that are subsequently cleared from circulation. Antithrombin III inhibits thrombin and IXa, Xa, XIa, XIIa. This anti-coagulant activity is dramatically increased in the presence of heparin and heparan sulfate [20, 21].
- Endothelial cells secrete several substances like NO, prostacyclin, and ectoADPase/CD39 to inhibit platelet binding and adhesion. Endothelial cells also produce anti-coagulant substances like antithrombin, TF pathway inhibitor (TFPI), heparan proteoglycans, and thrombomodulin. Mechanisms of hemostasis regulation are provided in Fig. 3.

Clinical Correlates

Bleeding disorders due to deficiency in components of primary and secondary hemostasis include VWF (von Willebrand disease), gpIb (Bernard-Soulier syndrome), gpIIb/IIIa (Glanzmann thrombasthenia) [1], factor VIII deficiency (hemophilia A), factor IX deficiency (hemophilia B), and factor XI deficiency (hemophilia C) [22].

Predisposition to thrombosis may occur due to endothelial injury, abnormal (stasis or turbulence) blood flow, and hypercoagulability as described in Virchow's triad. Endothelial injury may occur due to hypercholesterolemia and cigarette smoking and may involve decreased endothelial expression of anti-coagulant factors. Stasis prolongs the interaction between platelets and endothelial cells and results in inappropriate activation of endothelial cells. Conditions promoting abnormal blood flow include sickle cell anemia, polycythemic vera, mitral valve stenosis, aneurysm, etc. An example of a hypercoagulable state is the factor V Leiden mutation; arginine to glutamine substitution decreases the rate of factor V inactivation by activated protein C [1].

Immunogenic instances of hypercoagulable states include heparin-induced thrombocytopenia and antiphospholipid antibody syndrome. In heparin-induced thrombocytopenia, antibodies against platelet factor 4-heparin complexes result in both removal of platelets from the blood (thrombocytopenia) and platelet activation and may thus result in stroke or myocardial infarction. Antiphospholipid antibody syndrome may follow systemic lupus erythematosus and involves auto-antibodies against membrane phospholipids. This results in platelet and endothelial activation and is associated with unexplained pregnancy complications. Importantly, in vitro partial thromboplastin times is increased (due to antibodies against phospholipids) [1].

Summary and Conclusion

Hemostasis is the process in which clot formation prevents loss of blood following vascular injury. Hemostasis begins with reflex vasoconstriction, followed by primary hemostatic mechanisms and secondary hemostatic mechanisms. Primary hemostasis involves the activation and adhesion of platelets and terminates with the formation of a platelet plug. Secondary

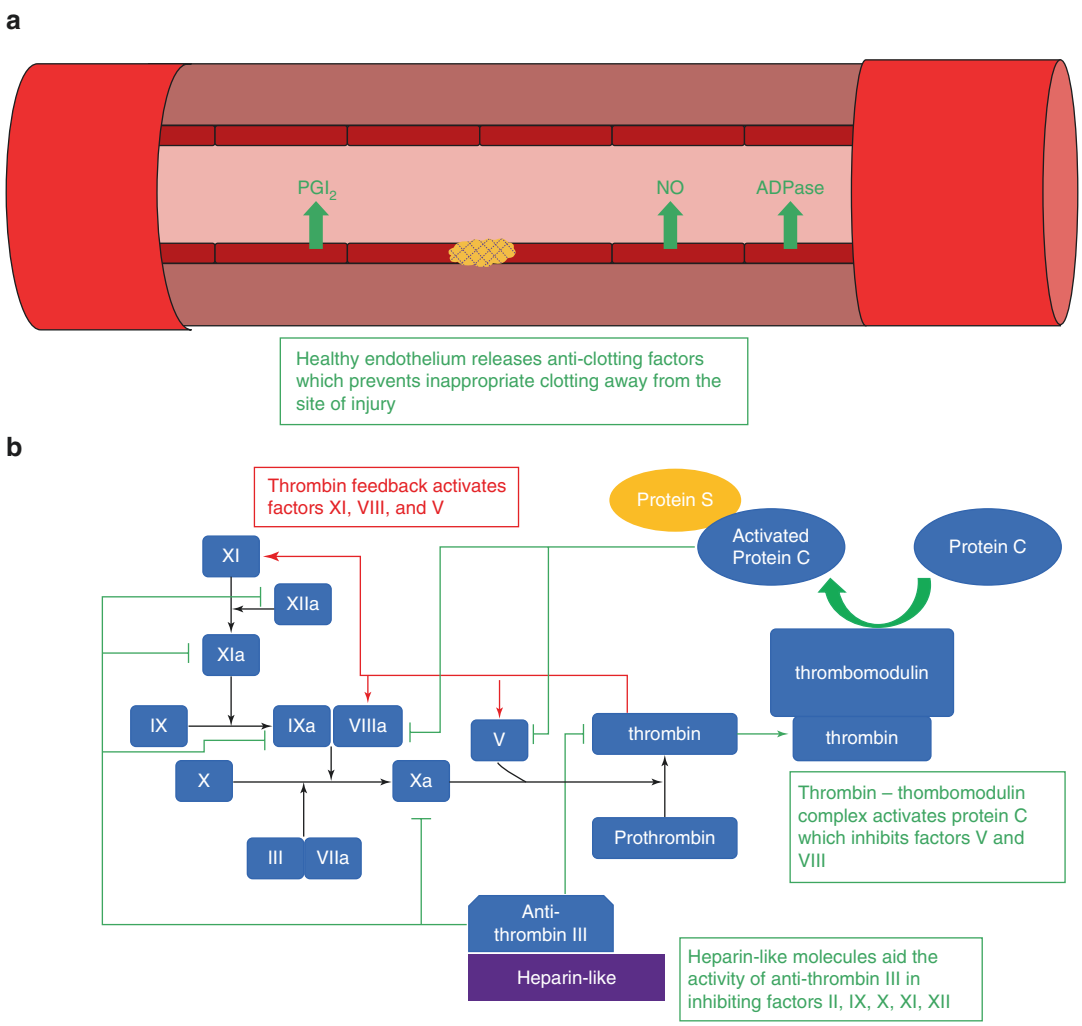

Fig. 3 Mechanisms involved in regulation of hemostasis. Panel **A**: mediators released by endothelial cells prevent inappropriate clot formation. Panel **B**: hemostasis regulation accomplished by thrombin and anti-thrombin III; red arrows, pathways promoting clot formation; green arrows, pathways inhibiting hemostasis

hemostasis involves a cascade of reactions that ultimately result in forming a stable fibrin clot. To prevent the adverse effects of inappropriate clotting, hemostasis is regulated by several mechanisms, and this regulation is primarily mediated by endothelial-derived factors. Dysfunctional hemostasis may result in bleeding disorders such as hemophilia. Dysregulation of hemostasis may also predispose individuals to thrombotic conditions such as factor V Leiden.

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Part VII

Blood and Blood Products: Blood and Components

Whole Blood and Packed RBCs

Suman Sokhal, Navdeep Sokhal,
and Dipti Ranjan Rout

Abstract

Over the years, to execute the increased blood transfusion requirement of patients, to make the transfusion safer, and to utilize one blood unit rationally, blood component therapy has been adopted worldwide. The blood components are separated by centrifugation of one unit of whole blood, since the different blood components have different sizes, sedimentation rates, and relative density. Apheresis is another method for the collection of a single component in blood donors. Yet, whole blood is considered the optimum for combat victims because of its unique benefit during the resuscitation of hemorrhagic shock.

Keywords

Blood transfusion · Hemorrhagic shock
Blood components · Red blood cells
Hemoglobin

S. Sokhal · N. Sokhal (✉)
Neuroanaesthesiology and Critical Care, AIIMS, New Delhi, India
e-mail: drsokhal.navdeep@aiims.edu

D. R. Rout
Transfusion Medicine, NCI-AIIMS, Jhajjar, India

Blood transfusion has been a mainstay of management during traumatic resuscitation, major surgeries, hematological genetic disorders, and anemia of chronic disorders, since the first successful transfusion in 1818, by the British obstetrician James Blundell [1]. Whole blood transfusion remained in practice until the 1970s, when technological advances paved the way for the preparation of blood components to efficiently meet the growing need for transfusion. Today, whole blood is rarely used in transfusion practice, with the exception of hemorrhagic shock in battlefields and out-of-hospital settings [2–4].

Whole Blood

Whole blood (WB) is the mixture of the venous blood collected in a sterile manner from a healthy eligible donor in an anticoagulant solution prepacked in a glass bottle or polyvinyl chloride blood bag containing 30–40% w/v of plasticizer Di-ethylhexyl phthalate (DEHP) [5, 6]. The anticoagulant-preservatives like citrate phosphate dextrose (CPD), citrate phosphate double dextrose (CP2D), or citrate phosphate dextrose adenine (CPDA-1) are currently used for the anticoagulation, preservation, and nutrition of stored cellular elements [7].

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Whole Blood Preservation and Storage

In 1915, Rous and Turner developed the first RBC storage solution (a citrate, glucose mixture) for rabbit RBCs and conserved RBCs at ice-box temperatures for up to 4 weeks [8]. However, the "caramelisation of dextrose" during the bulk blood sterilization process in the bottles of this storage solution made in vivo use impossible after long-term storage [9]. Loutit and Mollison showed that an acidic pH (< 5·8) successfully prevented the caramelization of dextrose while autoclaving the citrate-glucose mixture [9]. So, acid-citrate-dextrose (ACD) solution was used to store blood for 21 days during World War II; later it was modified to a citrate-phosphate-dextrose (CPD) solution for a further extended storage period of 28 days [10]. During storage, phosphate ions leak out from RBC and lead to a decrease in levels of adenosine 5-triphosphate (ATP) and gradual loss of functionality of RBCs. However, during the first 2 weeks of storage, breakdown of diphosphoglycerate (DPG) can provide adequate intracellular phosphate. Moreover, the addition of sodium phosphate helps maintain sufficient level of ATP and nutrition for longer storage of RBCs [11]. The advancement in blood storage containers led to the development of plastic blood bags in 1950 which turned out to be an enormous innovation in blood transfusion therapy. The lighter weight plastic bags and their small volume for storage, tensile strength, and tear resistance, sterilized closed-collection system to avoid bacterial contamination, less chances of air embolism during rapid pressure infusion, and transparency are all familiar distinct advantages [12].

It is now known that DEHP leaches out of the plastic bag because of the albumin present in the plasma (by hydrophobic interactions with DEHP) and enters the RBC membrane where it limits membrane loss by micro-vesiculation [6]. So the RBCs can be stored for twice as long in these PVC bags compared to other plastic bags without DEHP or glass bottles, although this benefit is clinically advantageous only if RBC storage could be extended beyond 3 weeks.

The addition of adenine in the storage solution further extended the shelf life to 35 days [13]. Adenine helps in maintaining high ATP levels, so the blood collected in CDPA is well supported by the anticoagulant-nutrient mixture, and 2–3 DPG levels are maintained for additional 12–14 days [14].

In nutshell, the blood can be stored at 2–6 °C for up to 21 days in ACD, 28 days in CPD, and 35 days in CPDA. The addition of additive solutions (e.g., saline-adenine-glucose-mannitol, SAGM) can further extend the shelf life of stored cells up to 42 days.

Types of Whole Blood

There are two types of WB:

(1) Stored whole blood (SWB) [15]
(2) Fresh whole blood (FWB) [16]

These both types of blood have different properties as mentioned in Table 1.

As FWB may be a reason for disease transmission, the use is reserved only for critically ill com-

Table 1 Comparison of stored vs fresh whole blood

Stored whole blood (SWB)	Fresh whole blood (FWB)
Collected from eligible normal individuals and stored by licensed blood banks	Collected from a walk-in healthy blood donor who is already tested for the blood group and infectious markers (pre-screened donors)
Stored at 2–6 °C temperature.	Stored at ambient temperature
SWB is released only after post-collection complete TTIs (transfusion-transmissible infections) testing	FWB undergo pre-collection donor testing but may not be possible to undergo complete post-collection TTIs testing
SWB is approved by FDA	FWB is not approved by FDA for civilian hospital use
Can be used up to 21–42 days depending upon the storage solution	Can be used within 24 h and then discarded in current practice

bat casualties where the urgency of WB transfusion overweighs the availability of tested blood products. But in civilian settings, WB which is stored for less than 48–72 h is released as fresh whole blood on demand (already undergone TTIs testing). To avoid transfusion reactions, group O WB with less anti-A and anti-B antibody titers (<1:256 units) are approved as "universal WB" and termed as "low-titer O WB" (LTOWB). LTOWB may be SWB or FWB [17, 18].

Donor Selection Criteria [19]

The quality of the whole blood and blood-derived components can be assured by stringent donor selection criteria which may be as follows but not limited to:

1. The donor must be in healthy conditions with adequate sleep, food, and stable vital parameters while going for a blood donation.
2. The prospective donor must be aged 18–65 years and weigh> 45 kg.
3. The minimum inter-donation interval is 90 days.
4. The prospective donor must be having a hemoglobin level of ≥12.5 g/dL.
5. The donor must not have any risky lifestyle behavior or professional attributes that may be attributable to an increased risk of any transfusion transmissible infections (TTIs), viz., HIV, HBV, HCV, syphilis, and malaria.
6. Female donors must not be pregnant, lactating, and/or menstruating at the time of blood donation.
7. The prospective donor must be free from any active infections with no history of any cardiovascular, neurological, hemato-oncological, and/or endocrine disorders.

Quality Control Criteria for Whole Blood [20]

At least 1% of total components prepared are subjected to quality control at random (Table 2). The individual parameters to be assessed are as follows and should be fulfilled by at least 75% of the components tested (Drugs and Cosmetics Act, 1940).

Indications for whole blood transfusion

1. Hemorrhagic shock in combat fields and out of hospital setting.
2. Exchange transfusions for neonatal jaundice.

Advantages of WB over blood components

1. WB is not a physiological and cytological image of 1:1:1 blood component therapy. FWB provides a hematocrit of 35–38%, a platelet count of 150,000–200,000/μl, and coagulation factors at approximately 85% of pre-donation levels up to the usual storage time. SWB may not be providing the required platelets due to cold-induced activation leading to accelerated clearance from the circulation upon transfusion [22]. Over the storage duration of whole blood in CPD-A, factor V falls to 15–21% activity and factor VIII to 16–20% [23]. Whereas, the presence of additive solutions turn 1:1:1 component therapy into a dilute blood mixture with a hematocrit of 29%, a platelet count of approximately 90,000/μl, and coagulation factors at approximately 62% [24].

Table 2 Quality control of whole blood

Parameter	Quality requirement	Frequency of control
Volume	350/450 ml ± 10%	1% of all units
Anticoagulants	49/63 ml	1% of all units
PCV (Hct)	30–40%	4 units/ month
TTIs	Negative	All units
Sterility	By culture	4units/ month whichever is higher
WBC content	$<5 \times 10^6$ WBC/unit	1% of all units

The term RBC storage lesion describes the changes in the RBCs during ex vivo storage and includes things like loss of membrane plasticity, diphosphoglycerate, adenosine triphosphate, nitric oxide, and other factors leading to potentially reduced delivery of oxygen to tissues and contribution to a variety of pathophysiologic processes [25].

2. WB is easy to handle as compared to many bags of component therapy demanding more attention and manpower.
3. FWB has been associated with improved survival in combat casualties compared to blood component therapy. Spinella et al. concluded from 100 combat casualties that transfusion with FWB with RBCs and plasma in hemorrhagic shock was associated with improved survival compared to the use of stored components only (FFP, RBCs, and PLTs) [26].

Selecting SWB or FWB

1. FWB possesses the risk of TTIs transmission, so not indicated for routine use. It is to be used only where any other stored blood products are not available to resuscitate the patient in hemorrhagic shock. However, the FWB, supplied in hospital settings, is free of such risk.
2. FWB has no loss of the labile clotting factors or platelet activity that is often associated with storage and has close to physiological hematocrit and is not impacted by the RBC "storage lesion."

Packed RBC

Red blood cells are separated from a unit of whole blood after removing most of the plasma. Hemoglobin concentration should not be less than 45–55 g per unit and hematocrit of 55–75% [27]. Red cell concentrates are subjected to periodic quality control during preparation and preservation (Table 3).

Table 3 Quality control of red cell concentrate

Quality control of red cell concentrate (prepared from 450 ml whole blood) [21]		
Parameter	Quality requirement	Frequency of control
Volume	280 ml ± 40 ml	1% of all units
PCV (Hct)	70% + 5%	Periodically
Sterility	By culture	Periodically (1% of all units)
WBC Content	$<5 \times 10^6$ WBC/unit	1% of all units
Quality control of red cell concentrate in preservative solution (SAGM) [21]		
Volume	350 ml ± 20 ml	1% of all units
PCV (Hct)	60% + 5%	Periodically
Sterility	By culture	Periodically (1% of all units)
WBC content	$<5 \times 10^6$ WBC/unit	1% of all units

Method of Preparation [13]

Blood components can be prepared by two main methods from whole blood (WB):

1. By centrifugation: To prepare the components from WB, large, high-speed centrifuge machines accommodating 4–16 units of WB are usually used. The recovery of cells from whole blood depends on the rotor size, centrifuge speed, duration of centrifugation, and acceleration/deceleration protocol.

   A. *Platelet-rich plasma (PRP) method* [28]:

   Blood component preparation by this method begins with a soft spin of the WB, followed by separation and hard spin of the PRP. In a unit of blood, the centrifuged products settle in layers, starting from the bottom: red blood cells, white blood cells, and platelet-rich plasma.

   B. *Buffy coat method* [28]:

   Compared to the PRP preparation method, the first step in the buffy coat method is high g-force centrifugation followed by a low g-force step. A buffy coat layer is obtained between the red cells and the plasma which appear after primary centrifugation. The red cell and the plasma are transferred to their respective bags and sealed [21].

2. By apheresis: Apheresis is another method of blood component preparation. During the apheresis procedure, whole blood is spun in the chamber of the apheresis machine and is separated into red cells, leukocytes, platelets, and plasma. Any of these components or a combination of several components can then be selected for the collection, while the remaining blood components are returned to a donor.

Red cell concentrates are subjected to periodic quality control during and after preparation from whole blood by described methods and preservation for prolonged use (Table 3).

A dramatic decrease in the level of 2,3-diphosphoglycerate (2,3-DPG) takes place during the storage of whole blood (WB) in CPDA (citrate-phosphate-dextrose-adenine), and a similar decrease occurs during the storage of red blood cells (RBCs) in SAGM (saline-adenine-glucose-mannitol). The addition of additive solutions is to further improve the shelf life and post-transfusion outcome by increasing the in vivo survival of transfused red cells by preventing lysis due to the mannitol [29].

Leukoreduction

In 1972, the first leukocyte depletion filter contained sterile cotton wool as a filtering agent and was designed by Diepenhorst which was subsequently replaced by better and more efficient cellulose acetate filters [30]. Other methods included centrifugation and buffy coat removal (1 log leukodepletion), red cell washing (1–2 log leukodepletion), freezing, and deglycerolization of red cells (2–3 log leukodepletion). The current generation of leuko-filters (3rd and 4th) has an excellent leukocyte removal efficiency of 99.99% which removes the leukocytes by charge-based adhesion of negatively charged leukocytes to the filter material by van der Waals and electrostatic forces [21, 31].

Timing of Leuko-filtration

Pre-storage (lab-side) leukoreduction is currently the most widely accepted mode with the following advantages over post-storage (bedside) leukoreduction while transfusing:

1. Efficient in the prevention of febrile non-hemolytic transfusion reactions (FNHTRs) by preventing the accumulation of inflammatory cytokines [32].
2. Minimizing the risk of HLA-alloimmunization in multi-transfused patients [33].
3. Minimize the risk of leukotropic virus transmission [21].

Benefits of Leukoreduction [34]

1. Proven benefits relevant clinically:
   a. Reduced frequency and severity of FNHTRs
   b. Reduced risk of cytomegalovirus (CMV) transmission
   c. Reduced risk of HLA-alloimmunization and platelet refractoriness
2. Probably clinically relevant
   a. The reduced infectious risk associated with immunomodulation (TRIM)
   b. Reduced organ dysfunction and mortality
   c. Reduced direct risk of transfusion-transmissible bacteria
3. Unproven clinically
   a. Avoidance of vCJD transmission
   b. Avoidance of human T-lymphotropic virus (HTLV) I/II, Epstein-Barr (EBV), etc.
   c. Reduced risk of graft vs host disease (GVHD)
   d. Reduced risk of transfusion-related acute lung injury (TRALI)

Packed red blood cells are transfused to increase oxygen delivery to the tissue and to treat hemorrhage.

Indications of PRBC Transfusion [35]

1. Acute blood loss greater than 30% of total blood volume
2. Acute sickle cell crisis for prevention of stroke
3. Patients with symptomatic anemia
4. Most adult patients with hemoglobin level equal or <7–8 gm/dl

Advantage

1. Removal of plasma efficiently decrease allergic and infectious reactions; leukoreduction further decreases it.
2. Concentrated low volume is beneficial to transfuse in patients with renal, cardiac, and liver insufficiency.
3. Judicious usage of the scarce resource.
4. Restrictive blood transfusion with a transfusion trigger of hemoglobin of 7–8 g/dl is safe and not associated with increased mortality compared with liberal transfusion at the hemoglobin of 9–10 g/dl [36].

Disadvantage

1. The logistics requirement is more demanding in terms of required infrastructure and technical expertise.
2. The lack of compensation of any clinically indicated hemostatic components (coagulation factors and/or platelets).
3. Cost constraints on the healthcare facility.
4. Multiple donor exposure resulting in multiple antigenic challenges to the recipient because of component therapies.
5. The rate of transfusion-related risks of citrate toxicity, electrolyte imbalances, and acid-base abnormalities.

Irradiation of Blood Components [37]

Cellular blood components (WB, PRBCs, and platelets) are irradiated before transfusion to prevent the proliferation of viable T lymphocytes which are the immediate cause of transfusion-associated graft versus host disease (TA-GVHD), again having a fatality rate greater than 90% [38]. Patients at particular risk of TA-GVHD include:

1. Fetal and neonatal recipients of intrauterine transfusions.
2. Selected immunocompromised recipients.
3. Recipients of cellular components are known to be from a blood relative(s).
4. Recipients who have undergone marrow or peripheral blood progenitor cell transplantation.
5. Recipients of cellular components whose donor is selected for HLA compatibility.

Irradiation of red blood cells and whole blood results in reduced post-transfusion red cell recovery and increases the rate of efflux of intracellular potassium [39]. It has no clinically significant effect on red cell pH, glucose, 2,3 DPG levels, or ATP. Irradiation of PRBC components must be done within 14 days of collection and, thereafter, stored for a further 28 days from the date of irradiation or the original expiry date of the component, whichever is earlier. PRBC components irradiated after 14 days of collection expire either 5 days after irradiation or at the original expiry of the unit, whichever is earlier [40]. In patients where hyperkalemia is a concern, red cells should be transfused within 24 h of irradiation. Examples include large volume neonatal transfusion such as exchange transfusions.

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Fresh Frozen Plasma

Barkha Bindu and Vasudha Singhal

Abstract

Fresh frozen plasma, though a commonly prescribed hemostatic agent, has proven beneficial effect in limited clinical conditions. FFP is rich in fibrinogen, albumin, protein C, protein S, antithrombin, and tissue factor pathway inhibitor. The processes of FFP preparation, pathogen inactivation, storage, and handling are important determinants of FFP quality. A standard dose of 10 to 20 mL/kg raises factor levels by around 20%. FFP is produced from whole blood by centrifugation or by apheresis. While identical ABO blood group plasma must be used as the first choice, ABO non-identical plasma might be acceptable in emergency situations. While most indications for FFP transfusion are not clear-cut, there is broad general consensus that appropriate use of AFFP/FP is limited to clinically significant bleeding due to a deficiency of one or more plasma coagulation factors. Adverse effects related to FFP transfusion are similar to those associated with other blood products. This chapter elaborates on all these aspects of FFP including a brief overview of some historical aspects as well.

Keywords

Fresh frozen plasma · Transfusion
Coagulopathy · Blood · Factors

Introduction

Fresh frozen plasma (FFP), as suggested by literature, is the most commonly prescribed hemostatic agent of modern era [1]. Several randomized controlled trials have been performed on FFP for a variety of clinical indications. However, beneficial effect of FFP has been shown in very limited clinical conditions [2, 3]. FFP transfusion has shown benefit in massive trauma patients when used as part of high ratio of FFP to PRBC and platelets transfusion [4].

In clinical practice, FFP is often transfused for elevated coagulation test results, which are presumed to be due to coagulation factor deficiency. However, prothrombin time (PT) and activated partial thromboplastin time (aPTT) are often elevated due to other causes, therefore making FFP transfusion fruitless in these situations. This chapter aims to provide an overview of fresh frozen plasma collection, storage, and handling and its utility in various conditions.

B. Bindu · V. Singhal (✉)
Department of Neuroanaesthesia and Neurocritical Care, Medanta The Medicity, Gurugram, India
e-mail: vasudha.singhal@medanta.org

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History of FFP

According to the ancient Greek humoral theory, human health and disease were thought to be a result of four humors: blood, phlegm, yellow bile, and black bile [5]. According to this theory, patients are in a state of good health when the four humors are in balance, whereas an imbalance of the four humors causes disease. Hippocrates and his Greek followers practiced this theory for a long time. Almost 500 years later, Galen, a Roman physician, suggested presence of two circulating systems in human body, venous system, and an arterial system. Galen's concept of circulatory system was followed until seventeenth century when William Harvey scientifically overturned Galen's theories. Harvey first proposed the circulatory system model that we understand today [6]. First human to human transfusions were reported in 1818 [7]. Almost 100 years later, Landsteiner discovered the ABO blood groups. Salt solutions and Ringer's solutions were the first blood substitutes developed in the 1850s [8]. The first plasma transfusion in humans was done in 1918 to treat Spanish flu. By the 1920s and 1930s, plasma (dried or frozen) came into routine use [9, 10]. However, it was soon realized that fresh frozen plasma was superior to dried plasma [9].

Mechanism of Action of FFP

Fresh frozen plasma is the fluid portion of a unit of whole blood that is frozen within a designated time frame, usually around 8 h. FFP is devoid of platelets, erythrocytes, and leukocytes. Important constituents of FFP include fibrinogen (400 to 900 mg/unit), albumin, protein C, protein S, antithrombin, and tissue factor pathway inhibitor. FFP corrects coagulopathy by replacing these plasma proteins and coagulation factors in patients who are deficient in them. A 10% increase in level of most factors is usually enough to achieve hemostasis. A dose of 10 to 20 mL/kg of FFP (4 to 6 units in adults) results in around 20% increase in factor levels [11, 12]. FFP also provides volume resuscitation, as each unit contains approximately 250 ml, although plasma should not be used with the sole purpose of volume replacement.

Preparation of FFP

FFP is produced from whole blood by centrifugation or by apheresis. Leucocyte depletion is done by filtration during whole blood processing. Immediately after collection from a donor, plasma contains approximately 1 unit/mL of each coagulation factor and normal concentrations of other plasma proteins. Plasma has to be stored in the frozen state at a temperature of −18 °C or lower. This is because coagulation factors V and VIII, known as the labile coagulation factors, are not stable if stored for prolonged periods at 1–6 °C. Quality monitoring of FFP is done using factor VIII (FVIII) level. Factor VIII is one of the most labile coagulation factors of plasma. It is a sensitive marker of changes in FFP due to inappropriate processing or handling. Immediately after thawing, standard FFP must contain at least 0.7 IU/ml of FVIII in at least 75% of units. The levels of most coagulation factors including factor V are not significantly decreased from baseline if plasma is frozen within 24 h of collection.

Table 1 gives brief description of different types of plasma components.

Pathogen Inactivation of Plasma

Pathogen inactivation of plasma can be done using three techniques. These include methylene blue, amotosalen, and riboflavin [13]. These systems use the addition of a photosensitizer to plasma followed by exposure to visible or ultraviolet light and subsequent removal of the photosensitizer. All systems provide almost >4 log reduction of enveloped viruses. However, activity against non-enveloped viruses (like hepatitis A virus, parvovirus B19, and hepatitis E virus) is variable.

Commonly used pathogen inactivation systems tend to reduce the levels of coagulation factors and inhibitors in plasma. The extent of

Table 1 Different plasma components

Type of plasma component	Approximate volume	Contents	Description
Frozen plasma CPD (FP)	283 ml	Contains all coagulation factors Has slightly reduced amounts of clotting factors V and VIII Contains 0.87 IU/ml of factor VIII	Separated from an individual unit of whole blood collected in CPD anticoagulant and placed in a freezer at ≤ −18 °C within 24 h after collection
Apheresis fresh frozen plasma (AFFP)	Sodium citrate anticoagulated AFFP: 494 ml ACD-A (acid citrate dextrose – solution A) anticoagulated AFFP: 249 ml	Contains both labile and non-labile coagulation factors Contain 1.29 IU/ml of factor VIII	Collected by apheresis and frozen within 8 h of collection
Cryosupernatant plasma CPD (CSP)	273 ml	Contains all coagulation factors Has reduced levels of the high molecular weight von Willebrand factor (vWF), multimers, and fibrinogen	Separated from an individual unit of whole blood prepared following cryoprecipitate manufacturing
Solvent detergent (SD) plasma	200 ml of cell-free plasma	A minimum of 0.5 IU/ml of all clotting factors are present Contains 9.0–14.0 g of human plasma proteins (45–70 mg/ml)	Pooled from many donors, treated with processing steps (solvent detergent, immune neutralization, sterile filtration) to remove or inactivate pathogens, cells, allergens, and antibodies
Convalescent plasma (CCP)	–	Similar to AFFP Also has a pre-specified titer of neutralizing antibody	Collected from people who have recovered from an infection Contains neutralizing antibodies against the causative pathogen

reduction varies with the system used [14]. Factor VIII, fibrinogen, and factor XI are the worst affected factors with losses of up to 30–40%. The solvent detergent process which includes a prion reduction step also significantly reduces protein S and antiplasmin levels [15].

Storage and Handling of FFP

FFP is stored at temperature below −18 °C, usually at −30 °C. Ideally, FFP must be transfused immediately after thawing. If it is not administered immediately after thawing, standard FFP and methylene blue-treated FFP can be stored for up to 24 h at +4 ± 2 °C in a temperature-controlled blood storage refrigerator or for 4 h at 22 ± 2 °C before administration to a patient. However, it must be transfused within 24 h of thawing. Any thawed FFP that is not used within 24 h must be discarded. Units must not be kept out of controlled temperature environment for durations longer than 30 min. Once thawed, plasma components cannot be refrozen.

Table 2 gives shelf life of different plasma components.

Table 2 Shelf life of different plasma components

Component	Shelf life when frozen	Shelf life after thawing
Fresh plasma	12 months	5 days at 1–6 °C
Fresh frozen plasma apheresis	12 months at −18 °C or colder	24 h at 1–6 °C
Cryosupernatant plasma	–	24 h at 1–6 °C

To avoid bacterial contamination, time out of controlled temperature storage must be minimized. Pre-thawed FFP that has been out of controlled temperature environment (+4 ± 2 °C) can be accepted back into storage only once and only if the duration is of less than 30 min. FFP must be transfused within 4 h of issue.

Between 24 and 120 h after thawing, levels of all clotting factors (except protein C), especially factor V and factor VIII, decrease. Factor VIII levels decrease more within the first 24 h after thawing, following which the rate of loss decreases. The loss of activity is more linear for other clotting factors [16]. However, mean levels of most clotting factors remain above 70% at 120 h, with the exception of factor VIII [17]. Factor VII has a half-life of 2 to 6 h. Hence, re-administration of FFP may be needed every 6 to 8 h to replace factor VII, if there is ongoing bleeding.

Before administration, the pack must be inspected to ensure no precipitation and intact component packaging. Any leakage, clots, or abnormal color must be excluded. Plasma components must be administered using a blood administration set with a blood filter. Infusion should be as rapid as can be tolerated by the patient.

Thawing of FFP

Frozen packages are relatively brittle and need careful handling. Stumps of the entry lines are especially vulnerable. Owing to the potential for invisible cracks and pinholes in the plastic wrap and risk of bacterial contamination, thawing procedures are designed very carefully. Procedures that do not expose FFP units to water directly are preferred. After thawing, packs with any flocculation, discoloration, or leaks should be discarded. Thawing may take from 12 to 30 min depending on the method used. Thawing can be done in a water bath at 30 °C to 37 °C over 20 to 30 min or using an approved device in 2 to 3 min. Higher temperatures must be avoided as it can affect the viability of plasma proteins.

Table 3 Thawing techniques

Thawing technique	Description
Dry heat methods	Use dry heat with agitation Have lower potential for microbial contamination Have limited capacity
Microwave ovens	Can defrost FFP in 2–3 min Have limited capacity "Hot spots" might be created in the packs There is potential for parts of the pack to act as an aerial causing arcing Quality of thawed plasma is similar to those using water bath methods
Water bath-based methods	The unit is placed in a pocket around which a water based solution circulates FFP pack must be placed in a vacuum-sealed over-wrap to protect it from bacterial contamination Average time needed for thawing is 20 min

Table 3 gives details of various thawing techniques.

Selection of Plasma Components

Incompatibility can occur when the plasma component contains ABO antibodies that are incompatible with the ABO antigens on patient's RBC. To avoid this risk, identical ABO blood group plasma must be the first choice of transfusion. In emergency situations when patient's blood group is not known, ABO non-identical plasma may be used provided the titers of anti-A and anti-B activity are low. A type and screen testing is required to determine compatibility in such situations. Group O FFP should be transfused only to group O patients.

Table 4 gives details of ABO compatibility for plasma recipients.

Very minute amount of red cell stroma is present in FFP and cryoprecipitate (<0.001 ml in 300 ml of FFP). Hence, the risk of sensitization or alloimmunization following administration of RhD-incompatible FFP transfusion is very little.

Table 4 ABO compatibility for plasma recipients

Recipient ABO group	Donor ABO group
O	O, A, B, AB
A	A, AB
B	B, AB
AB	AB

Patients who receive multiple units of FFP must be considered for vaccination against hepatitis A and B. Pathogen-reduced plasma must be preferred in these patients.

Dose of FFP

Single unit of FFP has plasma isolated from one unit of whole blood donated from a single donor. Typically single unit of FFP has an average volume of about 200 ml.

In general, a dose of 10–15 mL/kg of body weight is sufficient to achieve plasma clotting factor concentration of 30%. In adults, the typical dose of FFP is 1–2 units. For the treatment of warfarin reversal, a dose of 5–8 mL/kg body weight is usually sufficient. In pediatric patients, dose of 10–15 mL/kg is commonly used [18].

There is insufficient evidence to form a recommendation regarding the optimal dose of FFP in patients with abnormal clotting tests undergoing invasive procedures. For management of major bleeding, the commonly used dose of FFP is 15 to 20 ml/kg [19].

Indications for FFP Transfusion

FFP transfusion is clearly indicated in patients with abnormal coagulation tests and coagulation factor deficiency and in the presence of active bleeding [20]. FFP is also used in patients with abnormal coagulation tests who are undergoing invasive procedure [21]; for reversal of warfarin in the presence of active bleeding or planned invasive procedure when vitamin K is inadequate to reverse warfarin effect; for thrombotic thrombocytopenic purpura; and for congenital or acquired factor deficiency with no alternative therapy. There are several guidelines regarding FFP use [3], but presently, there is no clear consensus regarding indications for FFP transfusion [22]. The American Association of Blood Banks (AABB) guidelines recommend using FFP in patients who have warfarin-related intracranial hemorrhage [23], while other authors suggest that vitamin K and/or four-factor prothrombin complex concentrates may be better choices.

There is no clear-cut recommendation for or against the administration of FFP at a plasma-to-RBC ratio of 1:3 or more in trauma patients receiving massive transfusion [24]. FFP is widely used for the prevention of dilutional coagulopathy in patients with major trauma and/or massive hemorrhage [25]. Delaying therapy in these patients can result in dilutional coagulopathy, increased bleeding, and worse outcome.

Liver disease and disseminated intravascular coagulation cause deficiency of multiple coagulation factors and may require the administration of FFP. However, patients with liver disease may not tolerate FFP transfusion well due to the large infusion volumes necessary to achieve adequate levels of coagulation factors [26].

In patients with abnormal clotting tests but who are not bleeding, the use of prophylactic FFP transfusion prior to an invasive procedure is not supported by good-quality evidence [27, 28]. The impact of commonly used doses of FFP to correct clotting results, or to reduce the bleeding risk, is very limited particularly when the international normalized ratio (INR) is between 1.5 and 1.9 [29].

FFP (10–15 ml/kg) has traditionally been used in conjunction with vitamin K to reverse vitamin K antagonists. FFP is relatively inexpensive and widely available.

But, disadvantages include delay in administration, potential transfusion reactions, and large volumes needed for full INR reversal. Thus, there is now more widespread use of prothrombin complex concentrate (PCC) [30]. PCC is derived from plasma. Different preparations contain factors II, VII, IX, and X in variable proportions. PCC is administered rapidly in a small volume (25–50 U/kg). PCC has been demonstrated to

Table 5 Indications for FFP transfusion

Bleeding patients or patients undergoing invasive procedures who require replacement of multiple coagulation factors (such as patients with severe liver disease or DIC)
Patients with massive transfusion (replacement of patient's blood volume in less than 24 h) with clinically significant coagulation abnormalities
Patients on warfarin anticoagulation who are bleeding or need to undergo an invasive procedure before vitamin K can reverse the warfarin effect and for whom prothrombin complex concentrates are not indicated, or not available
Patients with rare specific plasma protein deficiencies for which no more appropriate or specific alternative therapy is available
Patients requiring treatment of thrombotic thrombocytopenic purpura (TTP) and adult hemolytic uremic syndrome (HUS) by plasma exchange

reverse INR to <1.4 and maintain INR reversal for >48 hours in the majority of patients who are on VKA therapy [31]. Both the AHA/ASA and the NCS/SCCM guidelines currently recommend considering PCC over FFP for VKA reversal in ICH [32, 33].

There is a broad general consensus that appropriate use of AFFP/FP is limited to the treatment or prevention of clinically significant bleeding occurring due to deficiency of coagulation factors. Table 5 gives a list of such situations.

Role of FFP in Neurosurgical and Neurological Patients

There is limited data regarding incidence of coagulopathy in neurologically injured patients. Incidence in general critical care patients ranges from 14% to 81% [34–36]. Hematoma expansion is a major cause of mortality in intracranial hemorrhage (ICH) related to vitamin K antagonists (VKA). The INCH trial showed that four-factor PCC might be superior to FFP in normalizing the INR in these patients. Faster INR correction was associated with smaller hematoma expansion. Although a clear-cut effect of PCC on clinical outcome remains to be shown, results from the INCH trial favor the use of PCC over FFP in ICH related to VKA [37].

Contraindications for FFP Transfusion

FFP is not indicated when specific therapy is available for correction of coagulopathy. Specific therapy includes vitamin K, cryoprecipitated antihemophilic factor, prothrombin complex concentrates, and specific coagulation factor concentrates like factor VII.

FFP is not indicated in patients with single coagulation factor deficiency and if specific recombinant products or plasma-derived virally inactivated products are available.

FFP should not be transfused to correct abnormal coagulation in patients who are not bleeding (unless undergoing invasive procedure or surgery with a risk of clinically significant bleeding) and patients who need reversal of a vitamin K antagonist.

FFP should not be used in the absence of coagulation factor deficiency and active bleeding with the sole purpose of volume expansion when other volume expanders are available for replacing blood volume.

FFP is ineffective and therefore contraindicated for reversing anticoagulation due to medications like heparin, direct thrombin inhibitors, or direct factor Xa inhibitors. Specific antidotes to reverse direct oral anticoagulants are better options.

Cryosupernatant plasma should not be used in conditions where fibrinogen, factor VIII, or von Willebrand factor replacement is needed.

Monitoring

The goal of administering FFP is cessation of bleeding. The effect of FFP transfusion is monitored using clinical (signs of bleeding) and chemical methods (coagulation studies, fibrinogen levels). One unit of FFP has a volume of approximately 200 to 250 mL. One unit of 250 mL FFP can raise fibrinogen level by approximately 5 to 10 mg/dl. The laboratory goal is to correct the PT/APTT to less than 1.5 times normal [38].

The utility of tests like thromboelastography (TEG) or ROTEM in predicting risk of bleeding

in non-bleeding patients who have abnormal coagulation parameters, or in monitoring the effectiveness of prophylactic FFP transfusion prior to invasive procedure or surgery, remains unknown [39, 40].

Safety and Adverse Effects of FFP

The adverse effects of FFP transfusion are similar to other blood product transfusions. Transmission of infectious agents, transfusion-related acute lung injury (TRALI), transfusion-related volume overload, allergic reactions, febrile reactions, and hemolysis are well-known complications associated with use of FFP. Thrombotic events related to FFP use have also been suggested in some reports [41]. FFP-associated complications are broadly categorized as non-immunologic, immediate immunologic, and delayed immunologic complications.

Commonly reported non-immunologic complications are transmission of infectious agents, transfusion-associated circulatory overload (TACO), and metabolic complications like citrate toxicity. Cytomegalovirus and graft-versus-host disease cannot be transmitted by FFP as it does not contain viable leukocytes. Common infectious agents that can be transmitted via FFP are HIV, hepatitis B, and C viruses [42]. Screening and pathogen inactivation procedures have reduced transmission rates of these infectious agents significantly.

Common immediate immunologic complications include hemolysis, febrile non-hemolytic reaction, allergic reactions, anaphylactic reactions, and transfusion-related acute lung injury (TRALI). Hemolytic transfusion reaction is caused by anti-A and anti-B antibodies due to ABO mismatch transfusion.

Delayed immunologic complications include alloimmunization to plasma proteins.

Acute Transfusion Reactions

Allergic, febrile, and anaphylactic reactions are the most commonly occurring reactions following FFP transfusion. These reactions usually occur within the first 15 minutes of transfusion, and the treatment of choice is adrenaline.

Pulmonary Complications

Transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and transfusion-associated dyspnea are the common pulmonary complications associated with FFP transfusions. TRALI is reportedly the most common cause of transfusion-related deaths. Clinical manifestations of TRALI are acute onset hypoxemia and non-cardiogenic pulmonary edema in the absence of other causes [43]. Blood components that stimulate TRALI include white blood cell antibodies from donors and pro-inflammatory molecules that accumulate in stored blood components. These stimuli trigger an inflammatory response resulting in injury to the alveolar-capillary membrane causing pulmonary edema [44]. With gradual transition to male plasma donors, risk of TRALI has reduced [42, 45]. TACO results from cardiogenic pulmonary edema. It can occur after transfusion of excessive volumes or transfusion at excessive rates [46]. Elderly patients are particularly vulnerable to TACO [47].

Toxicity

Most of the citrate present in whole blood products is seen in FFP and platelets. Citrate toxicity is therefore possible with FFP transfusion. Citrate intoxication causes hypocalcemia because citrate chelates calcium. Clinical manifestations of hypocalcemia include hypotension, arrhythmias, mental status changes, and tetany. Treatment is by calcium replacement.

Conclusion

Fresh frozen plasma contains a number of therapeutically useful components, especially coagulation factors. There are risks associated with

plasma transfusion. Noninfectious complications are the most significant cause of morbidity and mortality following transfusion. Although certain patients definitely benefit from plasma transfusion, the benefit in most patients is less clear. Based on current evidence, fresh frozen plasma is definitely indicated for patients with deficiency of coagulation factors with abnormal coagulation tests in the presence of active bleeding.

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Platelet-Rich Concentrates

Başak AKÇA

Abstract

Platelets are the component of blood whose function is to react to bleeding by initiating a blood clot. As platelets are vital components of blood for hemostasis, understanding the role of platelet transfusions and the critical thresholds for transfusion is crucial especially in neurosurgical patients.

Keywords

Platelets · Platelet concentrates · Platelet function tests · Antiplatelet agents

Histology and Physiology of Platelets

Platelets are critical elements of whole blood mainly responsible for clot formation. They are actively metabolizing cells which are evolved for the tasks of hemostasis and inflammatory reactions accordingly [1].

A normal platelet count is 150–450 × 10^3 cells/μL of whole blood, and considering the whole body, there are ~2 × 10^{12} platelets. One third of this number is sequestered in the spleen and two thirds remain in circulation [2]. Without any pathological events, baseline platelet count is relatively stable over the lifetime [3].

Platelets are discoid shaped, non-nucleated cells, and they circulate in the blood for 7–10 days under normal conditions (normal life span). Thrombopoetin is the hormone that is responsible for releasing mature platelets from bone marrow. They are exported from megakaryocytes in the bone marrow. Megakaryocytes react to the stimulation by thrombopoetin [1].

Platelets are the main structure of the coagulation cascade. They circulate freely in the plasma in an inactivated state. They are very small in size, so they are marginated to the walls of the vessels by blood flow [1]. Therefore, platelets have a tendency to interact with endothelial cells and glycocalyx [4].

There are several types of granules and organelles found within platelets. They contain binding ligands, platelet agonists, and growth factors. Platelets perform a series of actions related to a stimulation. A shape change occurs, from a discoid to an ameboid-like shape, and at the same time α-granule release occurs [1]. At the same time, organelles and granules are pushed towards the center and platelets' inner body become more concentrated [1].

The relationship between bleeding risk and platelet count is nonlinear and depends on several different factors. A normal platelet count is 15–40 times higher than is necessary to achieve hemo-

Başak AKÇA (✉)
Hacettepe University School of Medicine, Dept of Anesthesiology and Reanimation, Ankara, Turkey
e-mail: basak.kantar@hacettepe.edu.tr

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stasis [3]. In patients with a platelet count ≥10.000 platelets per μL, the risk of spontaneous bleeding is very low since this number of platelets are thought to be sufficient to allow for normal thrombin generation [5].

If a patient does not have "enough" platelets or if a patient has "dysfunctional" platelets due to antiplatelet drug use, transfusion of stored platelets is the only available therapy.

As platelets are vital components of blood for hemostasis, understanding the role of platelet transfusions and the critical thresholds for transfusion is crucial. The safe threshold for platelet transfusion in a hemodynamically stable hospitalized patient who does not have critical bleeding is 10.000 platelets per μL [6, 7]. The American Association of Blood Banks (AABB) also recommends transfusing only a single apheresis unit or equivalent of platelets at this situation [7]. As the major cost of a platelet transfusion is the platelets themselves, low-dose, frequent transfusions are recommended as long as hemostasis is maintained.

There are several situations where platelet thresholds need to be adjusted. One of these situations is for those patients undergoing neurosurgical procedures. The adverse outcomes associated with intracerebral bleeding during and after neurosurgical procedures are serious; therefore these patients should have platelet counts maintained over 100,000 platelets per μL [8].

Platelet Concentrates

Platelet concentrate production and transfusion medicine techniques were improved by technical developments, advanced progressions in apheresis techniques, storage conditions, and mediums (e.g., platelet additive solutions) [9].

When trying to understand the overall efficacy of platelet transfusion, we often make the mistake of trying to interpret this process through "normal" physiology; however, when blood is harvested, anticoagulated, and stored, the biological interaction between the endothelium and blood components ends. Starting from the first few moments of this procedure, normal platelet function ceases to exist [1]. Therefore, we need to understand the procedural techniques that are used while preparing the concentrates and make clinical decisions for the unique conditions of our patients.

Platelets must be stored at room temperature (20–24 °C) with continuous gentle agitation. The shelf life of platelet concentrates is limited to 5 days due to the risk of bacterial contamination and growth [7]. It is very important to keep in mind that, of all blood-related products, platelets are thought to be the most frequent source of sepsis following transfusion [10]. Bacteria may be introduced into a platelet concentrate either by a low-level bacteremia that is not identified during the review of health history or physical examination of the donor or by inadequate skin cleaning before phlebotomy [11].

There are two types of platelet concentrates available for transfusion: whole blood platelets and apheresis platelets. Whole blood platelets are derived from 4–6 different donations of the same ABO blood group (random donor platelets (RDP)). Apheresis platelets are derived from one single donor after a 2 h lasting procedure (single donor apheresis platelets (SDAP)) [6]. In this procedure, an entire platelet dosage for an adult patient can be collected from one single donor [12]. The major limitation of apheresis platelet concentrates is finding available donors. This limitation could also be considered as the advantage of the technique since using SDAP decreases donor exposure and also the risk of infectious diseases. The risk of bacterial contamination is reported to be 5–6 times higher, in addition to a twofold higher risk of transfusion-transmitted infection when RDP is preferred [13]. A reduced rate of febrile transfusion reactions are reported in literature with SDAP use compared to RDP use [14]. SDAP tend to be very expensive due to the specialized disposable kits and solutions for each donation. The use of SDAP is generally indicated for patients who are refractory to RDP units, though the use of apheresis platelet units as first-line treatment is increasing. Post transfusion platelet increments have been confirmed to be higher with the use of SDAP [5, 13, 15].

SDAP are less contaminated with red blood cells. Content of erythrocytes is approximately 0.00043 mL for SDAP and 0.036 mL for RDP [13]. This issue is very important for Rh (−) childbearing female patients. Although platelets do not express Rh antigens, due to the unintended quantity of erythrocytes, alloimmunization might occur.

These two different platelet concentrates are considered to be interchangeable in terms of safety and efficacy by most experts [6]. RDP are obtained from whole blood using two different methods: platelet-rich-plasma (PRP) (used commonly in the USA) and buffy coat method (used commonly in Europe) [13]. Both SDAP and RDP are suspended in special platelet additive solutions (PAS) or in plasma [13, 16]. A random donor unit is prepared in approximately 40 ml of plasma/PAS. In a stable, nonbleeding, adult patient; 4–6 units of RDP (single dose) will raise the host's platelet count by ~30.000 platelets per μl [2]. Apheresis platelets usually contain 3–4 × 10^{11} platelets in 280 mL. The expected increment in platelet count per single apheresis platelets is also similar [2]. The platelet content is reduced by 20% when PAS is used as a suspension. The purpose of using PAS is to improve life span of platelets and to reduce adverse reactions related to platelet transfusion in "plasma."

Platelet Function Tests

Platelet count is the main laboratory parameter assessed to guide platelet transfusion; however, this measurement does not provide any qualitative information about hemostatic functions of platelets [7]. In vitro functional testing could increase the quality of the transfusion process and remains as the key area of clinical investigation in transfusion medicine.

In the setting of antiplatelet therapy, there are no evidence-based guidelines to manage severely bleeding patients or patients who are about to undergo a major neurosurgical procedure. Therefore platelet function tests (PFTs) have gained significant value in the evaluation of bleeding risk pre-/perioperatively for surgical procedures or trauma [17]. The increased application of PFT leads to the progress of more simple techniques that are easy to use and do not require "specialized" staff.

The literature for platelet function tests to lead platelet transfusion are based highly on expert opinions [18]. These tests are mostly not useful in extremely urgent cases.

Light transmission platelet aggregometry is the gold standard test assessing platelet function. This test is usually expensive and may not be easily obtainable at many centers [19].

Platelet function analyzer (PFA)-100 uses cartridge membranes that are coated with collagen/epinephrine or collagen/ADP [16]. A prolonged collagen/epinephrine cartridge closure time is seen in aspirin use [20]. In patients on aspirin undergoing urgent surgery or presenting with major bleeding, a normal PFA-100 collagen/epinephrine closure time would rule out any significant anti-platelet effect from aspirin. PFA-100 test results are affected by low hematocrit and low platelet count [18].

VerifyNow is a system developed to evaluate high-on-treatment platelet reactivity on aspirin or P2Y12 inhibitors. Bonello et al. defined "High on-treatment platelet reactivity (HTPR)" as the lack of therapeutic levels of inhibition of a drug as measured by a well-validated assay that has acceptable sensitivity and specificity for a particular drug effect [21]. This system is used to tailor antiplatelet therapy for anti-ischemic purposes. In a bleeding patient or patient undergoing urgent procedure, VerifyNow could help with the timing of the surgery or the need to transfuse platelet concentrates [18]. When patients not taking aspirin were tested using VerifyNow, all had aspirin reaction units (ARU) ˃550. This cutoff is used to distinguish non-responders from adequate responders to aspirin [17]. P2Y12 reaction unit (PRU) is used to measure the effect of P2Y12 inhibitors in the urgent scenarios mentioned before. PRU ≥240 would be suggestive of a lack of significant P2Y12 inhibition [18].

Platelet-mapping assay (thromboelastography platelet mapping assay (TEG-PM)) is a point-of-care test to monitor platelet function [22]. TEG-PM can be used to detect the antiplatelet effect of aspirin and ADP receptor antagonists [18].

Neurosurgery and Platelet Transfusions

Platelet Transfusions in Neurosurgical Patients

Stored platelets are a complex biologic therapy, and transfusion indications depend on the current pathophysiology of the patient.

The aim of platelet transfusion is to stop (therapeutic transfusion) or to prevent (prophylactic transfusion) bleeding in patients with thrombocytopathy [6]. It is estimated that more than 70% of platelet transfusions are performed prophylactically [23].

For neurosurgical procedures, platelets are transfused for a pre-procedure platelet count <100,000 platelets per μL, although only low-quality data supporting this threshold is available [7].

Neurosurgical Patients on Antiplatelet Therapy

Population ages worldwide, and the use of antiplatelet agents (APA) is also increasing. Therefore, coagulopathy secondary to APA is a major problem in neurosurgical patients. Adequate reversal strategies for these agents are the vital arms against the medication-induced coagulopathy [24].

In patients taking APA prior to injury, platelet transfusions act as a hemostatic adjunct in restoring "functional" circulating platelets, resulting in the theoretical advantages of reducing the progression of intracranial hemorrhage, the need for surgical procedures, and mortality [25].

Preoperative platelet counts solely were not significantly associated with intra-/postoperative bleeding; therefore, for neurosurgical patients who are on antiplatelet medication, the decision of platelet transfusion requires the clinician's solitary act [7].

There are several types of antiplatelet drugs in clinical use. They are cyclooxygenase-1 (COX-1) inhibitors (acetylsalicylic acid; ASA/Aspirin), P2Y12 receptor inhibitors (clopidogrel, prasugrel, and ticagrelor), phosphodiesterase inhibitors (dipyridamole), and glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban). Aspirin is the most frequently preferred APA worldwide. Excluding ticagrelor, which is a reversible inhibitor of platelet function, the inhibitor effect of antiplatelet drugs take ~3–5 days to normalize after discontinuation of the drug [26].

Aspirin is an irreversible cyclooxygenase (COX-1) inhibitor that terminates thromboxane A2 production. Since platelets do not have nucleus, they cannot regenerate COX-1 and the effect of aspirin lasts for the life of the platelet [24]. This effect of aspirin can be seen within 15–30 min after ingestion, and the maximum inhibitor effect will occur at 60 min. Life span of a platelet is ~10 days, an otherwise healthy patient with a platelet count of 200,000 platelets per μL should be able to produce 60,000 platelets per μL normally functioning platelets in 3 days. This number of platelets is assumed to provide good hemostasis most of the times [18]. But as a consequence of long-term use of aspirin, the need for surgical intervention, morbidity, and mortality after spontaneous or traumatic intracerebral bleeding was found to increase [24, 27].

Clopidogrel blocks the P2Y12 component of ADP receptors on the platelet surface irreversibly. Due to the inhibition of the GPIIb/IIIa receptor complex, platelet aggregation is reduced [24]. Clopidogrel is metabolized into its active metabolites in the liver. Hepatic enzymes that are needed for this conversion exhibit high polymorphism [24]. This means that the effects of clopidogrel differ widely in individuals. Among patients receiving clopidogrel, one third are considered non-responders. These patients receive little to no antiplatelet benefit.

The half-life of clopidogrel's active metabolite is ~30 min. The normalization of platelet functioning occurs at 5–7 days after the last intake of the drug [18].

Prasugrel is an oral thienopyridine prodrug that inhibits P2Y12 receptors and prohibits ADP binding once converted to its active form. Hepatic enzymes are also required to convert prasugrel to its active form, but it does not carry the same non-responder profile as in clopidogrel [24], because the CYP enzymes used to convert the

drugs are different. The half-life of the active metabolite of prasugrel is 3.7 h, and it takes 7 days to normalization of platelet function [18].

Ticagrelor is an orally active non-thienopyridine. Ticagrelor does not require metabolic conversion so the effects of the drug is rapid. Ticagrelor is a reversible drug; platelet dysfunction is normalized after clearance of drug, but still there is no antidote available [24]. The estimated time to normalization of platelet inhibition is 5 days [18].

Dipyridamole inhibits ADP-induced platelet aggregation through inhibition of phosphodiesterase [18].

Abciximab, *eptifibatide*, and *tirofiban* are intravenous drugs which block GPIIb/IIIa receptors. They provide immediate, short-term inhibition of platelet function. The platelet function returns to normal in 24–48 h after the discontinuation of abciximab and ~4 h after the last dose of tirofiban or eptifibatide [18].

There are several trials conducted to provide guidance for clinicians in the management of neurosurgical patients with thrombocytopenia/platelet dysfunction.

In patients with intracerebral hemorrhage (ICH), traumatic brain injury (TBI), or with subarachnoid hemorrhage (SAH), platelet dysfunction can be seen even in the absence of antiplatelet agent usage [28].

Unlike anticoagulants, there are no specific reversal agents for antiplatelet agents, and platelet transfusions are considered to be the only option to reverse the inhibition of platelet function.

Real-time platelet function tests are thought to be useful for the decision to proceed/withhold platelet transfusion in patients on antiplatelet agents with ≥WHO-Grade 2 bleeding or those who need to undergo urgent neurosurgical procedures [18, 29].

A randomized trial by Li et al. evaluating the rate of postoperative hemorrhage in patients undergoing craniotomy for the emergent evacuation of basal ganglia hemorrhages can be highlighted to underline the importance of platelet function tests. In a total of 780 patients, 279 of the patients were found to receive no ASA therapy. The 135 patients of 501, who were receiving ASA therapy, were ASA resistant or semi-responsive, and 366 patients with abnormal platelet functions were randomized to three groups (one single unit platelet transfusion, two units of platelet transfusion, no transfusion). ASA-responsive patients received platelet transfusions, and the authors found a statistically significant decrease in disability and mortality rate with a significant decrease in postoperative hemorrhage in patients that received platelet transfusion [30]. There were no significant difference between non-ASA group and ASA-resistant group regarding the possibility of postoperative hemorrhage. Using platelet function tests, half of the patients were protected from the possible complications of platelet transfusion.

Another trial which was published in 2016 has led to a deep controversy whether to administer platelet transfusions in APA-induced ICH [31]. In this very first randomized phase 3 trial, 190 patients who do not need emergent surgical intervention were included. The effects of platelet transfusion in spontaneous intracerebral hemorrhage following APA use on patient outcomes were investigated. The authors concluded that transfusing platelets to reduce effects of APA and hemorrhage growth was shown to increase risk of death or disability compared with standard care [31]. This result was associated with the proinflammatory effects of platelets that possibly enhanced during storage.

In PATCH trial, patients that were assigned to the intervention group had significantly larger hemorrhages, perihematomal edema, and total volume of lesion than control group. Also number of patients on dual antiplatelet therapy is higher in intervention group [32]. In a commentary letter about this trial, it is underlined whether the results of PATCH could be explained by baseline imbalances in study arms alone or by a combination with a detrimental effect of platelet transfusion remained unclear [33].

Traumatic brain injury (TBI) is a particular class of ICH. Within the minutes after TBI, fibrin degradation products and D-dimer start to increase, and these are the first detectable pathologic laboratory parameters in TBI. Then a profound depletion in fibrinogen is observed.

Potential mechanism related to brain injury is massive release of brain tissue factor (TF). TF is a procoagulant factor that is normally isolated by blood-brain barrier and thereby not exposed to coagulation factors [34]. TF is released from damaged brain soon after the injury leading to the consumption of the coagulation factors. Due to the lack in coagulation factors, hematoma expands. Therefore, TBI-induced coagulopathy is thought to change its hypercoagulable nature rapidly to a hypocoagulable state [35]. Another challenging finding is that platelets undergo significant phenotypic changes after TBI, but the main causes of this finding are less understood than the consumptive coagulopathy mentioned above [36].

The relationship between TBI outcome and APA use is controversial too. It is not clear whether neutralization of APA by the means of platelet transfusion mitigates the hemorrhage progression or increase the patient outcomes. There are many studies evaluating the effects of platelet transfusion in TBI patients on APA. Most of the data shows no improvement in outcomes (hemorrhage progression, mortality, independence rate) between patients receiving and those not receiving platelet transfusion [37–39]. One prospective data indicates that platelet transfusion in TBI is likely to improve acetylsalicylic acid-induced, but not trauma-induced, platelet dysfunction [35, 40].

A targeted approach using platelet function tests could reduce the use of platelet concentrates in patients with TBI. Transfusing only inhibited patients would lessen the transfusion-related complications with better patient outcomes [41].

Unlike the two entities above, platelet function might play a different role in patients with aneurysmal SAH. Several key mechanisms in delayed cerebral ischemia (DCI) – a major complication of SAH, like vessel narrowing/vasospasm, parenchymal inflammation, and microthrombosis – are linked to regular platelet function or functioning of platelet granules [42]. It was shown that DCI occurred more often in patients with regular platelet function when compared with the rate of DCI who were confirmed to have impaired platelet function [42]. The data in that trial shows that platelet transfusion did not change the lower occurrence of DCI in the group with impaired platelet function. Toussaint et al. showed that permanent disability from vasospasm was less common among aspirin users clinically [43]. A Cochrane analysis had shown a reduced incidence of DCI as the potential effect of APA in SAH [44].

Conclusion Many trials in the literature have been conducted to end up with a conclusion in the field of transfusion medicine – especially platelet concentrate use in neurosurgical patients. To date, there is still no consensus in this era. In the light of these efforts, the recommendations of Neurocritical Care Society are the most applicable ones. These are:

1. Platelet transfusion is not recommended for TBI patients regardless of the type of platelet inhibitor, platelet function testing, hemorrhage volume, or neurological exam who will not undergo a neurosurgical intervention [41].
2. Platelet transfusion is recommended for patients with aspirin – or ADP inhibitor-associated intracranial hemorrhage who will undergo a neurosurgical procedure.
3. Platelet function testing is recommended prior to platelet transfusion if possible. When platelet function testing is not readily available, empiric platelet transfusion may be reasonable.
4. Platelet transfusion is not recommended for patients with laboratory documented platelet function within normal limits or documented antiplatelet resistance.
5. In candidates for platelet transfusion, an initial dose of one single-donor apheresis unit of platelets is recommended. Platelet testing is suggested prior to repeat platelet transfusion, if available and repeat transfusion should be used only for those with persistently abnormal platelet function tests and/or ongoing bleeding.

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Cryoprecipitate

Funda Arun

Abstract

The routine management of perioperative coagulopathy involves the administration of blood and fresh frozen plasma and their co-products. Cryoprecipitate is a pooled allogeneic frozen blood product that contains factor VIII, von Willebrand factor, fibrinogen, fibronectin, factor XIII, and platelet microparticles together. The primary purpose of the use of cryoprecipitate is to raise fibrinogen levels in patients with acquired hypofibrinogenemia and massive bleeding in which fibrinogen decreases to a critical level. Clinical indications and usage of cryoprecipitate vary worldwide. Although cryoprecipitate is one of the most common blood products being used over 50 years to achieve hemostasis in varying conditions, there is a lack of guidelines consisting of data from controlled studies on cryoprecipitate use specifically in neurosurgery and neuro-intensive care. Randomized, controlled trials are needed to determine the clinical efficacy of perioperative cryoprecipitate transfusion. In this chapter, information about the historical development, preparation, content, administration, clinical indications of cryoprecipitate, and its use in neurosurgery were discussed.

Keywords

Cryoprecipitate · Fibrinogen · Coagulopathy · Transfusion · Hemostasis · Neurosurgery

Introduction

Cryoprecipitate is a frozen blood product prepared from human plasma. It is prepared by slow-thawing of fresh frozen plasma (FFP) between 1 and 6 °C to precipitate high molecular weight proteins (coagulation factors), followed by centrifugation to remove the supernatant. The final product contains fibrinogen and other factors, including factor VIII (FVIII), von Willebrand factor (vWF), fibronectin, factor XIII (FXIII), and platelet microparticles [1]. This final product's official name is cryoprecipitated antihemophilic factor (AHF), and it is shortened to cryoprecipitate or cryo as accepted termination in the medical community.

Cryoprecipitate is originally developed as a therapy for patients with antihemophilic factor deficiency and hemophilia. Cryo was used in the past for many coagulation disorders, including hemophilia, liver failure, FXIII deficiency, and fibronectin deficiency [2–4]. Today, the primary purpose of the use of cryo is to raise fibrinogen

F. Arun (✉)
Selcuk University Faculty of Dentistry, Department of Pedodontics, Head of Anesthesiology Clinics, Konya, Turkey
e-mail: funda.arun@selcuk.edu.tr

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levels in patients with acquired hypofibrinogenemia and massive hemorrhage in which fibrinogen decreases to a critical level [5, 6].

Although cryoprecipitate is available for clinical hemostatic therapy in many countries such as the USA, UK, and Australia, its use differs worldwide. In some countries such as Japan, it is neither licensed nor produced. Fibrinogen concentrates (FCs) are available as an alternative product to cryo in treating congenital or acquired fibrinogen disorders in many countries. Also, there is a pathogen transmission safety problem in the cryo product. Therefore, cryoprecipitate has been withdrawn from many European countries [7–9].

In this chapter, information about the historical development, preparation, content, administration, clinical indications, and use of cryoprecipitate in neurosurgery were discussed.

History of Cryo

Edwin J Cohn firstly produced a stable protein solution in the 1940s by fractionating plasma with ethanol [10]. This plasma product was used as a treatment for hemophilia in the 1950s. It was in 1964 that Dr. Judith Graham Pool at Stanford University, who conducted studies to develop this product, described the preparation of cryoprecipitate by centrifuging frozen plasma dissolved at 0–4 °C. After the supernatant plasma was removed, the remaining plasma was frozen at −20 °C to create cryoprecipitate [11]. All plasma proteins, F VIII, vWF, and fibrinogen, remain concentrated in cryoprecipitate in the final stage. Bennet and Dormandy used cryoprecipitate for the first time, treating patients with von Willebrand's disease in 1966 [12]. Barrett's use of cryoprecipitate in hemophilia A (FVIII deficiency) patients in 1967 is a historical and critical development in the treatment of hemophilia [13]. After the 1980s, factor concentrates, which were found to be more reliable due to the high risk of infection of multi-donor product cryoprecipitate transfusions, and improvements in the production of factor concentrates (FVIII), superseded cryoprecipitate use in patients with hemophilia. Recently, cryoprecipitate has been withdrawn from many European countries, and it is mostly used to treat fibrinogen deficiency following massive bleeding in the other countries in which the product is available.

Preparation and Content of Cryo

Cryoprecipitate is a pooled, allogeneic blood product made from FFP, which has been separated and frozen for 8 h of whole blood collection. Each unit (U) of cryoprecipitate is commonly prepared from one unit of FFP. FFP is thawed at 1–6 ° C and followed by centrifugation to remove the supernatant which is called cryopoor or cryoreduced plasma. The cryopoor has been used to treat thrombotic thrombocytopenic purpura (TTP) because of its reduced content of high-molecular-weight multimers of VWF. However, still more clinical data is needed to use cryopoor plasma [14]. After removing supernatant, the remaining insoluble residue enriched with clotting factors is re-suspended in plasma and kept frozen at −18 °C or colder. As a result of this manufacturing procedure, the product has a general shelf-life of 12 months [15].

Each unit of cryoprecipitate contains fibrinogen, FVIII, FXIII, VWF, fibronectin, and platelet microparticles. The concentration of these clotting factors varies due to blood donor diversity and production process differences. In some countries, minimum concentrations of contents are stipulated. In the USA, a single cryo unit must contain minimum 80 IU of FVIII and 150 mg of fibrinogen mandated by the US Food and Drug Administration. In comparison, Australian standards indicate at least 70 IU of FVIII and 140 mg of fibrinogen, and UK Blood Transfusion Services indicate minimum 75% of packs should contain ≥140 mg of fibrinogen [16, 17].

Cryoprecipitate is usually prepared as a small pool derived from allogeneic donors. Five to ten units of fresh frozen plasma is required to form one bag of cryoprecipitate. Generally, blood centers prefer 5 single units of cryoprecipitate pooled in one bag. Two pools of cryoprecipitate (10 single units) increase fibrinogen levels by 1 g/L,

depending on the clinical condition of the recipient [3, 18]. Two cryo pools are the standard adult dose and might be transfused diluted in plasma, saline, or purely [19]. Cryoprecipitate can be pooled after thawing by licensed centers. Centers must have a license for pooling cryo in the EU (European Union) countries under the European Union Blood Directive [20]. Strict rules and supervision at licensed centers have led many facilities to leave the practice of pooling cryoprecipitate.

Administration

Cryoprecipitate must be thawed before the transfusion. After thawing, cryo pooled by the sterile method and can be stored at 20–24 °C for up to 6 h. If cryo is pooled in an open system, its storage time decreases to 4 h at the same temperature range. Green and colleagues extended the storage time to 72 h [21]. They tested 16 units of pooled cryoprecipitate thawed at 35 ± 2 °C for 20 min and held at room temperature for up to 72 h. There were no significant changes in levels of fibrinogen and FXIII and peak thrombin, endogenous thrombin potential, and all ROTEM variables which show hemostatic properties after 72 h. The point to be considered in future studies that will support this study is the need for bacterial contamination tests before clinical use. The risk of bacterial contamination in a blood product stored at room temperature cannot be underestimated.

The thawed cryo cannot be refrozen or refrigerated due to regulatory standards, and it would be wasted if thawed but not used [15]. Cryoprecipitate should be administered through a standard filtered blood set, and it is recommended not to be given with other medications or fluids through the same intravenous line at the same time. The recommended standard infusion rate is similar to the other blood products (1–2 mL/min), but the clinician can change the infusion rate due to the severity and emergency of the case [22]. Targeted dosing is not possible for cryo due to varying concentrations of fibrinogen in its content. Most guidelines recommend adjusting the dose of cryoprecipitate according to fibrinogen level falling below a certain threshold. Patients can be given appropriate amounts of blood product with fewer side effects and adequate treatment with hemostatic monitoring. Therefore, a test that is easy to implement and a short response time is needed. The Clauss fibrinogen test's response time is too long to effectively guide the administration of hemostatic therapy in patients with bleeding. Chandler and colleagues revised the Clauss fibrinogen test, and as a result of their study, the revised test was responsive in <20 min in most cases [23]. Viscoelastic methods such as ROTEM and thrombelastography (TEG) can be performed at the bedside and include special fibrin tests that allow rapid assessment of coagulation parameters. Recently, there has been an increase in the number of studies evaluating cryoprecipitate administration with viscoelastic tests [24–26].

Another issue related to cryo transfusion is the necessity of ABO-compatibility. AB0-compatibility is not sought for small volumes of cryoprecipitate transfusion, but a compatible donor may be required in patients receiving large volumes of cryoprecipitate relative to red blood cell (RBC) mass. A very recent study from Canada obtained robust data supporting the transfusion of cryoprecipitate units without the need for ABO-compatibility in adult recipients. This study reported that the cryo's anti-A/B activity was equivalent to the corresponding plasma, and no increased antibody activity was observed in the cryo [27]. On the other hand, only ABO-compatible cryoprecipitate should be given to neonates and small children because of their small body volume [28]. Rh compatibility needs not to be considered for cryoprecipitate transfusion, and cross-matching is unnecessary since cryoprecipitate doesn't contain red cells.

Risks and Adverse Events

Despite its clinical use for more than 50 years, there have been a minimal number of adverse events reported in the literature related to cryoprecipitate [29]. It is unclear whether there is not

enough data or if there is actually a low risk from its use. Theoretically, cryoprecipitate carries the same potential transfusion risks with the plasma from which it is obtained. Significant risks are the transmission of infectious diseases, volume overload, transfusion reactions, and thrombotic complications.

Infection

If the cryo does not processed with pasteurization or viral inactivation, the risk of viral transmission can be high. Infection risk is multiplied by the number of units in the cryo pool, which are collected from different donors and transfused to the recipient at the same time. Technological methods of pathogen inactivation (PI) are available to minimize infection risk in plasma transfusion. The four main PI methods are solvent detergent, visible light methylene blue, amotosalen with UV light, and riboflavin with UV light. Although PI methods reduce pathogens, standard fibrinogen concentration reduces approximately 35% after the procedure [29]. Most of the PI methods are generally effective on enveloped viruses, but their effect on reducing non-enveloped viruses (hepatitis A virus, parvovirus B19, and hepatitis E virus) is variable. Therefore, plasma used as a source of FFP in the UK has been tested for the latter virus [30]. Serious Hazards of Transfusion (SHOT) study reported that there were no cases of cryoprecipitate-related viral transmission in transfused cases examined between October 1996 and December 2014 in UK hospitals [31]. All PI methods are available in Europe. European Society of Anaesthesiology (ESA) recommends pathogen inactivation for FFP and platelets [32]. Non-pathogen-inactivated cryoprecipitate prepared by blood banks is still used to treat bleeding disorders due to fibrinogen deficiency in many countries. Therefore, it is necessary to develop easy-to-use, low-cost, and effective methods for viral inactivation of cryoprecipitate. Bacterial transmissions from plasma components have not been reported yet.

Volume Overload

Transfusion-associated circulatory overload (TACO) is a transfusion reaction that appears clinically as pulmonary edema caused by volume excess or circulatory overload. Patients with underlying cardiovascular insufficiency or receiving large amounts of transfusions over a short period are at risk of TACO. Although cryo is less likely to cause TACO than FFP, clinicians still need to be alert regarding infusion speed.

Transfusion Reactions

Transfusion reactions associated with cryoprecipitate can range from mild allergic reactions to severe life-threatening reactions such as anaphylaxis and transfusion-associated acute lung injury (TRALI). Cryoprecipitate appears to have a lower risk of inducing a hemolytic transfusion reaction than FFP, as it contains a small number of alloantibodies due to its small volume. There are only a few case reports in the literature about transfusion reactions related to cryo [33, 34]. If ABO-compatible cryo is used, the possibility of transfusion reaction is further reduced.

Thrombotic Complications

Another risk regarding the administration of cryoprecipitate is thrombotic events. It is known that high fibrinogen levels are always a risk factor for thrombosis. The risk of thrombosis increases with the use of cryoprecipitate or other prohemostatic agents (prothrombin complex concentrate and FC) in large volumes to treat patients with massive hemorrhage [35]. Cryo seems to have a higher risk of thrombotic event possibility than FCs because of containing both fibrinogen and other coagulation factors. However, the CRYOSTAT randomized controlled trial supported early cryoprecipitate use within 90 min in addition to standard hemorrhage therapy in patients with trauma-induced bleeding without

any additional thrombotic adverse event [36]. The strength and importance of the relationship between achieved fibrinogen levels and thrombotic events have not been elucidated yet. More clinical trials to identify the effects of cryo and FCs on thrombosis in hemorrhagic events are crucial.

Clinical Use of Cryoprecipitate

Cryoprecipitate is produced in the UK, USA, Canada, Australia, and New Zealand, where it is used to treat acquired hypofibrinogenemia. In Europe, many countries except the UK have phased out cryoprecipitate production. Instead, FCs are preferred in the treatment of both congenital and acquired fibrinogen deficiencies. However, FC is not universally licensed for acquired hypofibrinogenemia. For example, in the USA, Australia, UK, and Canada, FC is licensed only for the treatment of congenital deficiencies [37]. Indications of cryo differ worldwide. The differences between the recommendations regarding transfusion indications for the use of cryoprecipitate given in the National Blood Transfusion Committee (Table 1) in the UK and ASA (American Society of Anesthesiologists) (Table 2) guidelines in the USA can be given as an example for the variations between countries [38, 39].

In general, the purpose of cryoprecipitate's clinical use is to maintain the hemorrhagic patient's fibrinogen levels. FFP and FCs are alternatives of cryo for fibrinogen replacement in patients with massive bleeding. FFP, as the oldest among these three products, contains all coagulation factors. Its major advantage over other fibrinogen sources is providing volume substitution to patients with significant blood loss, whether this is a clinically unproven benefit [40]. However, FFP has several disadvantages, including dilution of red blood cells and platelets, increased turnaround time, lower fibrinogen content (varies widely with a range of 1–3 g/L), and low efficacy in improving the fibrinogen level (30 mL/kg of FFP is expected to increase plasma fibrinogen level by only 1 g/L) [41]. Thus, FFP is recommended in patients with massive blood loss only in the absence of point-of-care coagulation (POC) testing (TEG and ROTEM) and unavailability of better options such as FCs and specific coagulation factor concentrates (CFCs) [42]. Commercial FC is a sterile, preservative-free, lyophilized product of pooled human plasma. FCs have several advantages over FFP and cryoprecipitate, including standardized fibrinogen concentration (0.9–1.3 g per vial), storing as a lyophilized powder at room temperature, quick reconstitution with sterile water, low infusion volumes, rapid administration facility without any delay with thawing or cross-matching, and improved safety profile with minimal virus transmission risk [43]. According to the controlled trials in which FC and cryoprecipitate's efficacy were compared in the treatment of bleeding, both products were found to have similar effectiveness and rate of thromboembolic events [44, 45].

Although a wide range of clinical studies have been conducted comparing cryoprecipitate and FC, the optimal timing and dose of fibrinogen replacement in patients with massive bleeding remain unclear. There are only a few prospective studies on cryoprecipitate's optimal therapeutic

Table 1 Clinical indications for the use of cryoprecipitate in adults

- Clinically significant bleeding and a fibrinogen level <1.5 g/L (<2 g/L in obstetric bleeding)
- Fibrinogen level is <1 g/L and pre-procedure
- Bleeding associated with thrombolytic therapy
- Inherited hypofibrinogenemia where fibrinogen concentrate is not available

Table 2 ASA recommendations of cryoprecipitate indications

- When a test of fibrinogen activity indicates a fibrinolysis
- When the fibrinogen concentration is <80–100 mg/dL in the presence of excessive bleeding
- As an adjunct in massively transfused patients when fibrinogen concentrations cannot be measured in a timely fashion
- For patients with congenital fibrinogen deficiencies
- Whenever possible, decisions regarding patients with congenital fibrinogen deficiencies should be made in consultation with the patient's hematologist

use or effects. One of them is from the UK, a randomized controlled multicenter CRYOSTAT I study, which evaluated the early use of cryoprecipitate in trauma cases [36]. This study showed that early transfusion of cryoprecipitate within 90 min (median time = 60 min) might maintain fibrinogen levels >1.8 g/L. There were no significant differences in secondary outcomes (thrombotic events, organ failure, length of hospital stays, mortality) and blood transfusion requirements between standard therapy and cryo groups. In addition to cryoprecipitate's therapeutic use in trauma and hemorrhagic surgery, evidences are available for the clinical use in hereditary fibrinogen deficiencies, DIC, uremic bleeding, acquired hypofibrinogenemia, lack of FXIII, von Willebrand's disease, and liver diseases. If alternative factor concentrate therapies are available, cryoprecipitate is not recommended for the treatment of hemophilia, von Willebrand's disease, deficiencies of factor XIII, or fibronectin [17].

Cryoprecipitate in the Practice of Neurosurgery and Neuro-intensive Care

Although cryoprecipitate is one of the most common blood products used in low fibrinogen levels, there is a lack of guidelines consisting of data from controlled studies on cryoprecipitate use specifically in neurosurgery and neuro-intensive care.

Postoperative coagulopathy and hemorrhage in patients undergoing neurosurgery can have devastating effects. In patients undergoing craniotomy, fibrinogen deficiency is a factor that can increase the likelihood of perioperative bleeding [46]. Low fibrinogen levels were found to be associated with an increased risk of spontaneous intracranial hemorrhage, aneurysm rupture, rebleeding, and hematoma expansion. Cryoprecipitate has been suggested solely or combined with other fibrinogen sources in the treatment of intracranial bleeding originate from thrombolytic therapy [47]. The importance of low fibrinogen level as the most common coagulation abnormality due to blood transfusions in neurosurgical procedures was highlighted. Preemptive cryoprecipitate administration was recommended for suspected dilutional coagulopathy [48]. Although fibrinogen's recommended threshold for replacement in obstetric and cardiac surgical patients is approximately 1.5–2.0 g/L, the critical threshold in neurosurgical patients has not been defined yet.

Isolated traumatic brain injury (TBI) is one of the most severe forms of trauma. Possibility of coagulopathy, including fibrinolysis and platelet activation, which can result in progressive hemorrhagic injury after TBI was reported [49]. Moreover, coagulopathy in the head-injured patients is assumed to be augmented by different chemical reactions and genomic expressions [50]. Although fibrinogen supplementation with cryoprecipitate was reported to improve clot strength, reduce blood loss, and decrease mortality in trauma patients, there is no such consensus on the clinical use of fibrinogen sources in patients with TBI [36]. However, early correction of coagulopathy and normalization of INR with procoagulant agents such as FFP, cryoprecipitate, platelets, prothrombin complex concentrates, and tranexamic acid in the setting of isolated traumatic brain injury was strongly recommended [51]. The results of two retrospective studies investigating the effectiveness of early administration of cryoprecipitate in patients with severe TBI revealed decreased rates of coagulopathy, blood transfusion requirement, and in-hospital mortality without any adverse events [52, 53].

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Clotting Factor Concentrates

Funda Arun and Oguzhan Arun

Abstract

Coagulopathy and hemorrhages can be detrimental for all organs but mainly for the brain as it is exceedingly vulnerable to tissue hypoxia and increased pressure. Perioperative intracranial bleeding can be both a cause and a consequence of neurosurgery and associated with multiple factors such as anticoagulant medications, disordered coagulation system, and features of intracranial injury. Clotting factor concentrates such as human fibrinogen concentrate and prothrombin complex concentrates have been used to replace low levels of coagulation factors in managing perioperative coagulopathy. The main features of the clinical use of clotting factor concentrates are discussed in this chapter.

Keywords

Hemostasis · Coagulation · Coagulation factor concentrate · Fibrinogen concentrate · Fibrinogen · Prothrombin complex concentrate · Transfusion

F. Arun
Selcuk University Faculty of Dentistry, Department of Pedodontics, Head of Anesthesiology Clinics, Konya, Turkey

O. Arun (✉)
Selcuk University Faculty of Medicine, Department of Anesthesiology and Reanimation, Konya, Turkey
e-mail: oguzarun@selcuk.edu.tr

Introduction

Hemostasis is a protective and life-saving mechanism consisting of four different compatible components working in a perfect design: vascular endothelium, platelets, coagulation pathway, and fibrinolysis. Hemostatic problems in the neurosurgery practice disrupting this harmony are multifactorial and attributable to brain neoplasms, surgical complexity, trauma and brain damage, concomitant hematologic diseases, anticoagulants, thrombolytic, and antiplatelet drugs. Optimal perioperative management of hemostasis is crucial to prevent adverse clinical outcomes such as massive bleeding, arteriovenous thromboembolism, and death and can only be accomplished with the cooperation of surgeons, anesthetists, intensivists, and even hematologists.

Although a reduction in the estimated number of plasma components transfused in a year was reported both in the USA and UK, plasma products, mainly fresh frozen plasma (FFP) and frozen plasma (FP24), are still the most commonly used hemostatic agents in the clinical practice [1–3]. Limited hemostatic efficacy of plasma components is also hampered by long turnaround time for clinical availability and safety concerns such as transfusion of infectious agents, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), allergic reactions, febrile reactions, hemolysis, and thrombotic events [3]. In line with the goal of

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more targeted hemostatic therapy, clinicians have a chance to access clotting (coagulation) factor concentrates (CFCs) as safer and purer alternatives to plasma components.

CFCs can be divided into two groups according to the clinical scope: used in inherited and acquired bleeding disorders such as prothrombin complex concentrates, fibrinogen concentrates, and factor VII, XI, and XIII concentrates and used in inherited and acquired thrombotic disorders such as antithrombin concentrates and factor c concentrates. General and specific features and clinical use of CFCs used in bleeding disorders, particularly in neuroscience practice except for recombinant FVIIa, are discussed in this chapter. rFVIIa is the subject of another chapter in this book.

Short History of CFCs

CFCs are produced either from human plasma by using chromatographic and other fractionation techniques or recombinant DNA technologies. The history of CFCs was started with developing the freezing-drying methods and use of plasma under battlefield conditions in the late 1930s. After the development of plasma fractionation in the early 1940s by Edwin J. Cohn, in 1964, cryoprecipitate, the precursor of factor concentrates, which contains factors VIII, von Willebrand factor (vWF), fibrinogen, fibronectin, and factor XIII was discovered by J. Pool and commercially used. Shortly after, highly concentrated lyophilized FVIII preparations were developed and used in hemophilia A's treatment at the end of the 1960s [4]. Prothrombin complex concentrates (PCC) was first described in 1968 to manage Christmas disease and Stuart-Prower deficiency and used in the treatment of hemophilia B [5]. Identifying the transmission of human immunodeficiency virus (HIV) infection to hemophiliacs by factor concentrates led to the need to develop safer products. Additional virucidal methods involving solvents and detergents and recombinant DNA technologies have been introduced since then.

Human Plasma-Derived Fibrinogen Concentrate

Background

Fibrinogen (Fb) is an acute-phase protein that is part of the coagulation cascade (factor I). It is synthesized by hepatocytes as a 340 kDa hexameric glycoprotein at a rate of 2–5 g day^{-1}. As a most abundant coagulation factor, most Fb is found in the plasma with an average concentration of 200–450 mg dL^{-1} and present in platelets, lymph nodes, and interstitial fluid [6]. The half-life is 3–5 days. It forms a clot or insoluble gel by the action of thrombin, and the function of FXIIIa stabilizes the clot. It is also necessary for platelet aggregation. The minimum plasma level for hemostatic functions is 100 mg dL^{-1} [7]. There are more than one million non-identical molecular forms of Fb in a healthy individual that can show different functions [8]. There is little information regarding its catabolism.

Fibrinogen is the only coagulation factor that is considered to be kept within a normal range for a stable clot as >90% of the coagulation factors are mapped from Fb [9]. Low blood Fb levels can be acquired or congenital due to an inherited mutation of the two genes responsible for production. Acquired hypofibrinogenemia can be caused by reduced synthesis due to liver disease, increased consumption due to tissue plasminogen activator (tPA) therapy, cancer (lymphoblastic leukemia), and sepsis with disseminated intravascular coagulation (DIC) or hemodilution due to massive transfusion. Acquired dysfibrinogenemia can be determined due to drug-induced assay interference (direct thrombin inhibitors such as dabigatran, bivalirudin, argatroban, or other thrombin inhibitors like heparin) or caused by posttranslational modification due to abnormal sialylation in liver diseases, autoantibody

formation due to an autoimmune disease, and paraneoplastic structurally abnormal Fb production [10]. Fb can drop under the critical level due to consumption before other coagulation factors reusable during activation of coagulation or bleeding [11].

Fibrinogen supplementation can be performed in three ways: infusion of fresh frozen plasma (FFP), cryoprecipitate, or fibrinogen concentrate (FC). FC is a sterile, preservative-free, lyophilized product that is a concentrated formulation of pooled plasma-derived human Fb. In the production process, albumin is added as a stabilizer after pasteurization (for viral inactivation), precipitation, and purification steps. The concentration of Fb is standardized. It can be stored at room temperature as a lyophilized powder. It can be administered in a low infusion volume after preparation with sterile water without any delay for thawing or cross-match [12]. A comparison of components used in Fb replacement is displayed in Table 1. FCs have improved safety profile, rapid onset of action, dosing flexibility, small infusion volume, and ease of administration relative to FFP and cryoprecipitate [14]. Reduced risks of TRALI, multisystem organ failure (MOF), and acute respiratory distress syndrome (ARDS) are attributed to the lack of immune-stimulating proteins in FCs.

Indications for Fibrinogen Replacement Therapy (FRT)

The most widely available FC is officially licensed for congenital Fb deficiency but not universally for acquired deficiencies. Although some of the following indications can be considered off-label, recent guidelines recommend FCs, particularly in patients with active bleeding [11, 15].

1. *Congenital Fibrinogen Deficiency*: Patients with afibrinogenemia (complete absence of Fb), hypofibrinogenemia (Fb levels <150 mg dL^{-1}), dysfibrinogenemia (abnormal Fb function), and hypodisfibrinogenemia (reduced levels of dysfunctional and antigenic Fb) have varying clinical manifestations and risks. FCs are found well-tolerated and effective as a substitution therapy according to the severity and location of the bleeding besides non-transfusional treatments such as antifibrinolytic amino acids (e.g., ε-aminocaproic acid, tranexamic acid) [14, 16].

Table 1 Comparison of properties of the products used for fibrinogen replacement [13]

	FFP/FF24 (per unit)	Cryoprecipitate (per unit)	Plasma-derived fibrinogen (per vial)
Fibrinogen content ($g/g.L^{-1}$)	0.5/~2	0.3/~15	0.9–1.3/20
Volume (mL)	250	20	50
Factor content other than fibrinogen	• All coagulation factors • vWF • Albumin	• FXIII (2.8 IU mL^{-1}) • FVIII (6.3 IU mL^{-1}) • vWF (8.0 IU mL^{-1}) • Fibronectin • Platelet microparticles	FXIII (1 IU mL^{-1})
Production procedure	• Thawing • Blood type compatibility	• Thawing • Blood type compatibility	Dilution with sterile water
Storage	Frozen (≤−20 °C)	Frozen (≤−20 °C)	At room temperature (<25 °C)
Shelf life (months)	12	12	30
Pathogen reduction	Donor testing	Donor testing	• Cryoprecipitation • Heat treatment • Glycin precipitation • Lyophilization

FFP fresh-frozen plasma, *FP24* plasma frozen with 24 h, *vWF* von Willebrand factor, *IU* international unit of activity

2. *Massive Trauma*: Coagulopathy is one of the members of the "lethal triad" with hypothermia and acidosis, and it is one of the significant causes of mortality in massive trauma [17]. Blood loss and consumption of coagulation factors, including Fb (due to excessive thrombin generation), are the most likely coagulopathy reasons [18]. Fb concentrations are recommended to be maintained >150–200 mg dL^{-1} in patients with severe trauma [11]. Recent publications reporting the effectiveness of FC in Fb replacement in severe trauma patients are notable [18–20].
3. *Disseminated Intravascular Coagulation*: Clinicians should focus on the underlying causes of coagulopathy in the treatment of DIC. The decision of blood component therapy should be based on laboratory abnormalities and clinical factors such as active bleeding or invasive procedure requirement. The administration of FC is recommended in actively bleeding patients with persisting severe hypofibrinogenemia (<150 mg dL^{-1}) after FFP replacement [21]. Deposit of fibrin and thrombi in the microcirculation due to accelerated fibrin formation has been proposed to induce organ failure during FRT in DIC [12].
4. *Liver Diseases/Liver Surgery and Transplantation*: Although plasma Fb usually remains normal or even increased in chronic hepatitis, cholestatic jaundice, and hepatocellular carcinoma, dysfibrinogenemia can occur due to impaired functions. When the disease progresses, impaired synthesis causes quantitative problems [22]. Increased bleeding can occur due to various coagulation abnormalities in different phases of liver transplantation. FRT has been reported to optimize coagulation, reduce perioperative bleeding, significantly reduce transfusion requirement, and compensate for defects in fibrin cross polymerization and thrombocytopenia [23].
5. *Cardiovascular and Vascular Surgery*: Multiple factors are associated with acquired coagulopathy and excessive bleeding in cardiac surgery. Fb deficiency attributes are blood loss, hemodilution, platelet activation by cardiopulmonary bypass, a large wound area for clot formation, hypothermia, and acidosis [24]. FRT is strongly recommended in patients with continuous, significant, nonsurgical, and microvascular bleeding with deficient plasma Fb levels. If there are borderline plasma Fb levels under the same circumstances, the decision of FRT is left to the clinicians [25].
6. *Critical Obstetric Hemorrhage (COH)*: COH is still one of the leading causes of maternal death. Consumption and dilution are the two exact mechanisms of coagulopathy seen in COH. Consuming of Fb due to tissue factor-based exogenous coagulation factor activation leads to decreased blood levels [26]. Fb concentration can be used as an indicator of clinical severity, and early Fb supplementation is reported as critical to avoid coagulopathy in COH [27].

Assessment and Monitoring of Fibrinogen Levels

Plasma Fb level can be measured with various tests and assays, including Clauss assays, PT-derived tests, clottable protein assays, immunological assays, and gravimetric assays. Clauss method is quantitative, clot based, and functional and recommended for general use in clinical laboratories as a most reliable method [28]. This method is based on a comparison of standard plasma with citrated plasma in which thrombin is added and measures Fb's ability to form a fibrin clot.

Point of care (POC) testing with viscoelastic tests such as rotational thromboelastometry (ROTEM®), thrombelastography (TEG®), and viscoelastic analyzers ClotPro® and Sonoclot® is also available. Cytochalasin D and abciximab (GpIIbIIIa inhibitor) are used to inhibit platelet

contribution to the fibrin in fibrin-based thromboelastometry assay (FibTEM) for ROTEM® and functional Fb assay for TEG®, respectively. Viscoelastic methods measure clot formation and strength in the whole blood in real-time. Further, they give additional information regarding delayed coagulation initiation, diminished Fb level, an increased fibrinolytic activity, and platelet level in whole blood [29]. ROTEM® and TEG® parameters are comparable but not interchangeable, and a high degree of correlation was reported between parameters [30].

Critical Laboratory Threshold Level and Dosing

There is no consensus statement on the critical plasma Fb threshold level for replacement. 100–150 mg dL^{-1}, 400 mg dL^{-1}, 380 mg dL^{-1} are recommended thresholds for severe bleeding, post-partum bleeding, and excessive bleeding during cardiac surgery, respectively [12].

The initial dose of FC depends on the rate and amount of bleeding and initial plasma Fb level. Different dosage calculation methods were suggested, and POC tests have been the subject of various studies in determining the dose of Fb. Some formulations include:

1. If viscoelastic tests are not available:
   [Target fibrinogen (mg dL^{-1}) − measured fibrinogen (mg dL^{-1})]/correction factor (mg dL^{-1} per mg/kg body weight)
   (Correction factor: Different in various products, usually 1.7 or 1.8)
2. If viscoelastic tests are available:
   FC to be administered (g) = [target – actual A5-FIBTEM (mm)] × [body weight (kg)/70] × 0.5 g/mm [7]
   1 g of fibrinogen administration is expected to increase plasma fibrinogen level by 250–280 mg dL^{-1}. The required average fibrinogen dosage is given as 7.6 mg kg^{-1} to increase 1 mm in A10-FIBTEM in adult cardiac surgical patients [31].

Safety and Tolerability

Although FCs have a good safety profile, documented adverse events are as follows:

1. *Allergic-anaphylactic reactions*: The range of reactions varies between mild hypersensitivity to anaphylactic reactions and shock.
2. *Thromboembolic complications*: Myocardial infarction, pulmonary embolism, deep-vein thrombosis, arterial thrombosis, and cerebral infarction are reported thromboembolic adverse events in the literature. Administering excessive Fb has been suggested to increase the risk of micro thrombogenicity.
3. *Generalized reactions*: Include symptoms such as chills, fever, nausea, vomiting, and headache.

FCs are contraindicated in patients having immediate hypersensitivity or anaphylaxis to Fb concentrate or its components.

Fibrinogen in Traumatic Brain Injury

Coagulopathy after traumatic brain injury (TBI) can occur in two different ways depending on the injury complexity, severity, and elapsing time: hypocoagulation associated with bleeding and, therefore, loss of coagulation factors such as Fb, thrombin, and vWF initially after severe trauma and hypercoagulation due to inflammation-mediated increase in plasma Fb after mild trauma and 2–3 days later from the beginning. Increased plasma Fb can be associated with increased cerebrovascular permeability and vascular remodeling in brain vasculature. Furthermore, increased Fb causes hyper-viscosity and increased shear stress leading to activation of endothelial cells resulting in enhanced microvascular permeability [32].

Isolated severe TBI is also associated with low Fb levels, abnormal Fb functionality, and delayed clot formation. When TBI patients were evaluated with TEG, an abnormal alpha angle and

hypofibrinogenemia can be determined [33]. In a single-center analysis, Fb concentrations were found <200 mg dL^{-1} in 38.6% of 2570 TBI patients, and maintaining Fb levels between 250 and 300 mg dL^{-1} was suggested to improve outcomes [34]. However, there is a lack of randomized controlled trials and guidelines specifically recommending FCs in TBI management.

Prothrombin Factor Concentrates

Background

Prothrombin factor concentrates, also known as factor IX complex, are purified, preservative-free, lyophilized human plasma products containing vitamin K-dependent coagulation factors. According to the coagulation factor content, there are two variants both including FII, FIX, FX. 4-factor (4F) PCC, unlike 3-factor (3F) PCC, contains therapeutic amounts of FVII. Some PCCs also contain protein C, S, and Z in addition to heparin and antithrombin. There is also another form of 4F PCC called activated PCC (aPCC), which contains mostly activated factor VII along with mainly non-activated factors II, IX, and X.

PCCs are eluted from cryoprecipitate supernatant obtained from large plasma pools by ion-exchange chromatography after removal of factor XI. Strong ion exchangers are used for 4F-PCCs, while weak ion exchangers are preferred for 3F-PCCs. Adding antithrombin and heparin and keeping the pH <7.0 are the main precautions for the inactivation of clotting factors during the process. Also, there is a viral inactivation step (for lipid-envelope viruses) in which solvents, detergents, pasteurization, nanofiltration, and moist or dry heat are used [35].

Mandatory content features, activity levels, and potencies of PCC components were defined to guarantee a standard efficacy and quality level [36]. PCCs are standardized on their FIX content expressed in international units (IU), which shows a clotting factor's activity degree in 1 mL of plasma. A PCC's estimated potency should be between 80 and 125% of the given FIX potency. FII, FVII, and FX activities should not exceed the FIX potency more than 20%, 40%, and 20%, respectively. Protein c and s activities should be at least 40% that of FIX.

The PCCs have potential advantages over FFP, which is the only approved treatment for replacing clotting factors in bleeding patients. These include increased concentration of clotting factors leading to increased effectiveness in the reversal of coagulopathy, faster and easier administration, reduced fluid volume (safer in patients with cardiac and renal impairment), decreased incidence of infusion reactions, and reduced incidence of immunomodulatory side effects such as TRALI [37].

4F and 3F PCCs have been compared regarding effectiveness, safety, and clinical outcomes in several prospective and retrospective studies. 4F-PCCs were found more effective than 3F-PCCs in decreasing INR to a desired critical level, but a similar superiority was not reported regarding secondary clinical outcomes and in-hospital mortality rates [38]. 4F-PCCs are recommended rather than 3F-PCCs in patients with life-threatening bleeding such as intracranial hemorrhage (ICH) because of the hemostatic benefits of factor VII. If 4F-PCCs are not available, 3F-PCC is considered as an alternative. The addition of FFP to PCC has been found considerable only in patients who do not have adequate INR reversal following PCC administration [39].

Indications

1. *Urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA) therapy in adult patients with acute major bleeding*: This is the only FDA-approved indication of 4F-PCC. Warfarin is still the most commonly used VKA, particularly in patients with mechanical heart valves and hemodialysis requirements. Warfarin reduces the level of FIX, FVII, FII, and FX at around 40–50%, 30%, 20%, and 10% of normal levels, respectively [40]. Although FFP and vitamin K are the main traditional options in the clinical practice, PCCs are recommended for emergent warfarin reversal due to their capability of rapidly lowering INR [41].

VKAs are implicated in approximately 12–14% of all ICHs. Although ICH risk doubles with one increase in INR, most of VKA-related ICHs occur within the normal range [42]. In the first step of VKA-induced ICH management, discontinuing VKAs is recommended, except in neurologically intact patients with small hematomas and mild elevated INR in whom conservative management strategy is also considered reasonable. Abrupt discontinuation of warfarin is not associated with increased thromboembolic complications and is found safe. In the second step, an urgent reversal of VKA therapy is strongly recommended except in patients with cerebral venous thrombosis, symptomatic or life-threatening thrombosis, ischemia, HIT, and DIC in whom an assessment of risks and benefits is crucial. Initial reversal with PCCs alone (in weight- and INR-based dosing algorithm) rather than in combination with other therapies such as FFP and rFVIIa is suggested. INR testing, initially in the 15–60 min after PCC administration and then serially every 6–8 h for the next 24–48 h, is essential for the guidance of treatment. If INR is ≥1.4 after 48 h, FFP can be used. rFVIIa is not recommended as a sole or in combination with other drugs in VKA-induced ICH treatment. If PCCs are not available or contraindicated, FFP (10–15 ml.kg^{-1}) is recommended as an alternative treatment option. One dose of vitamin K 10 mg administration alone or concomitantly with other reversal agents is recommended and will ensure more effective INR decreasing. Another 10 mg of vitamin K should be considered if the INR is ≥1.4 after 48 h of the reversal agent administration [39].

2. *Reversal of direct oral anticoagulants (DOAC)-induced anticoagulation with major bleeding or requiring major surgery*: FIIa and FXa are the main targets of DOACs, also known as non-vitamin K oral anticoagulants, which have been mainly used for the treatment of venous thromboembolism and stroke prevention in patients with non-valvular atrial fibrillation [43]. Direct thrombin inhibitors (DTIs) such as dabigatran, bivalirudin, desirudin, argatroban, and lepirudin and direct FXa inhibitors such as rivaroxaban, apixaban, and edoxaban are a new category of anticoagulants with prominent advantages over VKAs including fixed dosing, rapid onset of action, short half-lives, more predictable pharmacokinetics, and relatively low drug interaction profile [44]. Although bleeding is generally reduced when compared with VKAs, DOACs may cause major intracranial and gastrointestinal bleeding.

In the case of an ICH, discontinuing the drug is the first step of reversing DOACs. Although this may be sufficient in patients with minor hemorrhage due to the relatively short half-life, clinicians should question the timing of the last dosage and possible drug interactions cautiously. Bleeding parameters should be the primary guidance for pharmacological reversal instead of laboratory testing.

In the management of dabigatran-related ICH, administering 5 g idarucizumab (in two divided doses) is recommended. Idarucizumab is a monoclonal antibody fragment that binds free and thrombin-bound dabigatran and neutralizes its activity [45]. If idarucizumab is not available or the hemorrhage is associated with a DTI other than dabigatran, 50 U kg^{-1} 4F-PCC or 50 U kg^{-1} aPCC are recommended. rFVIIa or FFP is not recommended in the management of DOAC-related ICH [39].

In the management of FXa-related ICH, 50 U kg^{-1} 4F-PCC or 50 U kg^{-1} aPCC are recommended. rFVIIa usage has not been suggested over PCCs because of a higher risk of thrombotic complications [39]. Andexanet alfa (AA) is a modified recombinant derivative of FXa, which binds and reverses FXa inhibitors' effects, various forms of heparin, and fondaparinux. FDA approved AA for the reversal of apixaban and rivaroxaban in patients with life-threatening and uncontrolled bleeding. A recent study in which AA was compared with 4F-PCC for the reversal of FXa inhibitors in adult patients with ICH reported no difference regarding neuroimaging stability, functional outcome, and thrombotic events [46].

3. *Treatment or prophylaxis of bleeding in congenital deficiency of any vitamin K-dependent coagulation factors*: PCCs are not indicated for the treatment of hemophilia B, congenital factor VII, and protein C deficiencies if specific clotting factor concentrates are available. Congenital prothrombin and FX deficiencies are the only congenital disorders treated with PCCs if there is manifest bleeding [35]. The FDA approves aPCC to treat bleeding episodes in hemophiliacs with alloantibody inhibitors to individual factor concentrates [47].
4. *To decrease bleeding in the perioperative setting in patients other than taking VKA and oral anticoagulants*: PCC administration has become a part of the multimodal approach, including tranexamic acid and FCs with the help of POC monitoring in the management of perioperative bleeding. PCCs can be considered in bleeding patients if there is a prolongation in prothrombin time or EXTEM clotting time [48]. Using PCCs and other factor concentrates in this setting will serve to minimize allogeneic blood product consumption. However, only a few randomized controlled trials support the perioperative PCC use in patients other than taking VKA and oral anticoagulants.
5. *Trauma-related bleeding with massive transfusion*: Trauma patients can present with acquired states of impaired thrombin generation. Current treatment options of trauma-induced coagulopathy (TIC) are tranexamic acid (TXA), FFP, cryoprecipitate, and CFCs, including PCCs and FCs. Reduced thrombin generation has been considered as a mortality increasing factor in the trauma setting. PCCs are increasingly attracting clinicians' attention for the restoration of thrombin generation in the trauma population, particularly in the elderly. In the bleeding trauma patient, the emergency reversal of vitamin K-dependent OACs with early use of PCCs has been recommended by European guidelines [11].
6. *Coagulopathy in liver disease*: The liver produces all clotting factors except for vWF and FVIII. There is a "rebalanced hemostasis" situation characterized by a balance between procoagulants and anticoagulants in severe liver disease [49]. The deterioration in this balance can cause a complex coagulopathy and major bleeding. Although some retrospective studies and case reports advocate the effectiveness of PCCs in reducing INR in patients with cirrhosis and undergoing liver transplantation, clinical benefits in acute bleeding have not been well defined yet.

Monitoring

Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (PTT), and fibrinogen level are the optional coagulation tests in the monitoring of PCC activity. While PT and INR are related extrinsic pathway and detect the time required for clot formation, PTT determines the rate of intrinsic pathway activation. Heparin and fibrinogen cleavage products influence PT, and PT and INR can be prolonged due to hypofibrinogenemia (<100 mg dL^{-1}) [50]. INR correlates well with the level of suppression of clot formation, and it is widely used as a monitoring tool, particularly in VKA therapy, due to the availability and lack of a better option. However, there is limited evidence to guide PCC therapy with INR alone in bleeding patients [51].

Recently, modern viscoelastic POC testing has shown promise in perioperative PCC therapy. Prolonged R time (clot formation time), prolonged K time (occurrence of clot firmness), and reduced alpha angle (kinetics in clot formation) in TEG® and prolonged clotting time or reduced alpha angle in ROTEM® assays are considered as the indications of PCCs [52]. EXTEM test, one of ROTEM® assays, is a screening test for extrinsic pathway and not influenced by heparin, unlike ITEM. EXTEM has been found more sensitive to FII, FIX, FX, and FVII and reported as a potential monitoring tool for 4F-PCC [53].

Dosing and Administration

There is no standard dosing schedule of PCCs, and dosage should be individualized based on

severity, extent, location of bleeding, patient clinical status, actual body weight, and pre-treatment INR. Dose calculation is made according to the FIX content that is varying among products. FDA recommended a dosing guideline for a 4F-PCC in which doses range from 25 to 50 units of factor IX per kg and are capped at a maximum bodyweight of 100 kg. Administering vitamin K concurrently with PCC was also emphasized to maintain vitamin K-dependent coagulation factor levels after the effect of 4F-PCC diminished. Repeat dosing is not recommended unless there is a life-threatening bleeding situation and a specific antidote is available. In this case, administering 50 units kg^{-1} with an additional 25 units kg^{-1} is recommended. Clinical responses and any adverse event during and after the treatment should be monitored. Rapid normalization of vitamin K-dependent coagulation factors within 30 min is expected according to the pharmacological data.

A lower fix-dosing strategy concept for VKA reversal can be seen in the literature. This strategy is assumed to have several advantages, such as avoiding treatment delays without dose calculations, cost savings, and reduced adverse events risk [54]. With this strategy, baseline INR values and body weight are not used in the protocols. There is a need for more definitive and reliable data from extensive, randomized studies on this strategy.

Safety and Tolerability

Serious adverse events associated with PCCs are allergic reactions, heparin-induced thrombocytopenia (if the preparation contains heparin), and thromboembolic complications such as pulmonary embolism, stroke, myocardial infarction, DIC, and deep venous thrombosis [55]. Recent commercial forms of PCCs include coagulation inhibitors (heparin, protein C and S, and antithrombin) and improved balance of reduced activated coagulation factor content to decrease the incidence of thromboembolic complications, which was found 9.2% in a recent retrospective observational study. Younger age, larger doses of 4F-PCC, longer hospital length of stay, and having risk factors for hyper-coagulopathy or taking anticoagulation therapy are reported as prominent risk factors for thromboembolic complications [56]. Accumulation of FII is significant for thromboembolic complications because of its longer half-life (approximately 60 h). Co-administration of vitamin K with PCCs may serve as a diminishing factor for thrombotic risk by reducing the need for repetitive administration of PCCs. Monitoring antithrombin activity and co-administration of antithrombin concentrate are proposed measures to avoid thrombotic complications in patients with severe liver diseases [57].

PCCs are contraindicated in anaphylactic or severe systemic reaction to PCC or any of its components, DIC, HIT, prior thromboembolic events such as cerebral vascular accident, transient ischemic attack, unstable angina pectoris, severe peripheral vascular disease, and MI within the last 3 months [58].

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The Use of Activated Recombinant Factor VII in Neurosurgery

A. Y. Lubnin

Abstract

At present time, recombinant activated factor VII is available as new highly effective hemostatic drug. It was originally approved for patients with hemophilia. However, today it is widely applied for various coagulopathies including those caused by severe blood loss and trauma. rFVIIa makes it possible to quickly stop bleeding due to unique mechanism of action when conventional methods are ineffective. There are special advantages of using rFVIIa in neurosurgery including patients with severe CCT, spontaneous ICH, spinal pathology, and brain tumors excisions. This is especially actual for children due to earlier severe hemostatic disorders. Correction of hypofibrinogenemia, thrombocytopenia, hypocalcemia, acidosis, and hypothermia is necessary to achieve effect of rFVIIa. Routine application of the drug is not advisable because of high cost. However, rFVIIa may be salutary in situation close to dead-end. Local utilization of rFVII may be helpful in some situations of severe bleeding in neurosurgical patients.

Keywords

Recombinant activated factor VII · Mechanism of action · Clinical situations Neurosurgery · Local utilization

Introduction

Hypocoagulation is an extremely undesirable phenomenon for any surgical procedure. It is associated with advanced intraoperative blood loss, difficulties of surgery per se, less radical surgery, and other problems [1–3]. Hypocoagulation is especially dangerous in neurosurgical practice due to impaired control of intraoperative bleeding and especially risk of postoperative hematoma ([4–7]). Currently, there are various pharmacological agents for correction of hypocoagulation. There are fresh frozen plasma (FFP), cryoprecipitate, fibrinogen, inhibitors of fibrinolysis, and concentrates of various hemostatic factors [1, 2, 8–14]. Their effectiveness is not boundless. Moreover, administration of some medications may be followed by certain complications.

At the end of the last century, principally new drug was synthesized for hypocoagulation correction—activated recombinant factor VII (rFVIIa) [15, 16].

The use of this drug in neurosurgery is reviewed in this chapter.

A. Y. Lubnin (✉)
Burdenko National Neurosurgical Center, Moscow, Russia
e-mail: lubnin@nsi.ru

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History

Protein molecule called factor VII of the hemostasis system is a vitamin-K-dependent serine protease. Activated form of the enzyme occurs after limited proteolysis. It is currently known that this polypeptide is synthesized in the liver and can exist in two forms—in-active and activated. Normally, only 1% of factor VII is in activated form and this it is quite sufficient for normal hemostasis [16]. In 1983, for the first time small amount of activated factor VII was obtained from human plasma to stop bleeding in two patients with inhibitory form of hemophilia A [17]. Positive clinical effect was achieved but it was clear that quantity of the drug sufficient for clinical purposes cannot be obtained by this way. Genetic-engineering technologies were useful to radically change the situation. They were first used by specialists of the Danish pharmaceutical company Novo Nordisk in the late 1980s [15, 16]. The molecule synthesized underwent all stages of preclinical and clinical trials and was approved by the US Food and Drug Administration and then the European Medical Agency for clinical use in patients with hemophilia, congenital deficiency of factor VII, and later in patients with certain thrombocytopathies (Glanzmann's thrombasthenia and some others) [15, 16]. Commercial name of rFVIIa medicine was NovoSeven. In 2009, original molecule of rFVIIa bio-analog was synthesized in AO "Generium" in Russia (commercial name Coagil-VII). The drug is currently approved in Russia for patients with hemophilia [18–21]. There are currently no other preparations of activated rFVII in the world.

Mechanism of action

The mechanism of action of rFVIIa is as follows. Ependymal cells of the vascular wall contact with plasma at the site of injury. This interaction results in formation complex of tissue factor and complex—factor VII/VIIa. This factor activates factors X and IX, while factor Xa combined with factor Va converts small initial amount of prothrombin into thrombin. Small amount of locally-formed thrombin facilitates activation of platelets at the site of vascular wall injury. Local activation of thrombocytes is accompanied by the so-called thrombin burst—massive generation of thrombin with subsequent transformation of fibrinogen into fibrin. Eventually, dense fibrin plug occurred. It should be noted that the density of this plug is higher than usual. Apparently, there are some other mechanisms besides above-described [15, 16].

There are several important findings considering mechanism of action.

1. Effect of rFVIIa is realized only within vascular wall damage. This is an extremely positive moment since it makes it possible to realize local hemostatic effect without undesirable systemic manifestations. However, there is certain risk of thrombotic complications in areas of previous vascular injury (for example, atherosclerotic plaques) where the effect of the drug may be also realized.
2. The effect of rFVIIa does not develop on its own but only in combination with other hemostatic factors. These are, first of all, fibrinogen and platelets. Clinically, this is also extremely important. Concentration of rFVIIa after intravenous injection is much greater that physiological but sufficient hemostatic effect may be absent due to lack of other necessary components. Hypofibrinogenemia and thrombocytopenia are typical for severe blood loss. This aspect is clearly emphasized in the instructions for both drugs. Normal level of fibrinogen and platelets, control of acidosis and hypocalcemia should be considered prior to rFVIIa administration in order to achieve effective hemostasis [15, 16].
3. Clearance of rFVIIa is 35 mL/kg/min that means reduction of concentration by 50% in 2 h after injection and dictates the need for re-administration to avoid the risk of recurrent bleeding [15].

Clinical Application of rFVIIa

It should be immediately said that there are currently two aspects of factor VII administration: on label (according to the instruction) and off label (outside the instruction). The drug is approved for hemophilia, hypoproconvertinemia, and thrombo-

cytopathy while in other situations it is used outside the instructions. It is surprising that on label administration is only a very small part of total world consumption of the drug (due to relatively small number of such patients) [22, 23]. In this respect, data of A. Logan et al. [22] are very demonstrative. The authors reported four-fold increase of rFVIIa administration in patients with hemophilia in a period of 2000–2008 and 140-fold augmentation of off-label application for the same period! Administration outside the instruction was noted in 97% of cases in US clinics for this period: mainly in cardiovascular surgery, injuries, and intracranial hemorrhage, total use of rFVIIa for cerebral pathology (neurosurgery, craniocerebral trauma (CCT), intracranial hemorrhage) exceeded its use even in cardiovascular surgery [22].

Some reviews and meta-analyses are devoted to off-label administration of rFVIIa [24–31]. They cover almost all surgical areas: cardiovascular, abdominal, neurosurgery, trauma, operative urology, obstetrics, and gynecology. The main indication is severe intraoperative blood loss when surgical hemostasis is ineffective.

However, let us return to *neurosurgery*. The only onlabel indication for rFVIIa in neurosurgery is neurosurgical interventions in patients with hemophilia (inhibitory forms first of all), thrombocytopathy, and congenital deficiency of factor VII. Fortunately, these difficult clinical situations are extremely rare. Nevertheless, there are certain reports devoted to this issue [32–38] which confirm favorable postoperative outcomes in patients with hematologic diseases. However, adequate hemostatic therapy and thoughtful perioperative management are mandatory in these cases to avoid major complications.

Off-label administration is much more difficult.

Let us call the indications for such application:

- CCT (especially penetrating) in patients with intact or impaired hemostasis;
- ICH on the background of intact or impaired hemostasis;
- neurosurgery of neoplasms complicated by massive intraoperative blood loss in adults and especially in children;
- spinal neurosurgery complicated by severe intraoperative blood loss.

Another possible indication is aneurysmal SAH. However, these data are rather negative and therefore inclusion of this pathology is undesirable (see below).

CCT

Patients with CCT should be considered as the main contingent in overall number of neurosurgical patients both in Russia and in the world in view of prevalence and social significance of CCT. Even isolated CCT is often followed by significant systemic and cerebral hemostatic disturbances in acute period despite advanced blood loss is absent as adverse concomitant factor of poly trauma [39, 40]. Incidence of these disorders is estimated from 15 to 100% by different authors that allows to consider these disturbances as additional secondary factor of cerebral damage [39, 41, 42]. This secondary injury is realized through secondary hemorrhage into affected cerebral areas with or without subsequent hematoma formation [39, 41, 42]. Recent meta-analysis convincingly confirmed the role of systemic post-traumatic coagulopathy in progression of hemorrhagic damage [43].

J. Zhang et al. [44] unambiguously confirmed positive effect of rFVIIa in experimental CCE on pigs. There was less area of post-traumatic brain injury within 3 days after trauma and no additional clots in cerebral capillaries. Data of microscopic examination of hippocampal neurons were absolutely surprising: alive to dead neurons ratio was significantly higher in rFVIIa group that, in the authors' opinion, convincingly demonstrates certain cerebroprotective effect of rFVIIa. Q. Yuan et al. reported more precise data about protective effect of rFVIIa in experimental CCT [45]. Protective effect of rFVIIa in CCT is realized through formation of tissue factor com-

plex—activated factor VII and factor Xa that stops progression of hemorrhage in brain tissue.

Two previously reported trials convincingly demonstrated positive effect of single intravenous injection of rFVIIa 40–90 μg/kg in adults and children with CCT. Normalization of hemostasis was achieved within 20 min after administration in all cases [46, 47]. Meta-analysis recently published of two randomized controlled trials (RCTs) confirmed that rFVIIa administration is followed by reduced 30-day mortality and decreased hemorrhagic component of cerebral injury (according to CT-data) in patients with severe CCT [48]. Later, Y. Qiang et al. [49] showed that single use of rFVIIa even in small doses (20 μg/kg) is associated with positive cerebral and systemic effect: faster normalization of hemostatic system, less area of cerebral damage due to reduced hemorrhagic component of traumatic injury, and consequently rarer need for neurosurgical intervention. Incidence of thromboembolic complications was similar in both groups while reduced mortality was estimated as a tendency.

Special and frequent clinical situation is CCT in patients taking constantly anticoagulants or antiplatelet medicines (warfarin or its analogs, new oral anticoagulants, clopidogrel, and aspirin) [50, 51]. Enhanced normalization of hemostatic system is desirable in these patients even if emergency neurosurgery is not required. So, the role of rFVIIa in this situation is seen very important or leading. Thus, D. Nishijima et al. [50] reported more favorable outcomes after standard doses of rFVIIa (90 μg/kg) alone compared with conventional approach to INR normalization (<1.2) including the use of vitamin K combined with FFP transfusion and fibrinolysis inhibitors injection. Normal INR was achieved within 1 h.

Intracerebral Hemorrhage (ICH)

ICH is still an important medical and social problem and it is likely to be the same in the future. Spontaneous ICHs occur in 10–15% (there are two-fold higher values (20–30%) in the Asian region due to not completely understandable reasons) [52–55] and are accompanied by high (up to 50%) mortality and even higher percentage of disability (up to 80%) [52, 53]. Spontaneous ICHs develop in intact (hypertension, amyloid angiopathy in the elderly, use of cocaine, etc.) or impaired hemostasis (congenital or drug-induced coagulopathies) [52, 54, 56–59]. There are narrow indications for prolonged neurosurgical interventions aimed at eliminating the consequences of ICHs according to various cooperative studies (for example, STICH [60]). At present time, medication or minimally invasive procedures are predominantly used in these patients [52, 54, 55, 57, 61–64]. One of the main factors of progressive deterioration in these patients is secondary augmentation of ICH volume. The last is observed in at least 30% of patients [52, 55, 57, 65, 66]. It would seem to be that large amount of thrombin within cerebral hemorrhage area makes it inappropriate to use hemostatic therapy especially rFVIIa administration [67]. However, it was shown that hyperactivation of fibrinolytic system within few hours after hemorrhage is followed by enlarged hemorrhage zone. So, rFVIIa application is absolutely justified in this situation [68]. Some trials found that early (within 4 h after ICH) administration of rFVIIa is useful to avoid further enlargement of hemorrhagic area. Moreover, emergency neurosurgical intervention was not required in some cases due to reduced volume of ICH after rFVIIa administration [52, 55, 65, 69]. rFVIIa may be especially advisable for severe ICH involving cerebral ventricles to reduce area of secondary hemorrhagic injury [66, 70]. This information follows from case reports and analysis of several samples. However, meta-analysis of RCTs revealed similar 30-day mortality and 90-day disability in control and main groups. Moreover, rFVIIa administration was followed by greater incidence of arterial thrombotic complications (from 7 to 13%) especially in patients over 70 years old [65]. RCTs data contradicting real clinical practice are always questionable regarding correctness of RCT design. Certain methodological errors may be suspected in this case. These findings are confirmed by the trial of S. Mayer et al. [71]. The authors analyzed the

outcomes in two groups of ICH patients (it was applied Factor Seven for Acute Stroke database which confirmed similar results in both groups). However, the authors excluded critically ill patients (atonic coma), those over 70 years old, and patients with baseline volume of hematoma over 60 mL. This approach was followed by significant improvement of the outcomes in group of rFVIIa administration.

The use of rFVIIa in patients with ICH and congenital hemostatic disorders is able to normalize blood clotting and to achieve positive clinical effect [56, 59]. Effect of rFVIIa was compared with traditional therapy including vitamin K (Konakion, Roche), FFP and hemostatic factors concentrate in case of ICH and drug-induced hypocoagulation (warfarin and clopidogrel). In rFVIIa group normal hemostasis (INR <1.2 in case of warfarin intake) was achieved within 1 h even without the use of traditional therapy [59, 69, 72–74].

Aneurysmal SAH

Literature data devoted to this issue is rather limited. The idea of very expensive therapy with rFVIIa to prevent recurrent hemorrhage in acute period of SAH is questionable per se. Nevertheless, J. Pickard et al. [75] used following scheme in 15 patients with aneurysmal SAH: initial bolus 80 μg/kg followed by prolonged infusion 3.5 μg/kg/h. The study was discontinued prematurely due to severe thrombotic complication: MCA thrombosis contralateral to aneurysm occurred in one patient.

Neuro-Oncological Interventions Complicated by Severe Intraoperative Blood Loss in Adults and Children

Initial work in this field is case report described by R. Gerlach et al. in 2002 [76]. Severe bleeding occurred in an 64-year-old patient during surgery for recurrence of giant basal hemangiopericytoma involving oropharynx and one of the internal carotid arteries. The authors do not point overall blood loss, but volume of transfusion is impressive: 39 packed red blood cells, 29 doses of platelets concentrate, 29 doses of FFP, antithrombin 5000 units, and prothrombin complex concentrate 2400 units. Nevertheless, all these measures were ineffective. Therefore, the authors used rFVIIa 120 μg/kg 2 times with an interval of 2 h. Effective hemostasis was obtained within 10 min after the first injection! So, the authors concluded that rFVIIa is able to stop the bleeding when conventional approaches are useless.

Several subsequent reports confirmed efficacy of rFVIIa for severe intraoperative blood loss in neurosurgical patients with different tumors [77–81]. These conclusions are true for adults and children. However, this issue is especially important for young children due to small circulating blood volume and consequent rapid decompensation of hemostatic system in case of advanced intraoperative blood loss [80–84].

Spinal Neurosurgery

Incidence of spinal neurosurgical interventions in the world has increased by 220% over the last 15 years [85]. Spinal neurosurgery is the second after CCT surgery both in Russia and in the world. Blood loss is still one of the key problems in spinal neurosurgery. Thus, combined anterior and posterior approaches as well as surgery for primary and metastatic tumors like a “hourglass” are followed by mean blood loss near 6–10 L [85]. Several reports demonstrated that rFVIIa administration during spinal procedures reliably reduces intraoperative blood loss (by 54–86%) and accordingly volume of blood products for transfusion (by 81–95%) [86]. So, rFVIIa is currently absolutely a necessary component in spinal neurosurgery complicated by advanced intraoperative blood loss. It is especially true if other methods are ineffective to achieve hemostasis [85, 86].

Complications

There are certain shortcomings of rFVIIa like in any drug. Thrombotic events are primarily considered due to “thrombin explosion” within the

area of vascular wall damage as the main effect of rFVIIa [87, 88]. Analysis confirmed that rFVIIa administration is associated with advanced risk of thrombotic complications in patients outside the situation of severe blood loss and hypocoagulation (CCT, ICH). Incidence of arterial (not venous) thromboses increases while the main contingent is patients over 70 years old [87–89]. Arterial thrombotic complications in advanced age patients are fully understandable due to high probability of atherosclerotic lesion of coronary and cerebral vessels and effect of rFVIIa only within injury of vascular wall. Perhaps, it is reasonable to use mild-to-moderate doses of rFVIIa in patients with initially intact hemostasis, for example, in case of ICH. In our opinion, no thrombotic complications on the background of de novo hypocoagulation (for example, severe intraoperative blood loss followed by coagulopathy) is clinically important fact. Children are also outside the risk group of possible thrombotic complications due to quite understandable reasons.

Causes of Possible Inefficiency

rFVIIa is just one of the factors of complex hemostatic system and other factors are required to realize adequate effect. It has been currently proved that preliminary correction of reduced contents of platelets, fibrinogen, calcium, management of acidosis and hypothermia are necessary for effective hemostatic effect of the drug [16, 89].

Cost

This is probably one of the most important problems of wide clinical application of rFVIIa. Cost is quite high but not huge: 2 USD per 1 μg. The cost of Danish and Russian analogs is similar. So, cost of treatment near $4200 may be supposed for patient weighing 70 kg and even low doses of the drug (30 μg/kg). Of course, these values are considerable [16].

Local Utilization of rFVIIa in Neurosurgery

In general, idea of local utilization of systemic hemostatic agents in surgery is very attractive [90–93]. It is obvious that it is quite difficult to reach high concentration of active procoagulants in site of hemorrhage after they i/v injection compared to its local administration. That is correct to rFVIIa based on different clinical situations.

1. In experimental setting in mice investigators from Karolinska University show that best hemostatic effect was achieved in group of animals with local application of rFVIIa [94].
2. Various clinical obstetric situations are often complicated by massive hemorrhage. The one of "classic" situations is "placenta previa" in which after placenta removal achieve adequate hemostasis is usually quite difficult. In 2017 in American Journal of Obstetrics and Gynecology was published series of 5 cases (initially 7 but 2 patients were excluded on a reason incorrect protocol) of "placenta previa" with local utilization or rFVIIa on surgical swabs. Adequate hemostatic effect was received in all cases [95].
3. Diffuse alveolar bleeding in patients with autoimmune disease is another instance of difficult control bleeding. In series of clinical reports and short review described very good results from local utilization of rFVIIa for stopping alveolar bleeding [96–100].
4. In our praxis we have now very restricted experience for local utilization of rFVIIa for stopping hemorrhage in neurosurgical patient with brain tumors [101]. This is probably first experience in this direction.

Conclusion

At present time, recombinant activated factor VII is available as new highly effective hemostatic drug. It was originally approved for patients with hemophilia. However, the medicine is widely applied for various coagulopathies including

those caused by severe blood loss and trauma. rFVIIa makes it possible to quickly stop bleeding due to unique mechanism of action when conventional methods are ineffective. Therefore, this drug is used in almost all surgical areas where advanced risk of severe intraoperative blood loss is present. There are special advantages of rFVIIa in neurosurgery including patients with severe CCT, spontaneous ICH, spinal pathology, and brain tumors. This is especially true for children due to earlier severe hemostatic disorders. Correction of hypofibrinogenemia, thrombocytopenia, hypocalcemia, acidosis, and hypothermia is necessary to achieve effect of rFVIIa. Redo injection after 2 h may be necessary to achieve reliable hemostasis. Routine application of the drug is not advisable because of high cost. However, rFVIIa may be salutary in situation close to dead-end. Additional possibility in effective stop of surgical bleeding will be probably local utilization of rFVIIa in neurosurgery.

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Part VIII

Blood and Blood Products: Anticoagulants

Anticoagulants in Use

Albert C. Zichichi, Abdalla A. Ammar, Mahmoud A. Ammar, Nicholas A. DeFilippo, and Kent A. Owusu

Abstract

Anticoagulation plays a critical role in the management of neurologic disorders. Selection of an anticoagulant must consider both drug-specific and patient-specific factors including type of neurologic condition. Hemorrhagic risk attributed to clinical conditions often influence decision to initiate, discontinue, or resume anticoagulation, with careful consideration for timing and duration of anticoagulant. This chapter describes commonly used anticoagulants in neurosciences. Knowledge of drug-specific properties will inform clinicians and guide appropriate application in the neurocritical care setting.

A. C. Zichichi · M. A. Ammar
Department of Pharmacy, Yale New Haven Hospital, New Haven, CT, USA

A. A. Ammar
Department of Pharmacy, New York Presbyterian, New York, NY, USA

N. A. DeFilippo
Department of Pharmacy, Yale New Haven Hospital, New Haven, CT, USA

School of Pharmacy, University of Connecticut, Storrs, CT, USA

K. A. Owusu (✉)
Department of Pharmacy, Yale New Haven Hospital, New Haven, CT, USA

Care Signature, Yale New Haven Health, New Haven, CT, USA
e-mail: Kent.Owusu@ynhh.org

Keywords

Anticoagulants · Vitamin K antagonist · Thrombin inhibitors · Direct oral anticoagulants · Heparin

Vitamin K Antagonist

Warfarin

Warfarin exerts its anticoagulant effect by inhibiting the activity of the enzyme vitamin K epoxide reductase complex subunit 1 (VKORC1) (Fig. 1A) [1]. The inhibition of VKORC1 blocks the regeneration of reduced vitamin K, and thus warfarin indirectly inhibits the posttranslational modification of vitamin K-dependent coagulation proteins, namely, factors II (prothrombin), VII, IX, and X, as well as the endogenous anticoagulants, proteins C and S [1]. The inhibition of this posttranslational modification of vitamin K-dependent coagulation proteins leads to dysfunctional factors [1] (Fig. 1F).

When administered orally, warfarin is rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentrations within 4 h, with a half-life of 20–60 h [1]. Warfarin is hepatically metabolized primarily via cytochrome P450 (CYP) 2C9 and to a lesser extent by the CYP 1A2, 2C19, 2C8, 2C18, and 3A4 isozyme pathways [2]. In general, hepatic metabolism of war-

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farin varies between individuals and results in interpatient variability in dosing requirements. Genetic variations in the CYP 2C9 isozymes and VKORC1 have been associated with differences in dose requirements [3].

Warfarin has no direct effect on the aforementioned circulating clotting factors. The time required for warfarin to achieve its pharmacologic effect is dependent on the elimination half-life of the coagulation protein factors II (42–72 h), VII

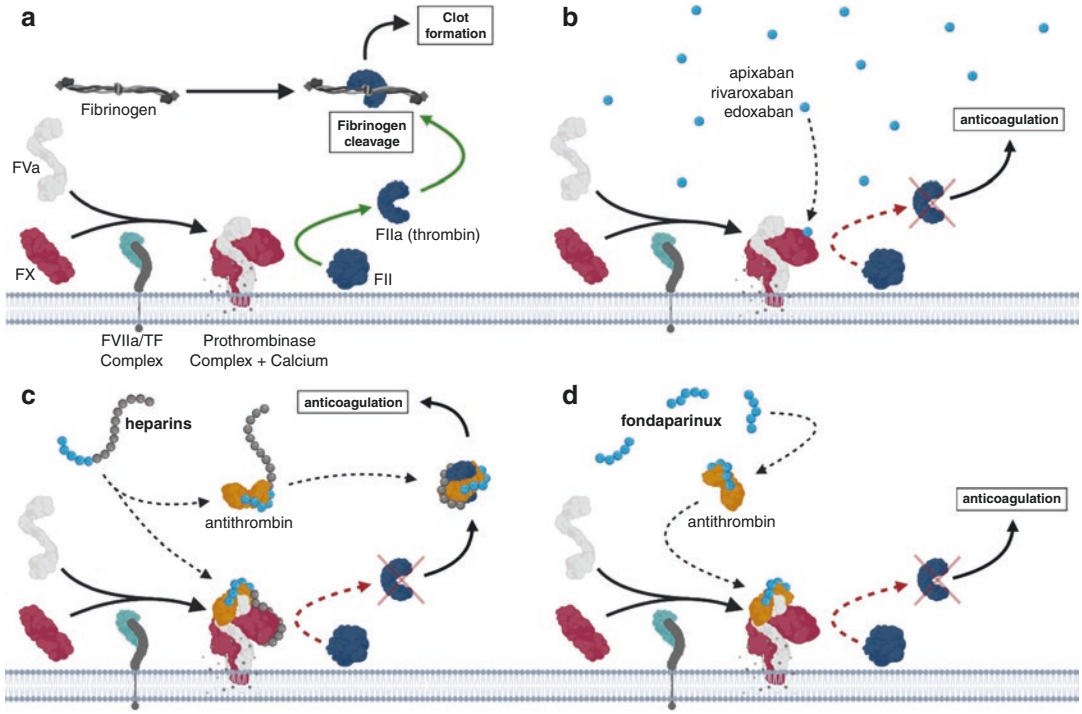

Fig. 1 Illustration of anticoagulant mechanisms. Created with BioRender.com. (**a**) Fig. A depicts the physiologic clotting cascade where the extrinsic and common pathways intersect. Tissue factor and factor VIIa together activate factor X. Factor Xa combines with factor Va, factor IVa (ionized calcium), and a phospholipid surface to form the prothrombinase complex. The prothrombinase complex then converts prothrombin (Factor II) to thrombin (Factor IIa) which cleaves soluble fibrinogen (Factor I) into insoluble fibrin (Factor Ia). Fibrin is then cross-linked by Factor XIIIa to form a mesh, stabilizing the thrombus. (**b**) Factor Xa inhibitors apixaban, rivaroxaban, and edoxaban bind directly to factor Xa to inhibit the conversion of prothrombin to thrombin by the prothrombinase complex. (**c**) Heparins potentiate the action of antithrombin by binding to antithrombin via the pentasaccharide domain. The variable-length heparin chain allows it to then wrap around thrombin or Factor Xa, stabilizing the interaction between antithrombin and the target factor. Low-molecular-weight heparins (LMWHs) such as enoxaparin and dalteparin work similarly, however, because of their shorter average length which is less able to wrap around thrombin after binding antithrombin. This results in LMWHs having higher ratios of antifactor Xa activity to antifactor IIa activity. (**d**) Fondaparinux is a synthetic pentasaccharide mimicking the pentasaccharide chain domain on heparins that binds selectively to antithrombin. It acts as an indirect factor Xa inhibitor, first binding to antithrombin to facilitate the interaction. (**e**) Direct thrombin inhibitors bind free and clot-bound thrombin, inactivating thrombin-mediated effects. Bivalirudin is a synthetic peptide while dabigatran and argatroban are small molecules. (**f**) Warfarin's effect on the posttranslational modification of clotting factors. Reduced vitamin K is a cofactor in the gamma-carboxyglutamation of inactive factors II, VII, IX, and X and proteins C, S, and Z. Oxidized vitamin K is a by-product of this process. Gamma-carboxyglutamic acid (GLA) domains improve the ability of factors to bind ionized calcium. Properly functioning factors bind ionized calcium to induce a conformational change and allow the factor to bind a phospholipid surface, which is necessary for its full function. Vitamin K Reductase Complex 1 (VKORC1) reduces the oxidized vitamin K byproduct. Warfarin inhibits VKORC1 thereby depleting active, reduced vitamin K over time and in turn hypofunctional clotting factors II, VII, IX, and X and proteins C, S, and Z are unable to undergo posttranslational modification and thus will not become fully functional factors

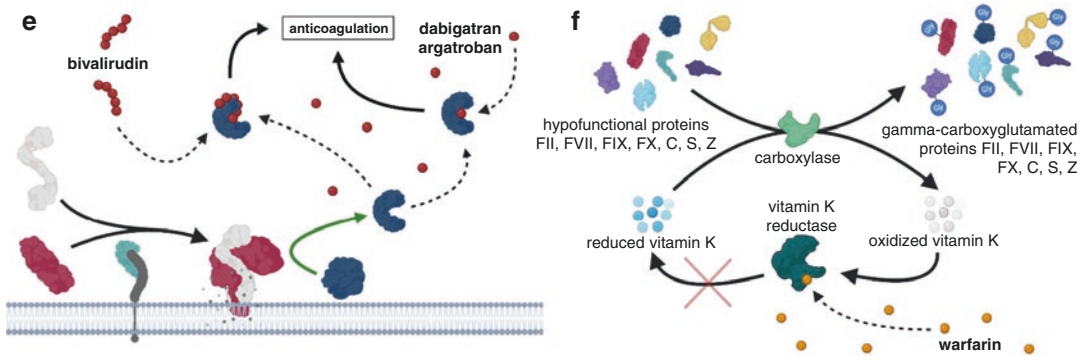

Fig. 1 (continued)

(4–6 h), IX (21–30 h), and X (27–48 h), protein C (8 h), and protein S (60 h) [4]. International normalized ratio (INR) is the most common test used to monitor the anticoagulant effects of warfarin. The recommended target INR and goal ranges are based on the clinical indication. For most indications, the acceptable target INR range is between 2.0 and 3.0. The target INR may be higher for other select indications, such as in the setting of mechanical prosthetic heart valves (2.5–3.5) and stroke prevention in non-rheumatic atrial fibrillation patients (1.5 to 2.7) [1, 5]. Frequent INR monitoring is recommended in patients with renal, hepatic dysfunction, heart failure, or acute illness as these diseases can affect the metabolism and elimination of warfarin [6].

Warfarin has numerous clinically significant drug-food and drug-drug interactions. Vitamin K and foods with high vitamin K content can reduce warfarin's anticoagulation effect [7]. Drugs that inhibit or induce CYP2C9, 1A2, and 3A4 isozymes have significant drug-drug interactions with warfarin [8].

Thrombin Inhibitor

Heparin

Thrombin has a main role in the formation of a thrombus as it transforms fibrinogen to fibrin and also activates platelets [9]. Once a thrombus is formed, thrombin activates factors V, VIII, and XI, which forms more thrombin [9]. Thrombin also activates factor XIII, which results in fibrin cross-linking and clot stabilization [9]. Thrombin contains three binding sites: active site, exosite-1, and exosite-2 [10]. The direct and indirect inhibition of thrombin results from the binding of drugs to one or two of these sites: exosite-1 serves as the fibrin-binding site, while exosite-2 serves as the heparin-binding site [10].

Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) block free thrombin by binding to both antithrombin and exosite-2, creating a heparin-thrombin-antithrombin complex (Fig. 1C) [11]. This complex potentiates the action of antithrombin, which in turn inhibits several clotting factors (IXa, Xa, XIa, XIIa, and thrombin) and prevents the conversion of fibrinogen to fibrin [12]. Factors IIa (thrombin) and Xa are the most sensitive to inhibition by the UFH-antithrombin complex [12]. Heparin products also bind to fibrin and thrombin, creating a bridge between them. This increases the affinity of thrombin to fibrin and increases thrombin-bound fibrin concentration. This fibrin-heparin-thrombin complex uses both thrombin exosites, leaving the active site protected from inactivation as the heparin-antithrombin complex can't bind to the fibrin-bound thrombin. This results in further thrombus growth [13]. Heparin products have an unpredictable dose-dependent anticoagulant effect as they bind to other plasma

proteins and require routine dose adjustments and monitoring [4]. Furthermore, heparin products can cause heparin-induced thrombocytopenia [4].

The onset of the anticoagulant effect of UFH is immediate after IV administration and within 20–30 min after subcutaneous injection [12]. Heparin is cleared and degraded primarily by the reticuloendothelial system, with a small amount of unchanged heparin is eliminated in the urine [12]. The half-life of UFH depends on the route and dose administered. When doses of 25, 100, or 400 units/kg of heparin are injected intravenously, the half-lives of the anticoagulant activities are 30, 60, and 150 min, respectively [14, 15]. The mean plasma half-life of UFH is 90 min [12]. The most common parameters to monitor UFH is activated partial thromboplastin time (aPTT) and heparin activity assessed by anti-factor Xa (anti-Xa) analysis. The aPTT is most frequently used because of its accessibility and cost [16]. Anti-Xa heparin assay has demonstrated less variability and is not influenced by other factors (such as lupus anticoagulants, elevated factor VIII, or presence of oral anticoagulants) compared to aPTT [17].

Therapeutic heparin anticoagulation is usually administered via continuous intravenous infusion with an initial loading dose. The loading dose can be omitted in patients with a high risk of bleed. Therapy is routinely monitored by the aPTT, with the target increase by 1.5–2.5 times the normal value [18]. The aPTT should be measured and the infusion rate adjusted no more frequently than every 6 h. The use of a nomogram may aid dose adjustments. Once a steady rate has been established, daily monitoring is generally sufficient [18]. Low-dose subcutaneous heparin therapy is administered every 8 or 12 h, prophylactically to prevent thrombosis and thromboembolism. Laboratory monitoring is generally not warranted when heparin is utilized for prophylaxis [19].

Direct Thrombin Inhibitors

As discussed previously, heparin and low-molecular-weight heparins possess unfavorable characteristics such as increasing thrombin-bound fibrin concentration, unpredictable dose-response relationships, and the potential to cause immune-mediated thrombocytopenia [18]. In contrast, direct thrombin inhibitors (DTIs) bind directly to thrombin without reliance on antithrombin to provide effective anticoagulation (Fig. 1E) [20]. As such, DTIs can inhibit both free and fibrin-bound thrombin, have a more predictable dose-response relationship, and do not cause immune-mediated thrombocytopenia [20–22]. The unique pharmacokinetic and pharmacodynamic properties of the most commonly used DTIs (bivalirudin, argatroban, and dabigatran) are summarized in Table 1.

3a. Bivalirudin

Bivalirudin is a synthetic analog of a natural DTI, hirudin, isolated initially from the salivary glands of medicinal leeches. Bivalirudin's direct thrombin inhibition activity is around 800 times weaker than hirudin [23]. Unlike hirudin, the binding of bivalirudin to thrombin is reversible, as once bound, it is slowly cleaved by thrombin. As such, the inhibition of thrombin is transient and the enzymatic activity is quickly restored. This transient effect might explain the lower bleeding risk of bivalirudin compared to the less commonly used recombinant hirudins (lepirudin and desirudin) [24]. Bivalirudin is administered intravenously and has a quick onset of action with therapeutic activated clotting times (ACT) achieved within 5 min and a half-life of 25 min [22]. Bivalirudin is metabolized hepatically and endovascularly via proteolytic enzymes [14]. However, almost 20% of the administered dose is eliminated renally and requires renal dose adjustments in patients with moderate renal insufficiency and contraindicated in patients with severe renal impairment (Table 1) [25]. Bivalirudin's effects can be monitored using ACT and aPTT. Bivalirudin has a crossover prolonging effect on international normalized ratios (INR) which may be challenging when transitioning from bivalirudin to warfarin [26]. Given the short half-life of bivalirudin, its anticoagulant effect is limited to 12 to 24 h after discontinuation of intravenous infusion. Table 2 provides recommendations for anticoagulant transition strategies.

Table 1 Overview of anticoagulants [1, 12, 18, 33, 39, 44, 45, 47, 54, 60]

Drug class	Agents	Mechanism	Dosing	Elimination	Onset of action (hours)	Half-life (hours)	Reversibility	Dose adjustments	Clinically significant drug-drug interactions	Special considerations
Direct thrombin inhibitors	Argatroban	Direct thrombin inhibition, preventing thrombin from cleaving fibrinogen to fibrin	2–10 mcg/kg/min. Titrate based on ACT and aPTT goals	Metabolism: hepatic Elimination: biliary excretion	Immediate	~ 45 min	Reversible binding to thrombin with short half-life, expected clearance within 12–24 h No reversal agent	**Hepatic failure**: 0.5 mg/kg/min. **Severe hepatic failure**: Avoid use	–	Lowest affinity to thrombin compared to other direct thrombin inhibitors PT/INR will falsely increase with administration of argatroban
	Bivalirudin		IV bolus dose of 0.75 mg/kg, followed immediately by a continuous infusion of 1.75 mg/kg/h. titrate based on ACT and aPTT goals	Metabolism: proteolysis and hepatic Elimination: 20% of the dose is renally eliminated	Immediate	~ 25 min	Reversible binding to thrombin with short half-life, expected clearance within 12–24 h No reversal agent	CrCl 15–60 ml/min: 15–50% dose reduction CrCl <15 ml/min: Avoid use	–	Intermediate affinity to thrombin compared to other direct thrombin inhibitors
	Dabigatran		**NVAF and VTE treatment**:150 mg PO twice daily Hip DVT prophylaxis: 110 mg PO on day 1, then 220 mg PO once daily × 35 days	Metabolism: hepatocytes and enterocytes; 20% metabolized to yield activated glucuronide conjugates Elimination: biliary 20%; renally 80%	1	12–17	Idarucizumab	**NVAF:** CrCl 15–30 ml/min: 75 mg twice daily CrCl 30–50 ml/min and P-gp inhibitor (dronedarone or systemic ketoconazole): 75 mg twice daily **VTE treatment and hip DVT prophylaxis**: CrCl ≤30 ml/min: Avoid use	Quinidine, verapamil, amiodarone, dronedarone, rifampicin, St. John's wort, strong P-glycoprotein inhibitors	Delayed absorption with food Opening, crushing, or chewing capsule increases oral bioavailability

(continued)

Table 1 (continued)

Drug class	Agents	Mechanism	Dosing	Elimination	Onset of action (hours)	Half-life (hours)	Reversibility	Dose adjustments	Clinically significant drug-drug interactions	Special considerations
Factor-Xa inhibitors	Apixaban	Inhibition of factor Xa	2.5–10 mg q12h (based on indication)	Renally (~ 27%) Feces	3–4	~ 12	Andexanet alfa 4FPCC	**NVAF**: If 2/3 following: SCr ≥ 1.5, weight ≤ 60 kg, age ≥ 80 y/o – 2.5 mg BID	CYP inhibitors: ketoconazole and ritonavir CYP inducers: phenytoin, carbamazepine, rifampin, St. John's wort	Least renally cleared oral factor-Xa inhibitor
	Dalteparin		5000 units q12h; 100 units/kg q12h or 200 units/kg daily (based on indication)	Renally	1–2	IV: 1.8–2.7 SQ: 3–5	Protamine (partial reversal)	CrCl <30 mL/min: monitor anti-factor Xa activity or use alternative	–	–
	Edoxaban		30–60 mg daily	Renally (35%)	1–2	10–14	Andexanet alfa 4FPCC	**NVAF**: CrCl >95 mL/min: not recommended CrCl 15–50 mL/min: 30 mg daily CrCl <15 mL/min: not recommend **VTE treatment**: CrCl ≥51 mL/min: none CrCl 15–50 mL/min: 30 mg daily CrCl <15 mL/min: not recommend	Rifampin Strong P-gp inhibitors	Least drug-drug interactions of oral factor-Xa inhibitors
	Enoxaparin		30–40 mg daily or q12h; 1 mg/kg q12h or 1.5 mg/kg daily (based on indication)	Renally	3–5	4.5–7	Protamine (partial reversal)	**VTE prophylaxis:** CrCl <30 mL/min: 30 mg daily **VTE treatment**: CrCl <30 mL/min: 1 mg/kg daily **STEMI treatment**: CrCl <30 mL/min: 1 mg/kg daily with 30 mg IV bolus	–	–
	Fondaparinux		2.5–10 mg daily (weight based)	Renally	2–3	17–21	Factor VII	No specific recommendations provided **VTE prophylaxis**: CrCl 20–50 mL/min: consider 1.5 mg daily	–	–
	Rivaroxaban		10–30 mg daily (based on indication)	Renally (66%)	2–4	5–9	Andexanet alfa 4FPCC	**NVAF:** CrCl 15–50 mL/min: 15 mg daily CrCl <15 mL/min: not recommend **VTE treatment:** CrCl ≥51 mL/min: none CrCl 15–50 mL/min: 30 mg daily CrCl<15 mL/min: not recommend	CYP inhibitors: ketoconazole, itraconazole, ritonavir CYP inducers: phenytoin, carbamazepine, rifampin, St. John's wort	–

Thrombin inhibitor	Unfractionated heparin	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa). By Inactivating thrombin, heparin prevents fibrin formation	Varies depending on therapeutic indication and targeted aPTT	Renally	IV: immediate SQ: 3	Varies depending on dose (0.5–1.5)	Protamine	–	–	–
Vitamin K antagonist	Warfarin	Inhibits vitamin K-dependent γ-glutamyl carboxylation of coagulation factors II, VII, IX, and X, proteins C and S	Varies depending on therapeutic indication and targeted INR	Hepatic metabolism; renally (92%)	Variable	20–60	4FPCC	Consider dose adjustment in renal and hepatic impairment	Vitamin K, foods rich with vitamin K Significant interactions with drugs that inhibit or induce CYP 2C9, 1A2, and 3A4 isoenzymes	Genetic variations in the 2C9 isoenzymes and VKOR1 have been associated with differences in dose requirements

NVAF non-valvular atrial fibrillation, *DDI* drug-drug interactions, *4FPCC* 4-factor prothrombin complex concentrate

Table 2 Transition strategies [1, 12, 33, 39, 44, 45, 47, 54, 60, 73]

From	To	Method for transitioning
Direct thrombin inhibitor		
Argatroban (Acova®) Bivalirudin (Angiomax®)	DOAC[b]	Stop DTI (IV) infusion and start DOAC
	UFH or LMWH[c]	Start within 2 h of stopping DTI (IV) infusion (argatroban: if hepatic insufficiency, start after 2–4 h)
	Warfarin	Overlap for at least 5 days. When INR > 4, stop infusion and check INR 4 h later: • If INR still 2–3, discontinue DTI (IV) infusion • If INR <2, restart DTI (IV) infusion • If INR >3, stop DTI (IV) infusion and consider warfarin dose adjustment
Dabigatran (Pradaxa®)	DTI (IV)[a], UFH, or LMWH[c]	Start 12 h after last dose of dabigatran (if CrCl <30 mL/min, wait 24 h)
	DOAC[b]	
	Warfarin	If CrCl >50 mL/min, start warfarin 3 days prior to dabigatran discontinuation If CrCl 30–50 mL/min, start warfarin 2 days prior to dabigatran discontinuation If CrCl 15–30 mL/min, start warfarin 1 day before dabigatran discontinuation
Factor Xa inhibitor		
Apixaban (Eliquis®)	DTI (IV)[a], UFH or LMWH[c]	Start 12 h after last dose of apixaban
	DOAC[b]	
	Warfarin	Consider use of heparin or enoxaparin bridge when transitioning to warfarin until INR therapeutic
Edoxaban (Savaysa®)	DTI (IV)[a], UFH, or LMWH[c]	Start 24 h after last dose of edoxaban
	DOAC[b]	
	Warfarin	Oral transition: Reduce edoxaban dose by 50% and initiate warfarin. Discontinue edoxaban when INR therapeutic Parenteral option: Discontinue edoxaban and initiate parenteral anticoagulant and warfarin at the time of next scheduled edoxaban dose; discontinue parenteral anticoagulant once INR ≥2; continue warfarin
Rivaroxaban (Xarelto®)	DTI (IV)[a], UFH, or LMWH[c]	Start 24 h after last dose of rivaroxaban. (If transitioning from 10 mg dose, can initiate parenteral anticoagulant as clinically needed irrespective of last dose)
	DOAC[b]	Start 24 h after last dose of rivaroxaban
	Warfarin	Consider use of heparin or enoxaparin bridge when transitioning to warfarin until INR therapeutic
Dalteparin (Fragmin®)	DTI (IV)[a], UFH, or LMWH[c]	If therapeutic dalteparin dose, initiate at time next dose would be due (e.g., 12 or 24 h after based on dosing interval) If prophylactic dalteparin dose, initiate as clinically needed irrespective of last dalteparin dose
	DOAC[b]	
	Warfarin	If therapeutic dalteparin dose, overlap for at least 5 days until INR within therapeutic range for 24 h If immediate anticoagulation not necessary, initiate warfarin as clinically needed irrespective of last dalteparin dose

Table 2 (continued)

From	To	Method for transitioning
Enoxaparin (Lovenox®)	DTI (IV)[a], UFH, or LMWH[c]	If therapeutic enoxaparin dose, initiate at time next dose would be due (e.g., 12 or 24 h after based on dosing interval) If prophylactic enoxaparin dose, initiate as clinically needed irrespective of last enoxaparin dose
	DOAC[b]	
	Warfarin	If therapeutic enoxaparin dose, overlap for at least 5 days until INR within therapeutic range for 24 h If immediate anticoagulation not necessary, initiate warfarin as clinically needed irrespective of last enoxaparin dose
Fondaparinux (Arixtra®)	DTI (IV)[a], UFH, or LMWH[c]	If therapeutic fondaparinux dose, initiate at time next dose would be due. If prophylactic enoxaparin dose, initiate as clinically needed irrespective of last fondaparinux dose.
	DOAC[b]	
	Warfarin	If therapeutic fondaparinux dose, overlap for at least 5 days until INR within therapeutic range for 24 h If immediate anticoagulation not necessary, initiate warfarin as clinically needed irrespective of last fondaparinux dose
Thrombin inhibitor		
Heparin infusion	DTI (IV)[a], UFH, or LMWH[c]	Initiate within 2 h after discontinuation of heparin infusion (after 4 h for edoxaban)
	DOAC[b]	
	Warfarin	Overlap heparin infusion with warfarin for at least 5 days until INR within therapeutic range for 24 h
Vitamin K antagonist		
Warfarin (Coumadin®)	DOAC[b]	Wait until INR <2 to initiate apixaban, dabigatran, LMWH. Wait until INR <2.5 to initiate edoxaban, and wait until INR <3 to initiate rivaroxaban

DOAC direct oral anticoagulant, *DTI* direct thrombin inhibitor, *UFH* unfractionated heparin, *LMWH* low-molecular-weight heparin

[a]DTI (IV) includes argatroban or bivalirudin; [b]DOAC includes apixaban, dabigatran, edoxaban, or rivaroxaban; [c]LMWH includes enoxaparin or fondaparinux

3b. Argatroban

Argatroban, like other DTIs, reversibly binds to the active site on thrombin to exert its anticoagulant effect [22]. Argatroban is administered intravenously and has a half-life of approximately 45 min, with steady-state plasma concentrations achieved within 10 hours from initiation of infusion [14]. Argatroban is mainly metabolized hepatically and excreted through the biliary system; thus it requires dose adjustments in patients with hepatic impairment but not in renal impairment (Table 1) [18]. Argatroban affects thrombin-dependent coagulation tests and thus influences prothrombin times (PT) and international normalized ratios (INR). Therefore, like bivalirudin, when concomitantly used with warfarin, the prolonged effect of argatroban on INR should be considered. In general, argatroban infusion can be discontinued when the INR during concomitant use with warfarin is greater than 4 [27]. Alternatively, chromogenic factor X (CFX) assay can be considered to evaluate anticoagulant effect of warfarin while receiving argatroban. This assay measures the enzymatic activity of factor X as percentage of normal activity. CFX level of 45% or less predicts an INR of 2.0 or higher with 93% sensitivity, 78% specificity, and 89% accuracy [28]. Similar to bivalirudin, argatroban effect can be monitored using ACT and aPTT, and its anticoagulant effect is limited to 12 to 24 h after discontinuation [27].

3c. Dabigatran

Dabigatran etexilate is an orally active prodrug that is rapidly converted to dabigatran, a low-molecular-weight molecule. Dabigatran is a potent inhibitor that directly and reversibly inhibits both free and clot-bound thrombin by binding to its active site via ionic interactions in a concentration-dependent manner [29]. Dabigatran has a low absolute bioavailability after oral absorption, independent of the prodrug dose. The prodrug, dabigatran etexilate, is also optimally absorbed in an acidic environment [30]. Dabigatran peak levels are achieved 2 hours after ingestion, and steady-state concentration is achieved within 3 days [31]. The oral bioavailability of dabigatran etexilate increases by 75% when the pellets are taken without the capsule shell compared with the intact capsule formulation [30]. Dabigatran is cleared renally thus requiring renal dose adjustment in patients with renal impairment, specifically those with an estimated creatinine clearance (CrCl) below 50 mL/min, and is contraindicated in patients with severe renal impairment (CrCl below 30 mL/min) [32]. Dabigatran does not require dose adjustment in patients with hepatic dysfunction [31].

Some advantages of dabigatran includes its fixed dose translating into ease of dosing, rapid onset of action, lack of routine monitoring need, and lack of CYP 450 drug-drug interactions [29]. Given dabigatran etexilate is a substrate of the efflux transporter P-glycoprotein (P-gp), co-administration of P-gp inhibitors with dabigatran etexilate, such as amiodarone, atorvastatin, and ketoconazole, can increase the absorption of dabigatran etexilate and thus increase plasma levels of active drug (dabigatran). Conversely, P-gp inducers, such as carbamazepine, phenytoin, and rifampin, can reduce the absorption of dabigatran etexilate, ultimately decreasing plasma concentrations of dabigatran [33]. Despite not requiring routine monitoring, dabigatran prolongs blood coagulation parameters, such as aPTT, PT, thrombin time (TT), and (ecarin clotting time) ECT [34].

Factor Xa Inhibitors

Direct Oral Anticoagulants

Apixaban, rivaroxaban, edoxaban, and dabigatran have historically been referred to as direct oral anticoagulants (DOACs). Dabigatran has a unique mechanism of action and was discussed previously. The remaining DOACs exhibit anticoagulant activity by binding directly to factor Xa, inhibiting thrombin generation (Fig. 1B). These agents do not require routine laboratory monitoring for efficacy, but their effects are most commonly monitored by anti-factor-Xa activity if necessary. Landmark trials demonstrated significantly reduced rates of intracranial hemorrhage when comparing apixaban, edoxaban, or rivaroxaban to warfarin for the treatment of non-valvular atrial fibrillation [35–37]. Recent evidence has also shown that DOACs are safe and effective for the management of heparin-induced thrombocytopenia (HIT) when enteral therapy is possible; however, the majority of evidence for DOAC use in heparin-induced thrombocytopenia pertains to rivaroxaban [38].

4a. Apixaban

Apixaban is absorbed rapidly from the gastrointestinal tract, reaching peak plasma concentrations within 3–4 h [39]. The half-life of apixaban is approximately 12 h [39]. Apixaban is metabolized hepatically mainly by CYP3A4; however, CYP1A2, 2C8, 2C9, 2C19, and 2J2 also play a role in metabolizing the drug to non-active metabolites. Apixaban has the least renal clearance of all DOACs at approximately 27% [39]. Recommended dose adjustments for apixaban differ based on the indication. Prescribing information recommends apixaban 2.5 mg twice daily for atrial fibrillation if the patient has two of the following criteria: a serum creatinine $\geq$ 1.5 mg/dL, weight $\leq$ 60 kg, or age $\geq$ 80 years [39]. Conversely, patients receiving apixaban for venous thromboembolism do not warrant dose adjustments [39]. Small pharmacokinetic studies and retrospective safety analyses have suggested

that no dose adjustments are necessary in patients with severe renal impairment or end-stage renal disease (ESRD) [40–43].

Apixaban does have clinically relevant drug-drug interactions. Medications which are combined CYP3A4 and P-glycoprotein (P-gp) inhibitors or inducers will increase or decrease the patients' exposure to apixaban, respectively. For example, if a patient is receiving a concomitant P-gp and strong CYP3A4 inhibitor, such as ketoconazole, itraconazole, or ritonavir, the apixaban dose should be decreased by 50% [39]. Alternatively, patients should avoid the combination of apixaban with P-gp and strong CYP3A4 inducers, such as phenytoin, carbamazepine, rifampin, and St. John's wort, because concomitant use may increase apixaban clearance and increase the patient's risk of developing a thrombosis [39].

4b. Edoxaban

Edoxaban is rapidly absorbed after enteral administration and achieves peak concentrations within 1–2 h [44]. The half-life of edoxaban is 10–14 h [44]. Edoxaban is minimally metabolized to an active metabolite by hydrolysis, conjugation, and CYP3A4 oxidation [44]. The active metabolite accounts for less than 10% of the parent compounds exposure, so variations in metabolism and drug-drug interactions are less of a concern [44]. Edoxaban is eliminated primarily unchanged and approximately 50% renally, while the remainder is metabolized and excreted in biliary and intestinal tissues [44].

It is recommended that the edoxaban dose be adjusted based on indication. For atrial fibrillation, edoxaban is not recommended in patients with CrCl > 95 mL/min due to decreased efficacy in preventing ischemic stroke. Patients with a CrCl between 15 and 50 mL/min should receive edoxaban 30 mg once daily; edoxaban use is not recommended in patients with a CrCl < 15 mL/min [44]. When treating venous thromboembolism, no dose adjustments are required for patients with CrCl ≥ 51 mL/min [44]. The recommended edoxaban dose is 30 mg once daily for patients with a CrCl between 15 and 50 mL/min, body weight ≤ 60 kg, or receiving specific P-gp inhibitors (verapamil, quinidine, azithromycin, erythromycin, itraconazole, or ketoconazole) [44]. Additional P-gp inhibitors have not been studied. Edoxaban's use is not recommended in patients with CrCl < 15 mL/min [44].

Concomitant use of edoxaban and rifampin is not recommended as pharmacokinetic studies have shown that rifampin can induce P-gp resulting in a reduction in edoxaban exposure [44]. Alternatively, strong P-gp inhibitors may increase the serum concentration of edoxaban [44].

4c. Rivaroxaban

Rivaroxaban reaches peak plasma concentrations within 2–4 h after enteral administration [45]. The bioavailability of rivaroxaban is dose dependent. Rivaroxaban doses less than 15 mg can be taken without regard to food, while doses at and above 15 mg should be taken with the largest meal of the day to maximize absorption [45]. Additionally, the administration of rivaroxaban distal to the stomach can lead to a decrease in rivaroxaban plasma concentrations and therefore should only be administered through a gastric tube if enteral administration is required. The half-life of rivaroxaban is 5–9 h [45]. Rivaroxaban is primarily metabolized by CYP 3A4, 3A5, 2J2, and hydrolysis [45]. The majority of rivaroxaban is eliminated renally with 36% as unchanged rivaroxaban and 30% as inactive metabolites [45].

Renal dose adjustments are necessary for rivaroxaban. Rivaroxaban should be dose reduced to 15 mg once daily for atrial fibrillation if the CrCl is between 15 and 50 mL/min [45]. Rivaroxaban should be avoided in patients with CrCl less than 15 mL/min due to increased risk of bleeding compared to warfarin in ESRD patients [46].

Concomitant administration of rivaroxaban and strong P-gp and CYP3A inhibitors or inducers should be avoided. As a 3A4 and P-gp substrate, medications that inhibit P-gp and CYP3A4 increase serum concentrations of rivaroxaban and medications which induce P-gp and CYP3A4 decrease serum concentrations of rivaroxaban [45]. Rivaroxaban should also be avoided in patients with renal impairment (CrCl 15–80 mL/

min) that are concomitantly taking a moderate P-gp or CYP3A inhibitor unless the benefits outweigh the risks [45].

Parenteral Factor Xa Inhibitors

Fondaparinux

Fondaparinux is a subcutaneously administered synthetic pentasaccharide containing the heparin binding sequence of antithrombin [47]. Fondaparinux exhibits its anticoagulant effect through antithrombin-mediated inhibition of factor Xa. Fondaparinux binds to antithrombin and potentiates its action nearly 300 times, inhibiting factor Xa effects on thrombin formation and thrombus development (Fig. 1D) [47]. Fondaparinux can be utilized for anticoagulation in patients with HIT because it has negligible cross-reactivity with HIT antibodies [48, 49]. While rare, an immune-mediated thrombocytopenia syndrome similar to HIT following fondaparinux administration has been described in case reports [50].

After subcutaneous administration, fondaparinux reaches peak anti-factor Xa activity within 2–3 h [47]. Fondaparinux has a long half-life of 17–21 h, which might preclude its use in patients who might require surgical or procedural interventions with a high risk of bleeding [47]. The anticoagulant effects of fondaparinux persist for 2–4 days after discontinuation of therapy in patients with normal renal function. Fondaparinux is also eliminated renally (up to 77%), which might preclude use in patients with renal dysfunction [47]. Clearance of prophylactic doses of fondaparinux is reduced by 25% in patients with an estimated CrCl between 50 and 80 mL/min, 40% in patients with an estimated CrCl between 30 and 50 mL/min, and 55% in patients with an estimated CrCl below 30 mL/min [47]. Low body weight patients (below 50 kg) who received fondaparinux for venous thromboembolism (VTE) prophylaxis have a significantly increased risk of bleeding compared to patients with body weight of 50 kg or more [46].

Dose adjustments are warranted when fondaparinux is used in patients with renal impairment; however, the prescribing information does not provide specific dose adjustments. Fondaparinux is contraindicated when CrCl is below 30 mL/min for both VTE treatment and for VTE prophylaxis per prescribing information; however, limited clinical and pharmacokinetic data suggests that fondaparinux 1.5 mg administered once daily might be used safely for prophylaxis in patients with moderate renal impairment (CrCl 20–50 mL/min) [51–53]. Prophylaxis with fondaparinux in patients with body weights under 50 kg is contraindicated, given the increased risk of bleeding [47].

Low-Molecular-Weight Heparins

Low-molecular-weight heparins (LMWHs) exert their anticoagulant effect through antithrombin-mediated inhibition of factor Xa and thrombin. LMWHs are derived from the depolymerization of unfractionated heparin (UFH) leading to a narrower range of molecular weight molecules compared to UFH. This depolymerization explains the differences in pharmacokinetics and physiologic effects of LMWH compared to UFH [18]. LMWHs have reduced binding capacity to many plasma proteins and cells due to this reduction in average molecular weight. The smaller average length of LMWH compared to UFH decreases the ability of LMWH to wrap around thrombin (factor IIa) after binding antithrombin, leading to higher ratios of anti-factor Xa activity compared to anti-factor IIa activity [18]. Decreased binding to plasma proteins provides a more predictable anticoagulant response compared to heparin [18]. LMWHs' half-lives are prolonged due to decreased binding to macrophages [18]. Reduced binding to platelets and platelet factor 4 (PF4) leads to reduced formation of HIT antibodies [18]. Finally, reduced osteoblast binding leads to a decreased risk of osteopenia with LMWHs compared to unfrac-

tionated heparin. The most commonly used LMWHs are dalteparin and enoxaparin [18].

5a. Dalteparin

Dalteparin is a parenterally administered LMWH with a molecular weight of approximately 3000 to 8000 daltons [54]. As described above, the smaller molecular weight compared to heparin explains dalteparin's higher ratio of anti-Xa activity compared to antithrombin-mediated inhibition of thrombin (approximately 2:1) compared to heparin [55]. Dalteparin's smaller molecular size compared to UFH prevents dalteparin from simultaneously binding to antithrombin and thrombin [18].

The onset of anti-factor Xa activity occurs within 1–2 h, peaking around 4 h after subcutaneous administration [54]. The half-life of dalteparin is route-dependent, with intravenous administration around 1.8–2.7 h and subcutaneous administration 3–5 h [54]. The duration of anticoagulant effect lasts more than 12 h [54]. Dalteparin is primarily eliminated by the kidneys. Limited evidence analyzing therapeutic doses of dalteparin in renal insufficiency suggests accumulation of dalteparin [56]. A study using prophylactic doses of dalteparin compared to UFH in end-stage renal disease or severe renal dysfunction (CrCl <30 mL/min) suggested no significant difference in the incidence of VTE or major bleeding [57].

Specific dose adjustments based on renal dysfunction are not available; however, the manufacturer recommends monitoring anti-factor Xa activity if dalteparin is utilized in these patients [54]. Routine anti-factor Xa monitoring outside of extenuating circumstances is not necessary. However, experts recommend targeting a range of 0.5–1 units/mL for mechanical heart valve bridging in non-pregnant patients and 0.8–1.2 units/mL for mechanical heart valve bridging in pregnant patients [58]. Recommended target anti-factor Xa levels for VTE treatment with dalteparin are 0.5–1.5 units/mL [54]. Anti-factor Xa targets for VTE prophylaxis in pregnant patients are 0.2–0.6 units/mL [59].

5b. Enoxaparin

Enoxaparin is a primarily subcutaneously administered LMWH that is similar to dalteparin in that it exerts its anticoagulant effect through inhibition of factor Xa with little effect on antithrombin-mediated inhibition of thrombin (approximately 3:1) [55, 60]. Enoxaparin's molecular weight is appropximately 4500 daltons [18]. The peak anti-factor Xa activity of enoxaparin occurs between 3 and 5 h following subcutaneous administration [60]. Enoxaparin is hepatically metabolized to lower-molecular-weight molecules which do not possess significant biologic activity [60]. The duration of anti-factor Xa activity lasts approximately 12 h following a 40 mg dose of enoxaparin with a terminal half-life between 4.5 and 7 h [60]. Enoxaparin is primarily cleared renally. Pharmacokinetic studies have shown an average increase in the anti-factor Xa area under the curve of 65% in patients with severe renal impairment (CrCl <30 mL/min) after sequential doses of 40 mg once daily [60].

Dose adjustments are required for severe renal impairment per the prescribing information. For VTE prophylaxis, patients with an estimated CrCl less than 30 mL/min should receive enoxaparin 30 mg once daily [60]. For treatment of a VTE or treatment of ST-segment elevation myocardial infarction (STEMI), patients with a CrCl less than 30 mL/min should receive enoxaparin 1 mg/kg subcutaneously once daily [60]. The manufacturer recommends adding a one-time dose of enoxaparin 30 mg intravenously for STEMI patients under 75 years old with concomitant renal dysfunction (CrCl <30 mL/min) [60]. Clinicians should utilize clinical judgment and weigh the benefits and harms in patients with rap-

idly changing renal function. Routine monitoring of anti-factor Xa concentrations is not necessary for all patients; however, obese, renally impaired, or pregnant patients might benefit from anti-factor Xa monitoring while receiving enoxaparin. For mechanical heart valve bridging, anti-factor Xa goals are similar to dalteparin: 0.5–1 units/mL in non-pregnant patients and 0.8–1.2 units/mL in pregnant patients [58]. For VTE treatment, anti-factor Xa targets should be 1–2 units/mL in patients receiving once-daily dosing and 0.6–1 units/mL in patients receiving twice-daily dosing [18]. Target anti-factor Xa level of 0.2–0.6 units/mL is recommended for VTE prophylaxis in pregnant patients [59].

Venous Thromboembolism Prophylaxis

Routine venous thromboembolism (VTE) chemoprophylaxis is recommended in neurocritical care patients, including those with acute ischemic stroke (AIS), intracranial hemorrhage (ICH), aneurysmal subarachnoid hemorrhage (aSAH), traumatic brain injury (TBI), and acute spinal cord injury (SCI), patients with brain tumors or neuromuscular disease, and patients who have undergone neurosurgical or neurovascular surgical interventions, with considerations for agent selection and timing of initiation [61]. Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and fondaparinux are commonly used for VTE prevention in this patient population [61].

Patient-specific factors such as weight, body mass index (BMI), renal function, patient acuity, neurological injury, and potential need for surgical intervention may influence the choice of pharmacological VTE prophylaxis. The shorter half-life of UFH relative to LMWH or fondaparinux renders it as a desirable choice, although LMWH appears to be superior in preventing VTE events in select neurocritical care patient groups [62, 63] and is recommended over UFH in certain neurocritical care populations [61]. Additional merits of LMWH include more predictable dose effects, simplicity of administration, and reduced thrombocytopenia risks [63].

While UFH necessitates relatively more frequent dosing than LMWH or fondaparinux due to UFHs moderately shorter half-life, renal impairment does not limit its utilization [18]. Fondaparinux is one of the recommended pharmacologic agents for VTE prophylaxis in critically ill patients with neuromuscular disease. However, at the time of the recommendation, studies addressing VTE prophylaxis choice in hospitalized patients with neuromuscular conditions were not available [61]. The relatively longer half-life of fondaparinux (17–21 h), versus that of UFH or LMWH, and the lack of an antidote make fondaparinux a less ideal agent in the acute setting [61].

While concrete recommendations in neurocritical care for chemical VTE prophylaxis in the setting of remote heparin-induced thrombocytopenia (HIT) are lacking, the American Society of Hematology (ASH) recommends administration of non-heparin anticoagulants (i.e., apixaban or fondaparinux) over UFH or LMWH in hospitalized patients [48]. Fondaparinux may be considered for pharmacologic VTE prophylaxis in neurocritical care patients with remote HIT recognizing the aforementioned limitations.

Therapeutic Anticoagulation

7a. Acute Ischemic Stroke Considerations

Routine anticoagulation in AIS setting is not recommended [64], although acute anticoagulation may be considered in suspected hypercoagulable states [65] or cases such as cervicocephalic dissection [66]. Pertinent available trials (including one favoring LMWH) at the time of the recommendations appear to have been excluded [64, 67], as such, the risk of complications in the absence of anticoagulation may influence the decision to initiate anticoagulation. When clinically appropriate, anticoagulation with UFH or LMWH appears reasonable, while direct throm-

bin inhibitors and factor Xa inhibitors are not recommended due to lack of well-established data in this setting [64].

An individualized approach is recommended when determining the time to initiate or reinitiate anticoagulation in a patient who has received IV alteplase [64], although some data suggests safe anticoagulation can begin 4 to 5 days after AIS or TIA in patients with NIHSS score 3 to 8 and low risk of hemorrhagic transformation [65].

7b. Cerebral and Cervical Artery Dissection

Therapeutic anticoagulation may be considered in patients with cervicocephalic arterial dissection presenting with AIS, and timing of anticoagulation is generally dependent on the reperfusion approach (i.e., intravenous thrombolysis and/or mechanical thrombectomy) [66]. In the absence of intravenous thrombolysis in patients with small- or moderate-sized infarcts, anticoagulation may be initiated at 24 h from symptom onset or after 24 h from intravenous thrombolysis with low risk of hemorrhagic transformation. When clinically indicated, anticoagulation with intravenous UFH [65, 68], subcutaneous LMWH, or DOACs may be reasonable, although the role of DOACs in this setting is even less established [66]. Anticoagulation may be deferred in patients with large infarctions or symptomatic hemorrhagic transformation. In patients with a transient ischemic attack secondary to a dissection, anticoagulation may be initiated immediately [66].

7c. Cerebral Venous Thrombosis

Anticoagulation is integral to the acute management of cerebral venous thrombosis (CVT), aiming to decrease the propensity of clot propagation [69, 70]. The 2017 European Stroke Organization guidelines recommend LMWH over UFH for the treatment of CVT in patients without a contraindication to LMWH and when urgent anticoagulation reversal is not anticipated [71]. In an open-label trial of 66 adult patients with CVT where patients were randomly assigned to receive treatment with either LMWH or UFH, lower in-hospital mortality rates in patients who received LMWH were reported. No statistically significant differences were noted between the LMWH and UFH groups in the patients with complete recovery at 3 months [72]. Although data is fairly limited, it suggests that LMWH is more effective than UFH and at least as safe for CVT treatment [71, 72].

Anticoagulants in the Pipeline

Anticoagulants that are currently under development include tecarfarin, thrombomodulin alfa, and TB-402. Tecarfarin is a vitamin K antagonist that is metabolized by carboxyl esterase, which eliminates the cytochrome-mediated metabolism variability associated with warfarin. A phase II/III trial failed to demonstrate the superiority of tecarfarin to warfarin in anticoagulation quality as determined with time in therapeutic range (TTR). The results were similar in patients with any CYP2C9 variant allele and on CYP2C9-interacting drugs. There was also no difference in thromboembolic or bleeding events [74]. A single-center randomized, open-label, drug interaction study showed that in comparison to warfarin, tecarfarin had a decreased potential for clinically significant pharmacokinetic interaction with fluconazole [75]. The Tecarfarin Anti-Coagulation Trial (TACT) aims to evaluate the safety and efficacy of tecarfarin and warfarin in patients who have an indication for chronic oral anticoagulation and taking at least one CYP2C9-interacting medication and have either chronic kidney disease or a genetic variant allele for CYP2C9 [76].

Thrombomodulin alfa (TM) assists with maintaining intravascular patency due to its anticoagulant, anti-inflammatory, and cytoprotective properties. TM suppresses thrombus formation by modulating thrombin's procoagulant effects. TM binds reversibly to the exosite-1 of thrombin,

interrupting thrombin binding to fibrinogen, protease-activated receptors, and coagulation factors V and VIII. Additionally, TM provides the binding surface for protein C and enhances its activation via thrombin bound to the adjacent portion of TM. As a result, activated protein C (APC), along with protein S, degrades coagulation factors Va and VIIIa, further inhibiting thrombin generation [77]. Furthermore, TM-thrombin complex activates Thrombin Activatable Fibrinolysis Inhibitor (TAFI) which in turn inhibits fibrinolysis and diminishes plasminogen binding to fibrin [78]. Several studies have shown significant improvement in coagulation parameters in patients who received recombinant-TM (r-TM) [79]. An open-label study showed r-TM to be efficacious for VTE prophylaxis following total hip replacement (THR) surgery [80]. Although TM is a vital physiologic anticoagulant, further clinical study is required to prove the efficacy of rTM as a viable anticoagulant [81].

TB-402 is a long-acting monoclonal antibody that partially inhibits factor VIII [82]. A single administration of TB-402 in escalating doses was effective and well-tolerated for the prevention of venous thromboembolism (VTE) after total knee replacement compared with enoxaparin [83]. These authors found that patients in the TB-402 group developed significantly less venous thromboembolisms compared to patients in the enoxaparin group. Another phase II study showed that TB-402 administered as a single postoperative dose had a similar efficacy compared to rivaroxaban for the prevention of VTE after THR surgery. However, the incidence of major and clinically relevant non-major bleeding was higher in the TB-402 groups compared to the rivaroxaban group [84].

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Other Antithrombotics: Antiplatelets and Fibrinolytics

Muhammad K. Effendi, Keaton S. Smetana, and Karen Berger

Abstract

Antithrombotic agents such as antiplatelets and fibrinolytics play a significant role in the care of patients with neurovascular diseases. As with all antithrombotic agents, bleeding complications are a potential risk with both drug classes and are dependent on several factors (e.g., the specific drug, pharmacokinetic/pharmacodynamic parameters, organ dysfunction, synergism, and patient-specific risk factors). Several oral and intravenous antiplatelet drug classes exist for both acute and chronic management of patients with neurovascular diseases. These agents may be used alone or in combination with other agents. In the setting of acute ischemic stroke, they are usually initiated after the use of fibrinolytic agents. While there are various monitoring tools for assessing the safety and efficacy of antiplatelets and fibrinolytics, widespread, quantitative standards are not as prevalent as with anticoagulants. In this chapter, we will discuss the nuances between specific agents within these drug classes and current monitoring techniques.

Keywords

Antiplatelets · Fibrinolytic agents · Aspirin P2Y12 inhibitors · Glycoprotein IIb/IIIa inhibitors · Platelet function assays Thromboelastography · Stroke

Introduction

Aside from anticoagulants, other types of antithrombotics are commonly used in a variety of management strategies for different neurovascular indications. Two common types of antithrombotics are antiplatelet and fibrinolytic agents. Both of these classes are integrated into the management of several neurovascular disease states, including acute and chronic management of acute ischemic stroke (AIS), transient ischemic attack (TIA), intracranial and extracranial stenosis, and endovascular stenting. While not the focus of this chapter, non-neurovascular indications for these two classes include cardiac-related diseases (acute coronary syndrome, coronary artery bypass graft surgery), acute pulmonary embolism, and peripheral artery disease. Overall, the

M. K. Effendi (✉)
Ernest Mario School of Pharmacy, Piscataway, NJ, USA

Capital Health Regional Medical Center, Trenton, NJ, USA
e-mail: muhammad.effendi@pharmacy.rutgers.edu

K. S. Smetana
The Ohio State University Wexner Medical Center, Columbus, OH, USA

K. Berger
NewYork-Presbyterian Hospital/Weill Cornell Medical Center, New York, NY, USA

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use of these agents, especially aspirin, is prevalent; some studies have demonstrated aspirin use in the United States (US) to be as common as 20% of all adults [1].

Within these classes of antiplatelets and fibrinolytic agents, there are differences in mechanisms of action, receptor binding, half-life, elimination, and restoration of hemostasis. An understanding of the unique pharmacokinetic/pharmacodynamic parameters between these agents, even of those within the same class, can optimize management of patients. This chapter will review antithrombotic agents including antiplatelet agents, fibrinolytic agents, and other miscellaneous antithrombotic agents. This chapter also highlights select molecules in the pipeline.

Antiplatelets

Antiplatelet agents interfere with one or more steps in the platelet release and aggregation process. Monotherapy and dual antiplatelet therapy (DAPT) have become the cornerstone of management of several different neurovascular and cardiac diseases. For non-cardioembolic stroke, antiplatelet agents have demonstrated a significant mortality benefit reducing the relative risk of stroke, myocardial infarction (MI), or death by 22% in patients with high risk of occlusive vascular events [2]. Antiplatelet agents are also used in the setting of neuroendovascular procedures to prevent acute stent thrombosis [3]. Strategies of antiplatelet selection, regardless of disease state, are variable and dependent on patient specific factors and institutional protocols.

Aspirin

The usage of salicylate containing plants (willow bark) for analgesia dates back thousands of years [4]. Aspirin is the most widely studied antiplatelet drug with hundreds of randomized trials conducted in high-risk patients [2, 5]. Aspirin is a mainstay of treatment for a multitude of neurovascular diseases, including but not limited to AIS, TIA, and neuroendovascular stenting.

Aspirin permanently inhibits cyclooxygenase (COX), through irreversible acetylation, which thereby inhibits the first step in prostanoid synthesis, the conversion of arachnoid acid (AA) to prostaglandin H2 (PGH2) [6]. PGH2 is the immediate precursor to thromboxane A2 (TXA2) which induces platelet aggregation and vasoconstriction. Figure 1 illustrates this mechanism of aspirin in platelet inhibition [7].

The irreversible inhibition from aspirin is a distinguishing characteristic from other salicylate and nonsteroidal anti-inflammatory drugs. While it has a plasma half-life of 20 min, its pharmacodynamic action lasts the lifespan of the platelet (10 days) [8]. Total daily doses of aspirin have ranged from 50 mg upward to 1500 mg daily. Generally, higher doses of aspirin have not shown greater efficacy at reducing serious vascular events (MI or AIS) compared to lower doses [2]. In fact, indirect comparisons of proportional effects from different doses of aspirin show greatest odds reduction of vascular events with daily doses ranging from 75 mg to 150 mg.[2] The American Heart Association and American Stroke Association recommend a dosing range of aspirin from 50 mg to 325 mg per day. In certain indications (e.g., MI and emergent intracranial stenting), a loading dose of 325 mg is utilized to achieve rapid and maximal platelet inhibition. Higher incidences of major and minor bleeding have been associated with higher doses of aspirin without an increasing magnitude of benefit [5].

Aspirin and Dipyridamole

Aspirin may also be combined at lower doses with dipyridamole. In the United States, a combination product exists that contains 25 mg of aspirin and 200 mg of dipyridamole in an extended-release formulation and is recommended as a twice-daily dosing regimen [9, 10]. Dipyridamole increases platelet cyclic-3′,5′-adenosine monophosphate (cAMP) through inhibition of adenosine uptake into platelets. Increasing cAMP concentrations affects platelet-activating factor, collagen, and adenosine diphosphate to inhibit platelet aggregation. Additionally,

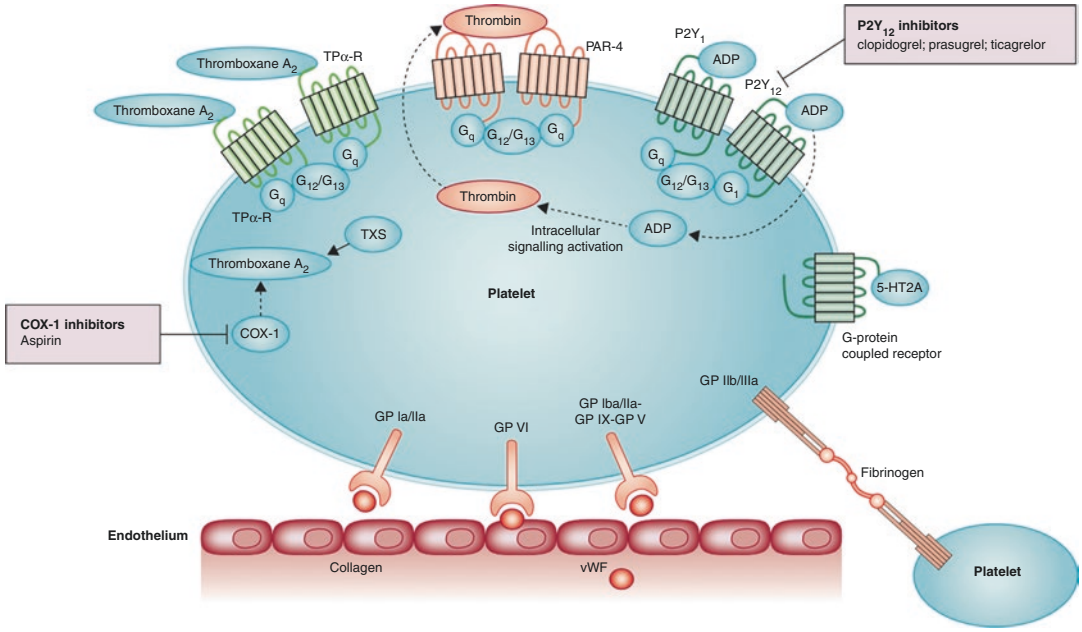

Fig. 1 Platelet pathways and commonly used oral antiplatelet treatments. Antiplatelet agents work on several different pathways (P2Y12 and COX-1 inhibition) to prevent activation of intracellular signaling pathways or directly block binding of activated platelets preventing aggregation (GIIb/IIIa inhibition). Intracellular signaling pathways result in the release of platelet activators, such as ADP, serotonin, thrombin, and thromboxane. 5-HT2A = serotonin receptor 2A. COX-1 = cyclooxygenase 1. PAR = protease-activated receptor. TP-R = thromboxane prostanoid receptor. TXS = thromboxane A2 synthase. G = G-protein. Dotted arrows show movement of molecules. Adapted from Mega and Simon, with permission from *The Lancet* [25777662 Mega Lancet]

dipyridamole also inhibits platelet cyclic-3′,5′-guanosine monophosphate (cGMP) phosphodiesterase [9].

There does not appear to be a significant difference in bleeding between combination aspirin and dipyridamole compared to aspirin alone. However, the higher incidence of headaches and inconsistent advantage over aspirin alone have limited the use of the combination product [10, 11].

$P2Y_{12}$ Receptor Blockers

Adenosine diphosphate (ADP) plays a crucial role in platelet activation in hemostasis and arterial thrombus formation [12]. ADP is secreted from platelet granules and binds to the $P2Y_{12}$ receptor on the platelet to activate platelet activation and secretion. Thienopyridines block the $P2Y_{12}$ receptor located on the platelet membrane, thereby inhibiting the binding of ADP and preventing this amplification process from occurring (Fig. 1). Oral $P2Y_{12}$ inhibitors may be used as monotherapy for secondary prevention after AIS or as combination therapy with aspirin for acute minor ischemic stroke, TIA, or neuroendovascular procedures requiring stents [13, 14].

The first two Food and Drug Administration (FDA)-approved $P2Y_{12}$ inhibitors were ticlopidine and clopidogrel. Ticlopidine, a first-generation thienopyridine, has been largely phased out as a therapeutic option due to extensive adverse effects (neutropenia, thrombocytopenia, and aplastic anemia). Clopidogrel, a second-generation thienopyridine, is one of the oldest and most commonly used $P2Y_{12}$ inhibitors. Clopidogrel is a pro-drug that goes through two sequential oxidative steps in its metabolism to be bio-transformed into its active form via cytochrome isoform CYP2C19. As such, genetic polymorphism of CYP2C19 may lead to variable patient response ranging from hyper- to hypo-

responders secondary to ability to metabolize clopidogrel into its active form [15]. CYP2C19*2 is the most commonly occurring loss of function allele, and its prevalence varies among ethnic groups, i.e., 12% in Caucasians, 15% in African Americans, and 29%–35% in Asians [16, 17]. CYP2C19*2 leads to a decreased ability to metabolize clopidogrel to its active form, thus leading to increased risk of therapeutic failure.

Clopidogrel is administered as a loading dose of 300–600 mg [18]. A loading dose of 300 mg provides approximately 40–60% platelet inhibition in 6 h; 600 mg achieves maximal platelet inhibition within 2 h [17, 19]. Due to the variable response to clopidogrel, point-of-care tests such as VerifyNow® that measures $P2Y_{12}$ reaction units (PRU) may be used to assess patient-specific response. Some patients will have high on treatment platelet reactivity; these patients have residual platelet activity following administration of a $P2Y_{12}$ inhibitor. This effect is more common with clopidogrel; however, the clinical significance of this and benefit of further loading doses are unclear [20, 21].

Prasugrel, a second-generation thienopyridine, offers several advantages over clopidogrel—faster onset of action, a more consistent pharmacodynamic profile, and a greater extent of platelet inhibition [22]. In a large landmark trial that compared prasugrel to clopidogrel in high-risk percutaneous coronary intervention (PCI), prasugrel was found to have significantly reduced rates of ischemic events, including stent thrombosis [23]. This was, however, at a cost of increased major bleeding and fatal bleeding. Additionally, a post hoc analysis of the trial found three criteria that led to lesser efficacy and greater bleeding: age ≥75 years, body weight <60 kg, and a history of stroke or TIA [23]. As such, and in contrast to other antiplatelet agents, prasugrel is contraindicated in patients with a history of prior TIA or stroke. Lower loading and maintenance dosing of prasugrel (20 mg and 5 mg, respectively) have been proposed as an alternative to traditional labeled dosing for prasugrel for endovascular treatment of cerebral aneurysms [24].

Ticagrelor is another oral $P2Y_{12}$ receptor inhibitor, with some key characteristic differences from clopidogrel and prasugrel. Unlike clopidogrel and prasugrel which are thienopyridines, ticagrelor is classified as a cyclopentyltriazolo-pyrimidine and reversibly binds to the $P2Y_{12}$ receptor via non-competitive binding. Another distinction from the other agents is that ticagrelor is not a prodrug and therefore does not require hepatic activation for its antiplatelet effects. Ticagrelor also has been found to weakly inhibit the uptake of adenosine by erythrocytes via equilibrative nucleoside transporter 1 (ENT1) [25]. This increase in circulating adenosine has been hypothesized to produce beneficial pleiotropic effects, but is also a culprit in a common adverse effect seen with ticagrelor, dyspnea [25, 26]. The effectiveness of ticagrelor may be reduced when used in conjunction with maintenance doses of aspirin above 100 mg [26]. Ticagrelor is used in neuroendovascular procedures, such as aneurysmal coil embolization, stent-coiling, and pipeline embolization to help decrease risk of intra- and postprocedural thrombosis.

Cangrelor is structurally similar to ticagrelor in its resemblance to adenosine triphosphate and is the first and only intravenous (IV) $P2Y_{12}$ inhibitor. Similar to ticagrelor, it does not require metabolic conversion to an active form. Cangrelor is FDA approved as an adjunct to PCI for reducing the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not on a glycoprotein IIb/IIIa inhibitor [27]. The use of cangrelor has also been investigated in patients requiring intracranial or extracranial stenting during neuroendovascular procedures [28]. The favorable pharmacokinetic characteristics of immediate onset of action, short half-life, predictability of response, and non-renal or hepatic elimination make cangrelor an appealing option in the acute setting for neuroendovascular procedures requiring stenting or high-risk procedures in which procedural thrombosis is of risk [28].

Transitioning from cangrelor to an oral $P2Y_{12}$ agent varies among the different agents. Both clopidogrel and prasugrel should not be given during a cangrelor infusion because their effects

may be attenuated due to competitive binding of the $P2Y_{12}$ receptor. The active metabolite of both clopidogrel and prasugrel have a short time window in which they can effectively exert their effect on the $P2Y_{12}$ receptor. Therefore, it is recommended to administer both thienopyridines (clopidogrel and prasugrel) as a loading dose immediately after discontinuation of cangrelor [29]. This drug-drug interaction between the thienopyridines does not appear to exist for ticagrelor. This is likely due to ticagrelor reversibly binding to an alternative site at the P2Y12 receptor [30]. As such, ticagrelor can be given at any point during or immediately upon discontinuation of the cangrelor infusion [29].

GPIIb/IIIa Inhibitors

The GPIIb/IIIa receptor is the most abundant receptor found on the surface of platelets. Activation of platelets leads to a confirmational change at the GPIIb/IIIa receptor site which allows for binding of different ligands, primarily fibrinogen [31, 32]. Inhibition of the GPIIb/IIIa receptor site interferes with platelet activity at the final common pathway of platelet-induced thrombosis (Fig. 1). A benefit of the GPIIb/IIIa inhibitors is inhibition of platelet aggregation irrespective of the specific platelet activating agonist (TXA2, ADP, etc.). Despite promising potential in the treatment of AIS (either alone or in combination with fibrinolytics) to assist in clot dissolution and prevent thrombus re-formation, the use of GPIIb/IIIa inhibitors has not transpired to provide any significant benefit and may increase bleeding risk [33]. However, due to their potent ability to inhibit thrombus formation, GPIIb/IIIa inhibitors have found themselves to be useful in neuroendovascular procedures [34]. These agents may prevent acute stent thrombosis during emergent stenting, the placement of intracranial stents, flow diverters, and thrombogenic coils in the setting of subarachnoid hemorrhage and during elective aneurysmal embolization [35]. In addition to IV route of administration, intra-arterial (IA) administration of GPIIb/IIIa inhibitors has also been explored, both alone and in combination with IV administration [36]. Theorized benefits of IA include administration of the drug directly to the site of action, the need for lower doses, and decreased hemorrhagic complications [36]. However, superiority of one route over another has not transpired in the literature [37]. Several questions exist regarding the use of GPIIb/IIIa inhibitors for neuroendovascular procedures, such as the optimal dosage, route of administration, combination of IA and IV administration, and the duration of the continuous infusion.

Abciximab (discontinued in the United States as of 2019) binds irreversibly to the GPIIb/IIIa receptor producing a longer duration of effect than tirofiban and eptifibatide. It is not recommended to give abciximab in combination with alteplase for AIS due to increased intracranial hemorrhage (ICH) that was noted in a phase III randomized controlled trial that was stopped early [38, 39]. Both eptifibatide and tirofiban are renally eliminated (50% and 65%, respectively), and their clearance may be prolonged in patients with renal dysfunction [40]. Due to the reversible binding of both eptifibatide and tirofiban, platelet transfusion is not a feasible strategy of reversal for these agents [41]. However, unlike abciximab which can affect hemostasis for up to 72 h, restoration of platelet activity following tirofiban and eptifibatide occurs within 4 to 8 h (Table 1). A potential adverse effect of this class is thrombocytopenia, thought to be mediated by formation of antibodies stimulated by the conformational change in the GP IIb/IIIa receptor [42]. The incidence of thrombocytopenia is estimated around 0.2–1% and may be increased with re-exposure [42].

Fibrinolytic Agents

Fibrinolytic agents convert the inactive proenzyme plasminogen to plasmin, a serine protease, which degrades fibrin within a blood clot. Fibrin-bound plasmin results in fibrinolysis of thrombus, whereas unbound plasmin can degrade other plasma proteins (e.g., fibrinogen, factor V, and factor VIII) and the serine protease inhibitor that inactivates plasmin (alpha 2-antiplasmin). Fibrinolytics

Table 1 Antiplatelet agents

Drug	IV or PO	Inhibition	Metabolic activation required	Loading dose	Maintenance dose	Time to maximal platelet inhibition	Time to normalization of platelet activity
COX inhibitor							
Aspirin	PO	Irreversible	No	162–325 mg	81–325 mg daily	2–6 h	7–10 days
$P2Y_{12}$ inhibitors							
Clopidogrel	PO	Irreversible	Yes	300–600 mg	75 mg daily	300 mg: 6 h 600 mg: 2 h	5–10 days
Prasugrel	PO	Irreversible	Yes	60 mg	10 mg daily	60 mg: 1 h	7–10 days
Ticagrelor	PO	Reversible	No	180 mg	90 mg twice daily	180 mg: 1–2 h	3–5 days
Cangrelor	IV	Reversible	No	30 mcg/kg	4 mcg/kg/min (0.75 mcg/kg/min for bridging)	2 min	1 h
GPIIb/IIIa inhibitors							
Abciximab	IV	Irreversible	No	0.25 mcg/kg	0.125 mcg/kg/min	10 min	24–72 h
Eptifibatide	IV	Reversible	No	180 mcg/kg x2 doses	2 mcg/kg/min	1 h	4–8 h
Tirofiban	IV	Reversible	No	25 mcg/kg	0.15 mcg/kg/min	5–10 min	4–8 h

can be divided into four generations (1st, streptokinase and urokinase; 2nd, recombinant alteplase and prourokinase; 3rd, reteplase and tenecteplase; 4th, desmoteplase) with the older agents inducing a global fibrinolytic state due to associating with free circulating plasmin, and newer agents mimicking naturally occurring plasminogen activators (i.e. tissue-type plasminogen activator or single chain urokinase-type plasminogen activator) targeting fibrin within formed clot [43]. Hypofibrinogenemia and drops in fibrinogen have independently been associated with increasing the risk of ICH [44, 45]. Usually this slowly corrects over the following 24 h but interpatient variability has been observed regarding the extent and timeline of recovery.

Streptokinase

Streptokinase (SK) was discovered in 1933 after observation that streptococci agglutinated in test tubes that contained human plasma but not in those with human serum. Originally named fibrinolysin, it was derived from culture filtrate of Lancefield group β-hemolytic streptococci and is an indirect activator of plasminogen through the formation of a 1:1 stoichiometric "activator complex" with free circulating plasminogen [46, 47]. It is a non-human protein that may illicit anaphylactoid reactions. There are two phases of clearance: the rapid phase due to inactivation by streptococcal antibodies and the slower elimination phase due to loss of enzyme activity. Individual differences will be observed in rapid phase elimination based on the titer of circulating antistreptokinase antibodies. Dissociated SK is cleared via hepatic elimination without known metabolites. After administration, subsequent doses will be neutralized for at least 4 days by the formation of antistreptokinase antibodies [48]. Normalization of fibrinogen levels occurs after approximately 30 h after infusion [49].

The discovery of SK occurred nearly 25 years before its first reported use as a fibrinolytic in AIS. Among the numerous trials in the 1990s, several evaluated SK as a fibrinolytic in AIS. The "Multicentre Acute Stroke Trial-Italy" (MAST-I)

trial compared SK alone, SK with or without aspirin 300 mg daily for 10 days, or neither in those with neurologic deficits attributable to stroke that arrived within 6 h of symptom onset [50]. This study was stopped early due to concerns of increased risk of early death in those who received SK with marginal reductions in severe disability at 6 months. Increased mortality and symptomatic ICH were observed in those who received SK alone compared to placebo in two other trials (MAST-E and ASK). A study has been proposed to use SK with stricter inclusion criteria in developing countries, as it is a lower-cost alternative to other fibrinolytics, but data has not been reported [51, 52]. However, this may not resolve the safety or efficacy concerns given SK antibody titers have been shown to correlate with poor responders and bleeding complications [53]. At this time, SK has fallen out of favor in the setting of AIS and is not recommended in current guidelines [39].

Urokinase/Prourokinase

In the 1940s, Macfarlane and Pilling described the fibrinolytic potential of human urine, leading to the extraction of urokinase (UK) [54]. Produced from cultured neonatal renal cells, there are two forms of UK which differ in molecular weight but have similar clinical effects [55]. Compared to SK, UK is a direct activator of plasminogen that is slightly increased in the presence of fibrin but maintains systemic fibrinolysis (Table 2) [46]. Given that endogenous UK levels are elevated two- to fourfold in moderate to severe cirrhosis, reduced clearance is expected in those with hepatic impairment. Single-chain urokinase-type plasminogen activator (rscu-PA) or pro-urokinase (proUK) is an equally potent inactive precursor to UK that directly activates plasminogen to plasmin with improved fibrin specificity and a shorter half-life of 7–8 min [46, 56].

In 1976, Fletcher et al. performed a pilot study of UK in AIS and found no appreciable benefit in the small cohort of 31 patients [57]. A decade later, Fijishima et al. found that UK and UK with dextran sulfate (UK-DS) when administered within 1 to 7 days from symptom onset improved symptoms with minimal hemorrhagic conversion (3.2% in the UK-DS group and 0% in the UK alone group) [58]. In the 1990s IA proUK was studied in the setting of a middle cerebral artery occlusion. The PROACT II study found that 9 mg of IA proUK with IV heparin compared to IV heparin alone resulted in improved recanalization rates and higher likelihood of attaining a mRS ≤ 2 at 90 days despite an increased frequency of symptomatic ICH (10% vs 2%, $p = 0.06$) [59]. In less developed areas, UK has been suggested as an alternative agent if rtPA is not available or affordable and is likely preferred over SK as it has been shown to be a more effective and safer local fibrinolytic [53]. Given its short half-life rethrombosis is a theoretic concern with a bolus approach. An ongoing study is evaluating the efficacy and safety of UK in those with minor stroke [60].

Recombinant Human Tissue-Type Plasminogen Activator (rtPA)

Originally discovered in 1947, tissue-type plasminogen activator (tPA) is a serine protease containing five distinct domain structures and composed of 527 or 530 amino acids [61]. tPA is synthesized in vascular endothelial cells, is a weak plasminogen activator without the presence of fibrin, and is secreted continuously into the plasma being lowest in the morning and peaking in the late afternoon [46]. Production is made by recombinant technology from a human melanoma cell line, and the commercially available product is referred to as rtPA [61]. The half-life of rtPA is 5–6 min mostly due to inactivation by endogenous plasminogen activator inhibitor-1 (PAI-1) [62]. Other inhibitors of tPA include LDL Receptor Related Protein 1-mediated liver uptake, placenta plasminogen activator inhibitor (PAI-2), protein C inhibitor (PAI-3), protease nexin, alpha 2-macroglobulin, trypsin inhibitor, and CI-inhibitor [61, 63]. While rtPA is rapidly cleared from the plasma, concentrations of endogenous tPA return normal (510 ng mL^{-1}) within 30 min, its effects at the thrombus persist

Table 2 Fibrinolytic agents

Agent	Plasminogen activation	Fibrin specificity	Half-life (min)	Elimination
Streptokinase	Indirect	+	α Elimination - 23 β Elimination - 83	*Streptococcus* antibodies/ hepatic
Urokinase	Direct	+	13	Hepatic
Prourokinase	Direct	++	8	Hepatic
Recombinant tPA	Direct	++	5–6	Hepatic
Reteplase	Direct	+	13–16	Hepatic/kidneys
Tenecteplase	Direct	+++	20–24 / 90–130	Hepatic

for 72 min, and fibrinogen levels may be reduced for 24 h [64, 65].

Apart from symptomatic ICH, another life-threatening complication of rtPA is orolingual angioedema. This has been reported to occur in 1.3–5% of patients receiving rtPA and has been associated with use of angiotensin-converting enzyme (ACE) inhibitors, as they inhibit metabolism of bradykinin, and signs of infarction involving the insular ribbon and frontal cortex anterior to the sylvian fissure (ASPECTS region—Insula, M1, or M4) [66].

Numerous randomized controlled trials evaluated the effectiveness and safety of rtPA in the setting of AIS in the 1990s [67–70]. After the NINDS trial, which showed improved clinical outcomes at 3 months when administered within 3 h of symptom onset, the FDA-approved rtPA for use in patients with AIS [68]. In the United States and Europe, the approved dosing strategy is 0.9 mg/kg (max of 90 mg) with 10% of the dose given as an IV bolus and the remaining 90% over 60 min [61]. In October 2005, 0.6 mg/kg (max 60 mg) was approved for use in Japan based on findings from the Japan Alteplase Clinical Trial (J-ACT) [71]. Subsequently, ENCHANTED found the lower dosing strategy was non-inferior to standard dosing in a trial involving predominantly Asian patients [72].

While the 3-hour window remains to be the cutoff in the US package insert, guidelines provide an extended window of 3 to 4.5 h in which rtPA can be administered. The extended window guidelines have relaxed what was previously considered exclusion criteria based on the ECASS III trial and state that rtPA can be safe and effective in those >80 years old, those on warfarin with an INR ≤1.7, is a reasonable option in those with diabetes mellitus and prior stroke, and has uncertain benefit in those with very severe stroke symptoms (NIHSS >25) [39]. In those who awake with stroke symptoms or have an unclear time of onset >4.5 h, rtPA can be beneficial with diffusion-positive FLAIR-negative lesions on MRI [39, 73]. Alternatively, IA fibrinolysis initiated within 6 h of stroke onset in select patients who have contraindications to the use of IV rtPA may be considered; however IA fibrinolytics are used less frequently given the more widespread use of mechanical thrombectomy [39].

While rtPA is the primary fibrinolytic recommended in AIS, it is an imperfect agent. Recanalization rates may differ despite similar reductions in hemostatic markers (e.g., fibrinogen, alpha 2-antiplasmin, functional thrombin activatable fibrinolysis inhibitor), hemorrhagic conversion is a known risk, and potential neurotoxic effects have been postulated due to its enhancement of calcium influx into the neuron via its interaction with N-methyl-D-aspartate (NMDA) receptors [74, 75].

Reteplase

Reteplase is a second-generation recombinant tPA and compared to rtPA has reduced fibrin binding, similar enzyme kinetics toward plasminogen, and a longer half-life (13–16 min) [76]. Given its longer half-life, it has been studied as a "double bolus" regimen mostly in the setting of MI. Normalization of fibrinogen levels is also longer in comparison to rtPA at approximately 48 h. Data are limited with the use of reteplase in AIS and should be interpreted cautiously. The first prospective trial found near or complete

recanalization in 88% of patients ($n = 16$) with IA administration [76, 77].

Allergic reactions (dyspnea and hypotension) are rare occurring in 3 out of 2965 patients in the INJECT trial, and in postmarketing studies 8 out of 9938 patients experienced allergic and/or anaphylactoid reactions [76]. Its current formulation (TAPS, tranexamic acid, phosphate, sucrose) contains 8 mg of tranexamic acid as a solubilizing agent, but unfavorable effects have been described as extremely improbable.

Tenecteplase

Tenecteplase (TNK-tPA) is a three-point-mutated variant of tPA with amino acid substitutions that result in a prolonged half-life and improved resistance to PAI-1 [78]. TNK-tPA has an initial half-life of 20–24 min and a terminal half-life of 90–130 min. Compared to the previous agents discussed, it has the highest degree of fibrin specificity, can be administered as a single bolus dose, and has also been shown to have more potent antiplatelet properties compared to rtPA [78].

In patients who were within the 4.5 hour fibrinolytic window, two trials compared various doses of TNK-tPA (0.25 mg/kg—ATTEST; 0.4 mg/kg—NOR-Test) to rtPA. No differences were noted in the percentage of penumbra salvaged, functional outcomes, or incidence of symptomatic ICH [79, 80]. The EXTEND-IA trial found in those with large vessel occlusion (LVO) with planned mechanical thrombectomy (MT) TNK-tPA (0.25 mg/kg) improved rates of reperfusion based on angiographic assessment, no difference in symptomatic ICH, and improved functional outcomes based on ordinal shift analysis of mRS that were not appreciated in the binary analysis compared to rtPA [81]. Similar results were found comparing 0.4 mg/kg to 0.25 mg/kg of TNK-tPA [82]. Both of these trials found a reperfusion rate of 19–22% on angiography [81, 82]. Studies are ongoing which will help decide if rtPA or TNK-tPA should be the first-line fibrinolytic in AIS.

The AHA/ASA guidelines for the management of AIS state that TNK-tPA 0.25 mg/kg may be reasonable to choose over rtPA in patients who are also eligible to undergo MT [39]. The European Stroke Organization (ESO) consensus statement provides the following expert opinion in regards to TNK-tPA: 1) in LVO AIS patients eligible for IVT before MT, suggest the use of TNK-tPA (0.25 mg/kg) over rtPA if the decision on IVT is made after vessel occlusion status is known [73].

Desmoteplase

Isolated from the salivary gland of the vampire bat (*Desmodus rotundus*), desmoteplase (DSPA) is an extremely fibrin-specific agent that is almost inactive in the absence of fibrin [83]. There are numerous variants of DSPA that have been discovered, but the molecule chosen for clinical application is DSPAα1. This was due to it having the highest fibrin selectivity and is 180-fold more specific compared to rtPA [84]. DSPA has biphasic elimination with the terminal half-life being 2.8 h allowing for bolus dose administration. The use of DSPA as a fibrinolytic 3 to 9 h after stroke symptom onset was promising in dose finding studies given low rates of symptomatic ICH and improved reperfusion rates [85, 86]. However, in a larger prospective, randomized controlled trial (DIAS-2), no benefit was observed in clinical response at 90 days compared to placebo [87].

Molecules in the Pipeline

Numerous molecules have been entered into clinicaltrials.gov as phase 2/3 trials over the last decade, but few have updated results at this time. The following molecules are discussed as they had recent publications and were relevant to the content of this chapter. A novel delivery method of rtPA is being evaluated by coating superparamagnetic iron oxide nanoparticles with a mixture of rtPA and albumin in conjunction with magnetic fields. Early findings suggest a dissolution rate 100 times higher than free rtPA [88]. A novel anti-von Willebrand factor (vWF) aptamer (DTRI-031) that selectively binds and inhibits

vWF-mediated platelet adhesion and arterial thrombosis is in development. In addition to promising recanalization rates in animal models, its antidote (DTRI-025) has been developed so that hemostasis can be quickly restored [89]. A recombinant variant of activated protein c (3K3A-APC) which activates protease-activated receptor (PAR) 1 is being evaluated in the setting of AIS [90]. DLBS1033 (Disolf), a protein isolated from *Lumbricus rubellus*, possesses "quadruple activity" that inhibits platelet aggregation, inducing fibrinogenolysis, fibrinolysis, and thrombolysis [91]. It is currently being studied as an add-on oral agent in AIS to assess improvement in 30-day functional status (NCT04425590). SP-8203 (Otaplimastat), derived from extracts of *Eisenia andrei*, competitively inhibit NMDAR-mediated excitotoxicity through inhibition of calcium influx. Given that rtPA may possess neurotoxicity due to NMDAR activity, this molecule is being studied in conjunction with rtPA [92, 93].

Monitoring

There are several available tests to determine the degree of coagulopathy from antiplatelet and fibrinolytic agents. For antiplatelets, platelet function tests (PFT) can help determine the degree of antiplatelet activity. Generally, PFT may be considered for assessment of platelet function in a variety of situations, including monitoring for response from antiplatelet therapy, evaluation of perioperative hemostasis, and identification of bleeding disorders.

VerifyNow (ITC, Edison, NJ, USA) is a rapid, point-of-care test that assesses platelet aggregation in whole blood by a turbimetric-based optical detection using a system cartridge containing fibrinogen-coated beads and platelet agonists; it is a fast and easy to use method of PFT that can produce results with a rapid turnaround time [94]. The resulting rate and extent of platelet-induced agglutination is reported in a value of platelet reaction units (PRU). A significant advantage of the VerifyNow system, compared to other commonly utilized PFT, such as light transmission aggregometry (LTA), is the rapid results [95].

The majority of clinical trials on PFT come from cardiac literature showing a lack of clear significance or consistent benefits in clinical outcomes. This results in low-level recommendations for use of platelet function monitoring tests in clinical guidelines from the American Heart Association, American College of Cardiology, and European Society of Cardiology [96]. However, the widespread use of antiplatelet medications for several different neurovascular disease states certainly prompts a strong rationale for the usage of a test such as VerifyNow to assess platelet function. Although no consensus, evidence-based recommendations are available for routine monitoring of PFT in patients with neurovascular diseases, there may be some utility in testing individuals with recurrent events despite appropriate empirical dosing of antiplatelet agents and/or patients deemed as "high risk" for thrombosis. Difficulties in interpretation of assessment of neurovascular literature for platelet reactivity include lack of large prospective randomized trials and heterogenicity from those conducted [97, 98]. Additional consideration should be made regarding a lack of consensus cutoff values for standardized PRU cutoffs [99]. The optimal range of platelet reactivity is not well defined for neurointerventional procedures; however, a goal of a PRU 60–240 has been suggested [17]. Lastly, there may be interference with the VerifyNow testing with GPIIb/IIIa inhibitors, and it is recommended to wait 48 hours after administration of eptifibatide and tirofiban and 14 days after abciximab [100].

Thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) are point of care tests of the viscoelastic properties of whole blood, providing real-time functional analysis of hemostasis. This includes formation of clot time, enzymatic coagulation factors/anticoagulants/fibrinogen/platelet time, fibrinogen and platelet kinetics, dysfunctional fibrinogen/platelets, and fibrinolysis percentage. These characteristics describe qualitative, rather than quantitative, assessment of the coagulation process. Both assays determine a graphical output that represents clot formation and dissolution that is generated by the translation of torque along a torsion pin during

thrombogenesis and fibrinolysis [101, 102]. Despite differences in reporting nomenclature and specific logistics of the operation of the tests, both tests report essentially the same information on clot formation kinetics and strength [103]. By measuring multiple components of hemostasis, both TEG® and ROTEM® can help rapidly identify both hypercoagulable and hypocoagulable states. The use of both TEG® and ROTEM® requires trained and qualified personal to perform and interpret the testing. Additionally, although there has been positive published data in regard to the potential of prognostication, risk stratification, and treatment decisions, more data is needed in the neuroscience patient population to establish thromboelastography as the standard of care.

Thromboelastograph® Platelet Mapping™ (TEG-PM®) (Haemoscope Corporation, Niles, IL, USA), a modification of the standard TEG, evaluates platelet function through direct activation of arachidonic acid (AA) and adenosine diphosphate (ADP) receptors, with analysis of the resulting formation of TEG curves [104]. It measures percentage platelet aggregation in the presence of arachidonic acid (AA) and adenosine diphosphate (ADP). It was designed to evaluate the therapeutic inhibitory effect of clopidogrel or aspirin on platelet aggregation. Similar to TEG® and ROTEM®, most of the data for its used is derived from cardiac surgery literature. Although this information may be beneficial in assessing the degree of a causative agent in relation to contribution to bleed, its clinical utility is not yet well elucidated as a predictor or hematoma expansion or response to platelet transfusion [105, 106].

Conclusion

Antithrombotic agents such as antiplatelets and fibrinolytics are commonly used in a variety of different neurovascular disease states. An intricate understanding and awareness of their different pharmacological properties is critical in management of patients receiving these medications. With this knowledge, therapy can be individualized to reduce thromboembolic complications and manage hemorrhagic complications.

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Antithrombotic Reversal Agents

Nidhi Gupta, Pooja Chapegadikar,
and Piyush Srivastava

Abstract

Antithrombotic therapy comprising of either anticoagulants, antiplatelets, or fibrinolytic agents is commonly being prescribed worldwide for the prevention and treatment of thromboembolic events. However, despite having a morbidity and mortality benefit, these agents have an innate potential of bleeding risk, thereby increasing the propensity for major bleeds like intracranial hemorrhage. In recent years, several new antithrombotic agents have been introduced into clinical practice which presents unique challenges in the emergency reversal of their coagulopathy. In life-threatening situations, the antithrombotic reversal agents tilt the delicate balance of the coagulation cascade back toward thrombosis just long enough to stop the bleeding or facilitate an emergenent or urgent surgical intervention. The recent approval of specific reversal agents has provided new drugs in the neurosurgical armamentarium in combatting antithrombotic-induced coagulopathy.

In this chapter we discussed the varied existing and new reversal agents in pipeline for the emergency reversal of antithrombotic agents in the setting of intracranial hemorrhage and need of urgent neurosurgical intervention.

Keywords

Antithrombotics · Anticoagulants · Antiplatelets · Fibrinolytic agents · Vitamin K_1 · Prothrombin complex concentrate · Fresh frozen plasma · Protamine · Recombinant Factor VIIa · Idarucizumab · Andexanet alfa · Ciraparantag · Platelet transfusion · Desmopressin · Antifibrinolytic agents · Cryoprecipitate · Fibrinogen concentrate · Neurosciences

Introduction

Antithrombotic therapy comprising of either anticoagulants, antiplatelets, or fibrinolytic agents is commonly prescribed for the prevention and treatment of thromboembolic events, including venous thromboembolism (VTE), deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), and acute ischemic stroke (AIS) and in patients with atrial fibrillation (AF) and/or mechanical heart valve [1]. However, despite having a morbidity and mortality benefit,

N. Gupta (✉) · P. Chapegadikar
Department of Neuroanaesthesia, Indraprastha Apollo Hospital, New Delhi, India

P. Srivastava
Department of Liver Transplant Anaesthesia and Critical Care, Fortis Hospital, Noida, Uttar Pradesh, India

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these agents have an innate potential of bleeding risk, thereby increasing the propensity for major bleeds like intracranial hemorrhage (ICH).

In patients presenting with ICH, rapid restoration of hemostasis is critical to prevent hematoma expansion and the associated neurological sequalae [2]. In life-threatening situations, the reversal agents are of paramount importance as they tilt the delicate balance of the coagulation cascade back toward thrombosis just long enough to stop the bleeding or facilitate an emergenent neurosurgical intervention [3, 4]. In recent years, several new antithrombotic agents have been introduced into clinical practice, having an increasingly complex and multiple sites of action (discussed elsewhere in book). This presents unique challenges in the reversal of their coagulopathy, particularly in the absence of specific reversal agents and updated guidelines [5]. In this chapter, we provide a comprehensive review of the various existing and new reversal agents in pipeline which are vital in combatting antithrombotic-induced coagulopathy in neurosciences.

1. Reversal of Anticoagulants

The commonly prescribed anticoagulant in clinical practice includes warfarin and other vitamin K antagonists (VKA), heparin and derivatives [unfractionated heparin (UFH) and low molecular weight heparin (LMWH)], and direct oral anticoagulants (DOACs) including direct thrombin (factor IIa) inhibitor (DTI), dabigatran, or specific activated factor Xa inhibitors (FXaIs), apixaban and rivaroxaban. Warfarin-associated major hemorrhage has been observed at a rate of 1.7% to 3.4% in clinical practice and requires rapid reversal of anticoagulation [2, 6].

Compared to VKAs, DOACs have been associated with lower rates of life-threatening bleeding including ICH and extracranial hemorrhages in patients requiring long-term anticoagulation [7–9]. In a recent systematic-review of 55 randomized controlled trials (RCTs) comparing the risk of ICH between DOACs and other antithrombotic drugs, Wu et al. have observed a 46% reduced incidence of ICH with DOACs in comparison with warfarin [relative risk (RR) 0.54], while the risk was similar to aspirin [9]. Dabigatran reduced the risk of ICH by 60%, apixaban by 57%, edoxaban by 56%, and rivaroxaban by 41%. The FXaIs (apixaban, edoxaban, and rivaroxaban) and LMWH had a similar risk of ICH and were found to be equally safe. Among DOACs, apixaban appears to be safest with lowest risk of major bleeding compared to rivaroxaban and dabigatran, based on comparisons from RCTs and observational studies [10].

Since ICH-associated mortality is directly related with the extent of hematoma expansion, an immediate withdrawal and rapid reversal of anticoagulation is of utmost importance to restore hemostasis and improve clinical outcomes in this patient population. If an anticoagulant-associated bleeding is suspected, detailed history regarding the type of medication used, exact time of last intake, comorbidities, and concomitant medications should be taken from the patient or relatives. However, in emergency situations, a detailed reliable history of recent anticoagulant use may be unavailable. In such situations, an anticoagulation screening test and certain validated assays suitable for measuring the anticoagulant activity [including prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time [aPTT], diluted thrombin time [dTT], ecarin clotting time (ECT), ecarin chromogenic assay, thrombin time, specific chromogenic anti-factor Xa (anti-FXa) assay calibrated with the drug of interest, whole blood clotting time and whole blood viscoelastic assays such as thromboelastography (TEG), and rotational thromboelastometry are of immense value to decide the further course of treatment [discussed elsewhere in book] [11–19].

The reversal strategies for VKA-related coagulopathy are well established and consist of prothrombin complex concentrate (PCC), fresh frozen plasma (FFP), and vitamin K_1 [Fig. 1]. All recent anticoagulation reversal management guidelines recommend immediate discontinuation of VKA and administering 4-factor PCC (4F-PCC) as an approved specific reversal agent for VKAs, in cases of severe and life-threatening

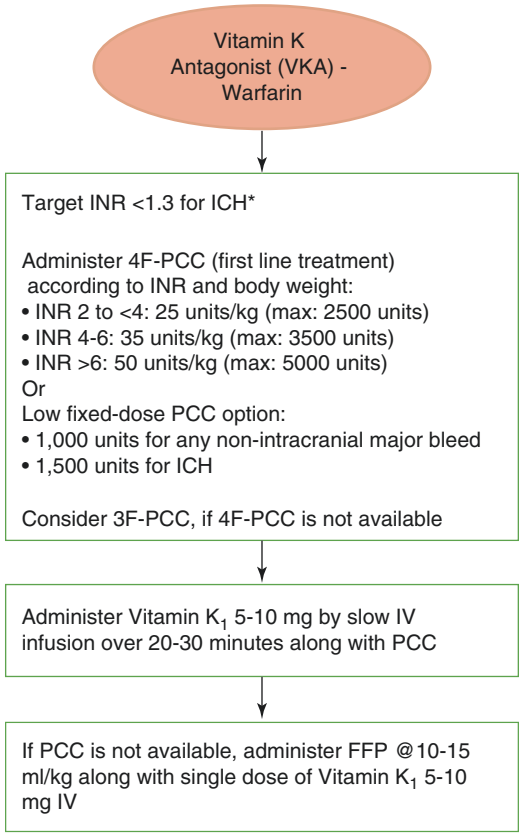

Fig. 1 Reversal strategies for vitamin K antagonists in neurosciences. PO, per oral; IV, intravenous; INR, international normalized ratio; ICH, intracranial hemorrhage; 4F-PCC, 4-factor prothrombin complex concentrate; 3F-PCC, 3-factor prothrombin complex concentrate; FFP, fresh frozen plasma. * Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA. 2015 Feb 24;313(8):824–836

bleeding or prior to emergency surgery [2, 6, 11, 17, 18]. In absence of 4F-PCC, 3-factor PCC (3F-PCC) can be used. At present, there is limited role of FFP in VKA reversal, except in circumstance when PCC is not available. Vitamin K_1 (5–10 mg, intravenous (IV)] should always be co-administered with FFP and PCC to promote hepatic production of vitamin K-dependent coagulation factors (factor II, VII, IX, and X), protein C, and protein S.

For coagulopathy associated with UFH or LMWH (dalteparin and enoxaparin), protamine serves as an effective antidote in the setting of ICH or emergent neurosurgical procedures [2, 20] [Fig. 2]. For fondaparinux, protamine is not effective, and 4F-PCC or activated PCC (aPCC) is used for nonspecific reversal of anticoagulation [2, 20]. Recombinant factor VIIa (rFVIIa) can be tried in case PCC is not available, though there is very limited data to support this recommendation [2, 21, 22]. Andexanet alfa is a new specific reversal agent that has been shown to reverse enoxaparin but is not approved by United States Food and Drug Administration (US FDA) yet [23].

Compared to warfarin and heparin, there is a lack of high-quality evidence for the reversal strategies used for managing DOAC-related coagulopathy [11, 13–16, 18, 19]. Furthermore, in many clinical settings, ideal laboratory tests that accurately and precisely measure the anticoagulation effect of DOACs (dTT, ECT, and specific anti-FXa) assay) are either not available or are delayed. Hence, for life-threatening/emergency situations and presumably DOAC-associated bleeding, administering general supportive measures and specific reversal agents immediately without waiting for coagulation assay are recommended. Recently, two specific DOAC reversal agents have been approved for clinical use that sequester and neutralize the anticoagulants, including idarucizumab for dabigatran and andexanet alfa for rivaroxaban and apixaban [24, 25]. At present, revised guidelines from the American College of Cardiology (ACC) on the management of bleeding in patients on oral anticoagulant, American Heart Association (AHA)/ACC/Heart Rhythm Society, Anticoagulation Forum, American College of Emergency Physicians, Emergency Medicine Cardiac Research and Education Group, French Working Group on Perioperative Hemostasis, and International Society on Thrombosis and Hemostasis recommend considering specific reversal agents (i.e., idarucizumab for reversal of dabigatran and andexanet alfa for reversal of FXaIs), as first-line therapies in patients with life-threatening bleeding or uncontrolled bleeding [Fig. 3] [11, 13–16, 18, 19]. However, there are certain limitations to the use of these specific reversal agents including their limited availabil-

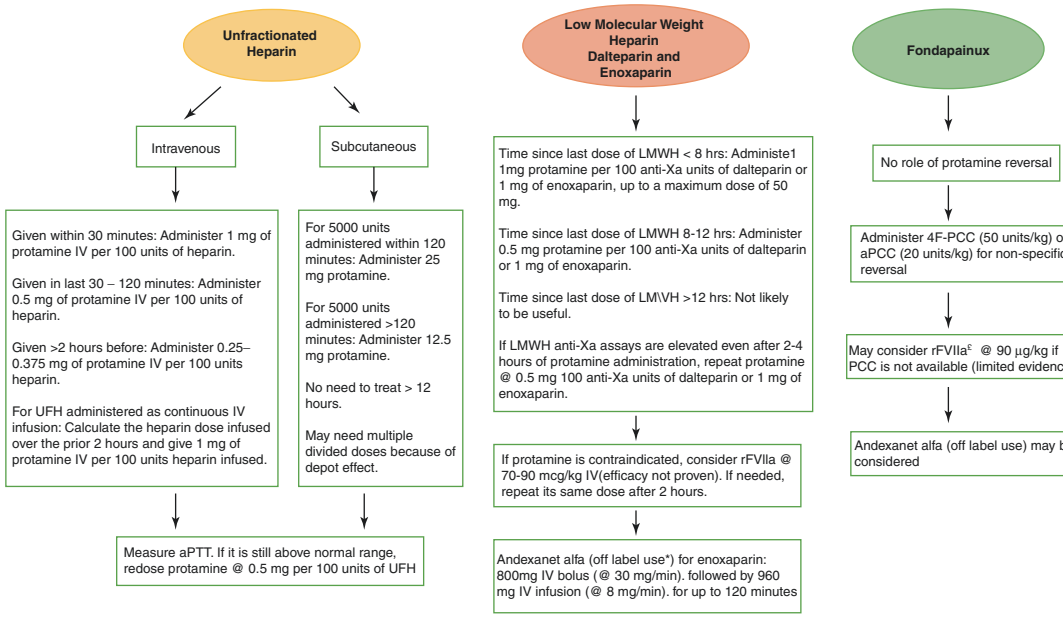

Fig. 2 Reversal strategies for heparin and derivatives in neurosciences. UFH, unfractionated heparin; LMWH: low molecular weight heparin; IV, intravenous; aPTT, activated partial thromboplastin time; anti-Xa, anti-factor Xa; rFVIIa, recombinant factor VIIa; 4F-PCC, 4-factor prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate. * Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2019 Apr 4;380(14):1326–1335. £ Bijsterveld NR, Moons AH, Boekholdt SM, van Aken BE, Fennema H, Peters RJ, et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. Circulation. 2002 Nov 12;106(20):2550–2554

ity and exorbitantly high costs ($3482.50 for a pair of 2.5 g vials of idarucizumab and $3300 per 100 mg vial of andexanet alfa).

In emergency conditions, second-line reversal strategies, including nonspecific procoagulant agents, such as 4F-PCC, aPCC, or rFVIIa, may be used if the specific reversal agents are not available [2, 11, 13–16, 18, 19]. Compared to rFVIIa, 4F-PCC or aPCC provides reliable reversal of anticoagulation along with a lower thromboembolism risk [2]. An oral suspension of activated charcoal (50 g) may be considered in patients with known recent ingestion (within 2–4 h) of all the DOAC [2, 11]. However, there exists a risk of aspiration in neurological patients with impaired consciousness, which mandates securing of airway. The Neurocritical Care Society (NCS) and Society of Critical Care Medicine (SCCM) guidelines also recommend considering hemodialysis in patients with dabigatran-associated ICH and renal insufficiency, or dabigatran overdose, in absence of idarucizumab [2]. Hemodialysis is essentially ineffective for rivaroxaban and apixaban, since they have high degree of protein binding, which can result in lower dialysis clearance. In clinical practice, reversal strategies aimed at removing anticoagulant agent using either activated charcoal or through hemodialysis remain of limited utility in neurosurgical patients, owing to the time-critical nature of these interventions [2]. Compared to dabigatran, DTIs, bivalirudin, and argatroban have no antidotes or other agents that can reliably reverse their anticoagulant properties. In severe life-threatening emergencies, 50 units/kg PCC may be attempted [20].

The most common post anticoagulant reversal-associated complications include incomplete anticoagulant reversal and continuation of bleeding, thrombotic events (ischemic stroke or MI) secondary to failure to re-institute anticoagulant therapy in patients with baseline prothrombotic

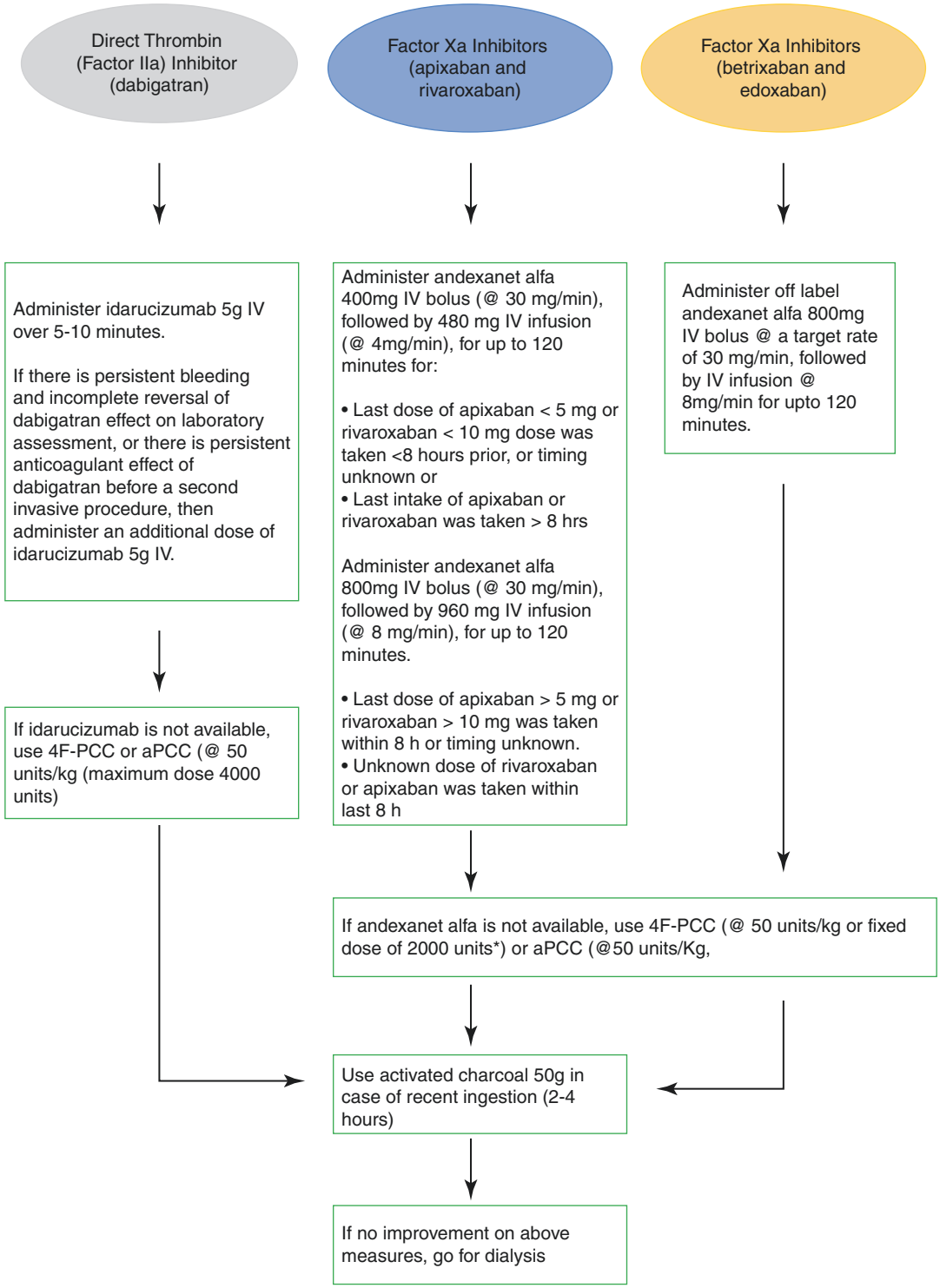

Fig. 3 Reversal strategies for direct oral anticoagulants in neurosciences. IV, intravenous; 4F-PCC, 4-factor prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate. * Schulman S, Gross PL, Ritchie B, Nahirniak S, Lin Y, Lieberman L, et al. Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study. Thromb Haemost. 2018 May;118(5):842–851

state and death, secondary to the life-threatening bleeding episode or associated comorbidities.

Anticoagulant Reversal Agents

Vitamin K_1 (Phytonadione)

Phytonadione is a synthetic lipid-soluble form of vitamin K_1. It acts as a cofactor in hepatic production of the vitamin K-dependent clotting factors II, VII, IX, and X and proteins C and S and thereby reverses anticoagulant effect of warfarin [26]. The recommended routes of administration are oral and IV [2, 6, 11, 16]. Compared to oral route, IV administration of vitamin K_1 allows for rapid decrease in INR (18 to 24 h with oral route versus 1–2 h after IV). Hence, for critical bleeding events, it is imperative to administer 5–10 mg vitamin K_1 intravenously, while for non-emergent cases, IV route has no advantage over oral route [6]. Overall, vitamin K_1 takes up to 24–48 h for complete reversal of warfarin's anticoagulant effect and hence must be accompanied by a repletion strategy, using FFP or PCC, to quickly supplement factor levels [2, 6, 11, 16].

Vitamin K_1 has been approved by the US FDA as therapy for anticoagulant warfarin reversal [26]. The American College of Chest Physicians (ACCP), however, does not recommend vitamin K_1 if the INR is 10 or less, except in cases with critical, life-threatening bleeds or awaiting urgent surgical intervention [6]. Patients with acute ICH should be given FFP or PCC along with vitamin K_1 to minimize the risk of early hematoma expansion [2]. However, when achieving emergency reversal of warfarin, the vitamin K_1 dosage should be kept as low as possible, as the overzealous therapy with vitamin K_1 may make the patient refractory to later warfarin therapy.

Being poorly water soluble, the injectable aqueous dispersion of vitamin K_1 contains an emulsifier such as polyoxyethylated castor oil (PEO-CO), polysorbate-80, or mixed micelles (MM). In addition, the parenteral formulation has 0.9% benzyl alcohol which is added as a preservative, which has been found to be associated with toxicity in newborns and manifests as the "gasping syndrome" [26, 27]. Among its side effects, vitamin K_1 can cause pain, swelling, and tenderness at injection site, transient flushing sensations, and altered taste. In addition, rare episodes of dizziness, profuse sweating, tachycardia, brief hypotension, dyspnea, and cyanosis have been reported in literature.

A boxed warning exists with IV administration of vitamin K_1 due to the possibility of severe anaphylactic/anaphylactoid reactions, in the form of urticaria, severe hypotension, bradycardia or tachycardia, dyspnea, bronchospasm, angioedema, cardiac or respiratory arrest, and death [26]. These reactions may occur secondary to either vitamin K_1 itself or the emulsifying agent (more with POE-CO than MM) [26, 27]. They appear immediately or within 20 min of vitamin K_1 administration and are seen predominantly with IV route of administration, higher doses, inadequate dilution, and rapid infusion [27, 28]. The ACCP guidelines advocate that when administered IV, the lowest effective dose should be administered (i.e., 5–10 mg), after appropriate dilution in at least 50 mL of fluid (either 0.9% sodium chloride, 5% dextrose, or 5% dextrose and sodium chloride) at a rate not exceeding 1 mg per minute, over a minimum of 20 min [6]. However, these adverse reactions have been observed more frequently in the past and are not observed with the current preparations. Nonetheless, extreme precaution should be taken whenever IV route is sought for emergency reversal of warfarin-associated coagulopathy in ICH patients.

Fresh Frozen Plasma

Allogenic fresh frozen plasma is obtained from whole blood and contains factors II, VII, VIII, IX, X, and XI and von Willebrand factor (vWF), at the same concentration as present in plasma, fibrinogen (400 to 900 mg/unit), plasma proteins (particularly albumin), electrolytes, physiological anticoagulants [protein C, protein S, antithrombin, tissue factor (TF) pathway inhibitor (TFPI)], and added anticoagulants. When used as a reversal agent, FFP provides nonspecific repletion of clotting factors compared to factor concentrates (PCC and cryoprecipitate) and recombinant products. Unlike PCC, it requires

ABO blood group typing and matching followed by thawing before transfusion, which may delay its administration by up to 90 minutes. Furthermore, compared to 4F-PCC, FFP achieves poor control of INR within an hour of administration (achieved INR of 2.2–12 with FFP versus 1.4–1.9 with 4F-PCC) [29]. Hence, despite its easy availability, it does not carry a favorable profile for urgent reversal of VKA-induced coagulopathy in ICH settings [30].

Variable dosing ranges (from 5 to 30 mL/kg) have been used to achieve normalization of INR, with an average of 10–15 ml/kg of body weight (4 to 6 units in adults) [2, 5]. In addition, transfusion of 4–6 units of FFP (with 250 ml per unit volume) provides an added intravascular resuscitation of approximately 1.5 L. This high transfusion volume may increase the risk of transfusion-associated circulatory overload in susceptible patients, especially those with poor renal function and compromised heart and lung mechanics, leading to heart failure and pulmonary edema [31–33].

Other known potential adverse effects include risk of allergic reactions, transmission of infectious agents, and risk of transfusion-related acute lung injury (TRALI). In the literature review of studies comparing 4F-PCC with plasma for VKA reversal, both PCC and FFP were found to be associated with a similar thromboembolic risk [29, 33]. Brekelmans et al. have reported thromboembolic complications and mortality ranging from 0 to 18% (mean 2.5%) and 0 to 43% (mean 17%), respectively, in the PCC and 6.4% and 4.8–54% (mean 16%), respectively, in the FFP recipients [29].

Prothrombin Complex Concentrates

PCC typically consists of purified and highly concentrated vitamin K-dependent coagulation factors (II, VII, IX, and X) obtained from pooled human plasma. It can be stored at room temperature as a lyophilized powder, rapidly reconstituted and infused. Currently, there are three different formulations available: 4F-PCC, 3F-PCC, and aPCC. 4F-PCC contains variable amounts of coagulation factors II, VII, IX, and X and proteins C and S [34]. 3F-PCC contains factors II, IX, and X with negligible levels of factor VII, protein C, and protein S. In addition, both 3F-PCC and 4F-PCC contain heparin which avoids activation of these factors, thus necessitating their physiological activation by the coagulation cascade for them to be effective. aPCC, on the other hand, contains activated form of factor VII, along with non-activated factors II, IX, and X. FEIBA is a freeze-dried sterile human plasma fraction with factor VIII inhibitor bypassing activity and prothrombin complex factors [35].

Currently PCCs are indicated primarily for supplementing clotting factors in patients with VKA-induced coagulopathy and for nonspecific reversal of FXaIs. In patients with VKA-associated ICH, NCS/SCCM recommends urgent administration of either 3F-PCC or 4-F PCC, in comparison to FFP [2] Likewise, the recent ACC guidelines recommends the use of 4F-PCC for rapidly reversing VKAs in the event of bleeding complication or prior to high-risk surgery [11]. Results of several clinical trials, including the INCH trial (International Normalized Ratio [INR] Normalization in Coumadin Associated Intracerebral Hemorrhage), have shown the superiority of PCC over plasma in rapidly reducing INR and achieving effective clinical homeostasis [30–32]. In addition, PCC carries several other advantages over FFP which makes it a preferable choice for rapid warfarin-anticoagulation reversal, including lack of ABO blood group compatibility and thawing, faster rate of administration, and low administration volumes. Thus, PCC may be safe to administer in patients with poor preload tolerance owing to renal or cardiac compromise. Furthermore, PCC are associated with lower risk of transfusion-related adverse effects (including TRALI), transfusion reactions, and viral transmission.

Current guidelines also recommend the use of PCCs and aPCC for nonspecific reversal of both FXaI and DTI (dabigatran) anticoagulant activity when a more specific reversal is unavailable or in situations where the anticoagulant agent is unknown [11, 13–16, 18, 19]. In a single-center cohort UPRATE trial, authors observed effective hemostasis (in 69.0% of patients) and a low risk of thrombosis (3.6%), with 4F-PCC therapy in

patients with FXaI (rivaroxaban or apixaban)-associated ICH (70.2%) or gastrointestinal bleed (15.5%) [36]. Schulman et al. evaluated the hemostatic efficacy of 4F-PCC in 66 patients with major bleeding (including 36 ICH patients) and found it to be good, moderate, and poor in 67%, 17%, and 17% of the ICH patients, respectively, along with a thromboembolic event rate of 8% [37]. Recent retrospective case series comparing hemostatic efficacy of 4F-PCC with andexanet alfa for reversal of FxaIs demonstrates variable findings, with an overall hemostatic efficacy of 4F-PCC ranging from 60 to 88% along with a high thrombogenic potential as high as 31% [38–40]. Though not indicated, PCCs may be used to rapidly replace the clotting factors in cases of major and trauma-related bleeding [41, 42]. In addition, PCC may also be used to reverse parenteral anticoagulants like argatroban and bivalirudin.

The specific activity of PCC products is expressed in terms of factor IX activity. The amount and frequency of PCC administration should be calculated individually on the basis of patient body weight, baseline INR, target INR, critical or non-critical site of bleeding, extent of bleeding, and the patient's clinical condition. However, given the availability of different PCCs, the optimal agent and dosing regimen is yet to be established to maximize its efficacy and safety [43]. 4F-PCC is usually dosed at 25–50 units/kg, as per the treating clinician discretion, with a maximum dose of 5000 units. PCC must be used within 4 h of reconstitution and infused over 10–15 min for VKA reversal. The onset of action is within 30 min, and its duration of action is 6–24 h. Compared to PCC, warfarin has longer half-life and requires sustained reversal. Hence, while reversing warfarin with PCC, vitamin K must always be co-administered to achieve near normalized clotting factor levels in the circulation.

aPCC (FEIBA) administration has also been found to be relatively safe and effective in reversing warfarin and DOACs in the setting of ICH with a trend toward shorter time to neurosurgical interventions [44–46]. However, compared to 4F-PCC, aPCC administration was found to be associated with lower achievement of INR ≤1.5 (aPCC = 70.9% vs. 4F-PCC = 88.4%), along with comparable incidence of thrombotic events (6.3% and 7.6%, respectively) and mortality while achieving VKA reversal in patients with warfarin-associated major hemorrhage, including ICH [43].

PCCs have a potential prothrombotic risk and carry a boxed warning on their labels for venous and arterial thrombosis [29, 34, 35, 47]. In a cohort of 542 patients receiving PCC for anticoagulation reversal (76.6% warfarin/23.4% DOAC reversal), 50 patients (9.2%) experienced thromboembolic events, mostly (62%) within 7 days of 4F-PCC administration [47]. Authors also observed an independent association between thromboembolic risk and younger age, indication for anticoagulation, and total length of hospital, which may have an influence on anti-coagulation management. Both 3F-PCC and 4F-PCC share common thrombotic risk [48]. Current PCC formulations, however, carry a lower risk of thrombosis owing to the presence of natural coagulation inhibitors including heparin, antithrombin, protein C, and protein S. Nonetheless, thrombotic complications may arise secondary to accumulated levels of factor II, following excessive PCC administration. Immediate allergic reactions and heparin-induced thrombocytopenia (HIT) are other documented side effects of PCC.

aPCC may be administered to patients with a prior history of HIT.

Protamine Sulfate

Protamine (sulfate or chloride) is a polycationic, highly positively charged protein which binds to negatively charged heparin molecules in a 1:1 ratio, thus displacing antithrombin III (ATIII) from the heparin-ATIII complex and blocking its anticoagulation effect. The heparin-protamine complex is immediately removed from the circulation by the reticuloendothelial system. In addition to neutralization of heparin, protamine has its own anticoagulant properties at doses higher than those needed to reverse heparin molecules. The possible mechanisms include interference with platelet function and thrombocytopenia, enhanced fibrinolysis, and reducing the genera-

tion and activation of clotting factors including factor II, factor V, factor VII, and factor VIII.

Protamine was originally derived from salmon sperm and is now increasingly being produced through recombinant technology. Currently, it is the only FDA-approved reversal agent to neutralize the excessive anticoagulant effect of UHF in the settings of separation from cardiopulmonary bypass, dialysis, invasive vascular procedures, and AIS [49, 50]. It is also used by clinicians for partial reversal of LMWH including enoxaparin, dalteparin, and tinzaparin, but the degree of reversal is unclear, and this use has not been FDA-approved. Compared to UFH, LMWHs have a longer half-life and are only partially reversed by protamine. LMWHs have anti-factor Xa (anti-Xa) to anti-factor IIa (anti-IIa) activity ratios between 1.6:1 and 8:1, depending on their average molecular weight and molecular size distribution. Protamine sulfate fully neutralizes LMWHs' anti-IIa activity, but its action against anti-Xa activity is limited to approximately 60%, likely owing to poor binding by protamine to the small molecular moieties of LMWHs [51]. Heparins with the highest amount of sulfate per saccharide unit (tinzaparin, dalteparin) are more efficiently inactivated than enoxaparin. Likewise, new-generation LMWH is found to be more efficiently neutralized by protamine sulfate than enoxaparin [52].

Dosing of protamine is dependent on the duration since the most recent heparin dose [Fig. 2]. Since heparin is cleared rapidly from the circulation, the dose of protamine required for its neutralization also decreases rapidly with the time elapsed following its administration. For immediate reversal of UFH (used IV), 1 mg protamine neutralizes 100 units of UFH, administered within the last 30 minutes [49, 50]. However, if UFH has been given subcutaneously (and therefore is cleared with a longer half-life), prolonged or repeated administration of protamine sulfate may be required. For LMWH anticoagulation reversal, 1 mg of protamine neutralizes 1 mg of LMWH which is equivalent to 100 anti-Xa units. Protamine has an immediate onset of action (5 min), elimination half-life of 7 min, and its duration of action is 2 h. Because the action of protamine is shorter than that of heparin, follow-up coagulation tests should be performed to detect a "heparin rebound" effect, which may contribute to postoperative bleeding and increased transfusion requirements. The celite or kaolin ACT is typically used to assess the heparin-neutralizing effects of protamine 5–15 min after its administration.

Higher doses are known to cause significant adverse anticoagulant effects which may contribute to bleeding and increased transfusion requirements [49, 53, 54]. Rapid infusions may result in transient flushing, a feeling of warmth, bradycardia, and hypotension. Though rarely reported, protamine can cause severe life-threatening anaphylactic/anaphylactoid reactions (0.19–0.69%) with rash, urticaria, severe systemic hypotension, pulmonary hypertension, bronchospasm, noncardiogenic pulmonary edema, and/or circulatory collapse [53, 54]. Hence, protamine should be given IV slowly (over 10 min) not exceeding 5 mg/minute (maximum recommended dose is 50 mg), with epinephrine and isoproterenol ready for immediate management of cardiovascular collapse if it occurs. Common risk factors for these anaphylactic reactions include past history administration (earlier cardiac surgery)/allergy of protamine and current or previous use of protamine-containing drugs (NPH insulin, protamine zinc insulin, and certain beta-blockers), fish allergy, and previous vasectomy. Protamine should ideally be avoided in patients with these risk factors, with consideration given to alternative therapy for heparin anticoagulation, with bivalirudin.

Recombinant Factor VIIa

rFVIIa is an activated form of clotting factor VII, which has been approved by the US FDA for the management of bleeding in patients with hemophilia A or B with inhibitors, acquired hemophilia, or congenital factor VII deficiency [55]. At pharmacological doses, it has also been shown to boost hemostasis in patients with normal coagulation by directly activating factor X on the surface of activated platelets (without the need for factor VIII and factor IX) and by increasing the activity of the extrinsic TF-associated coagula-

tion pathway. By increasing thrombin generation, it facilitates formation of a firm, well-structured fibrin hemostatic plug, which is resistant to premature lysis. However, despite its ability to rapidly reduce INR, it may not restore thrombin generation effectively as it does not replenish all of the vitamin K-dependent factors. Hence, rFVIIa is currently not recommended for VKA reversal in patients presenting with ICH [2]. Nonetheless, it has been used off-label in emergency management of VKA-associated ICH (in the event of non-availability of PCC), acute spontaneous ICH, and reversal of newer parenteral anticoagulants (particularly fondaparinux), with limited success [21, 22, 56].

Though the most effective dose for warfarin reversal has not been established, it has been used widely in varying doses ranging from 15 to 90 mcg/kg. It is available as a white lyophilized powder in single-use vials at 1 mg/mL concentration and can be easily and rapidly administered in large doses (bolus injection over 2 to 5 min), with an almost instantaneous effect. It has a half-life of approximately 2.5 h. Results of the large clinical trials in patients with acute hemorrhagic strokes (FAST, SPOTLIGHT, and STOP-IT trials) suggest that though the use of 80 mcg/kg of rFVIIa does reduce the growth in the volume of ICH, it does not improve survival or functional outcome of patients [57, 58]. In addition, rFVIIa therapy has been found to be associated with a higher incidence of arterial and venous thromboembolic events (12.8% –24%) and hypersensitivity reactions [2, 55–57, 59].

Idarucizumab

Idarucizumab is a humanized monoclonal antibody fragment, which is developed by Boehringer Ingelheim (maker of dabigatran) for emergency reversal of coagulopathy from dabigatran [24] It has high specificity and affinity for dabigatran and its acyl glucuronide metabolites (approximately 350 times higher than the binding affinity of dabigatran to thrombin), thus rapidly neutralizing and reversing dabigatran's anticoagulant effect. It binds to both free and thrombin-bound dabigatran, readily displacing it and allowing normal fibrin formation. Dabigatran's efficacy and its reversal by idarucizumab is best assessed by measuring the ECT, dTT, and the amount of free or unbound dabigatran in circulation [11, 12].

Its recommended dose is 5 g given in 50 ml infusion intravenously over 5–10 min. Though the elimination half-life of idarucizumab is approximately 45 min, the observed onset of action and duration of action has been reported to vary widely from immediate to up to 4 h of administration and for 12–72 h of duration, respectively. Idarucizumab is known to completely reverse dabigatran in >98% of patients regardless of age and renal function [60]. Clinically, the time to bleeding cessation and the extent of hemostasis during procedures remain the same, despite re-elevation of dabigatran levels within 12 to 24 h, commonly seen in patients with renal impairment [61]. However, massive dabigatran accumulation as in renal failure necessitates either repetitive idarucizumab boluses or combined therapy along with hemodialysis/renal replacement therapy. Consideration should also be given for a second dose in patients with new-onset or re-current bleeding and in patients who require a second emergency surgery/urgent procedure [62, 63]. Though it's safe in geriatric population, its safety has not yet been proven in hepatic impairment, pediatric population, and pregnancy and lactating women.

Recent guidelines recommend use of idarucizumab as a gold standard reversal therapy for dabigatran in patients with critical or uncontrolled bleeding or scheduled to undergo emergency surgical procedures associated with a high risk of bleeding [11, 13–16, 18, 19]. In case of emergency surgeries, assessing plasma dabigatran level prior to reversal could decrease the inappropriate or excessive use of idarucizumab that may have significant financial implications considering the exorbitantly high cost of idarucizumab [64]. Idarucizumab was first approved for emergency use by the US FDA in 2015 following an initial analysis of data from the RE-VERSE AD trial which was later followed by the full cohort analysis of 503 patients on dabigatran, confirming its efficacy and safety [62, 63]. From neurosurgical perspective, out of total 301

patients presenting with bleeding, 98 (32.6%) had ICH, and of the rest 202 patients presenting for an urgent procedure, only 140 underwent surgical procedures including 8 neurosurgical interventions [65]. The median time from the first vial of idarucizumab to neurosurgical procedure 3.3 h (range 0.4–130.4 h) with normal surgical hemostasis achieved in all eight cases.

Recent literature recommends the use of idarucizumab during IV thrombolysis treatment of dabigatran-treated patients with AIS and in dabigatran-treated patients with ICH [66]. The biggest advantage of idarucizumab in AIS patients is the instant reversal of dabigatran anticoagulation, thus enabling timely IV thrombolysis and thrombectomy [67] and limiting hematoma expansion in ICH patients [65, 68]. In a systematic review of literature, Lu et al. described clinical outcomes in 23 dabigatran-associated cases of ICH (10 SDH, 3 SAH, and 10 ICH presentations) managed by idarucizumab, supporting both the efficacy and safety of idarucizumab, with favorable complication and mortality incidences. Hemorrhages were observed to stabilize or resolve in 20 (87%) patients following dabigatran reversal, with no drug-related adverse effects [68]. Authors reported an in-hospital mortality rate of 4%, which was comparable to the 9% mortality rate reported by Pollack et al. in the idarucizumab-reversed ICH in the RE-VERSE AD study [63].

The most frequently reported adverse drug effects include headache in healthy volunteers and hypokalemia, delirium, constipation, pyrexia, and pneumonia in patients [24]. In addition, hypersensitivity reactions, manifesting as bronchospasm, hyperventilation, rash, and pruritus, have been observed. In such cases, idarucizumab should be immediately discontinued, along with institution of appropriate supportive treatment. The recommended dose of idarucizumab contains 4 g sorbitol as an excipient, which predisposes to a risk of serious adverse reactions in patients of hereditary fructose intolerance. Fatal reactions are seen in form of hypoglycemia, hypophosphatemia, metabolic acidosis, hyperuricemia, and acute liver failure. Idarucizumab reversal has an associated thromboembolic risk, secondary to unmasking of the underlying prothrombotic disease state. However, recent literature suggests a comparatively lower risk of thrombosis with idarucizumab [3.3% (95% CI 0.7–7.2%)] than that associated with use of PCC or andexanet alfa [10.6% (95% CI 1.9–23.7%)] [29, 47, 69, 70].

Andexanet Alfa

Andexanet alfa is a recombinant decoy protein, with two important structural modifications of the factor Xa molecule [25]. First the serine active site, which binds to and cleaves prothrombin to thrombin, is substituted by alanine, which makes the catalytic site inactive. Another modification includes cleavage of gamma-carboxyglutamic acid domain at the opposite end of the molecule, thus eliminating the protein's ability to assemble into the prothrombinase complex to generate thrombin. It avidly binds to FXaIs with high affinity, thus enabling the native factor Xa to function in clotting cascade. Thus, andexanet alfa may have some intrinsic procoagulant activity as well, thereby creating the potential for adverse thromboembolic events in certain subjects. It also binds to heparin-antithrombin III complex, reversing the actions of LMWH and UFH. Andexanet alfa is, thus, a specific reversal agent that completely reverses direct (apixaban, edoxaban, rivaroxaban, and betrixaban) as well as indirect (e.g., fondaparinux and the LMWH enoxaparin) FXaIs [71].

It is available as a lyophilized powder in 100 mg or 200 mg dose vials, refrigerated at 2 °C–8 °C. Andexanet dosing is time-sensitive and depends upon the type of FXaI the patient is taking, its dose, and the time-elapsed since last intake [25]. Current dosing recommendations includes IV bolus dose of 400–800 mg over 15–30 min, followed by 2 h of continuous infusion of 480–960 mg [Fig. 3]. Its anticoagulant reversal activity is seen within 2–5 min after its administration and is measured by reduction (mean percent change) in anti-factor Xa activity and unbound plasma concentrations of FXaIs. Its reversal effect lasts for 12 h after stopping the infusion. It has a mean apparent volume of distri-

bution of ≈5 L and an elimination half-life of 5–7 h, which remains unaffected by age.

Recent guidelines recommend andexanet alfa for rivaroxaban- and apixaban-associated bleeding and either the use of andexanet alfa or 4-factor PCCs for edoxaban- and betrixaban-associated bleeding, in the event of life-threatening or uncontrolled bleeding [11, 15, 16, 18, 19]. Andexanet alfa received US FDA approval as a specific reversal agent for rivaroxaban- or apixaban-induced life-threatening or uncontrolled bleeding via accelerated approval pathway in 2018, based on the change from baseline in anti-FXa activity in healthy human volunteers [72] and the interim analysis of ANNEXA-4 (andexanet alfa for acute major bleeding associated with factor Xa inhibitors) trial [73]. The full study results of a prospective multicenter ANNEXA-4 trial were published in 2019, after its FDA approval [73]. The ANNEXA-4 trial evaluated the efficacy and safety of andexanet in a single cohort of 352 patients with acute major bleeding [ICH (64%), gastrointestinal (26%), other bleeding (10%)] and had taken their last dose of FXaIs (apixaban, rivaroxaban, or edoxaban at any dose or enoxaparin at a dose of at least 1 mg/kg per day) within 18 hours of presentation. Study results showed 92% reduction of median anti-factor Xa activity in patients taking apixaban and rivaroxaban. Excellent or good hemostatic efficacy was observed in 82% of the patients at 12 h, with thromboembolic event rate of 10% and mortality of 14% at 30 days. ANNEXA-4 study, however, has significant study limitations and criticism secondary to the lack of control arm. The clinical efficacy and safety of intraoperative use, re-dosing, or extended infusions of andexanet alfa needs to be validated in future studies. Recently, a trial has been started in January 2019, to study the hemostatic efficacy of andexanet alfa in acute ICH in patients receiving an oral FXaI [74]. The results of the RCT are expected to be published by 2023.

Compared to PCC, andexanet alfa reversal costs exorbitantly higher and may even take a longer time to institute therapy, secondary to reconstitution and institution of 2-hour-long infusion [75]. Furthermore, recent literature has revealed similar hemostatic effectiveness of PCC and andexanet for the treatment of major bleeding in patients using FXaIs [76]. The commonly reported side effects of andexanet alfa include pneumonia, urinary tract infections, and infusion-related reactions, in addition to the black boxed caution issued against life-threatening thromboembolic events [25]. Recent literature reviews have revealed a higher incidence of thrombotic events with andexanet alfa compared to idarucizumab (10.6% versus 3.3%, respectively) as well as with PCC (pooled proportion of patients with thromboembolic events 0.11 in andexanet versus 0.03 in PCC studies, respectively) [69, 76]. To minimize the thrombosis risk, it is advisable to restart anticoagulant therapy as early as feasible in predisposed patients.

New Agents in Pipeline

Ciraparantag

Ciraparantag (formerly aripazine; PER977; developed by Perosphere Inc. Danbury, CT) is a small, synthetic, water-soluble, cationic molecule that was specifically designed to bind parenteral IIa/Xa inhibitors, UFH, and LMWH through non-covalent hydrogen bonds and charge-charge interactions [77]. However, it has shown similar binding and reversal characteristics to the oral FXaIs (apixaban, edoxaban, rivaroxaban) and to the oral DTI (dabigatran) as well, thus having a potential to become a universal reversal agent in the near future.

To date, it has been evaluated for its hemostatic efficacy and safety in bleeding animal models (rat tail transection and liver laceration) and non-bleeding healthy normal subjects on edoxaban and LMWH [78, 79]. It has been used in doses varying from 100 to 300 mg, showing complete reversal of the anticoagulant effect of edoxaban within 10–30 min of administration and sustained for at least 24 h [78]. It has rapid onset of action (5–10 min) and short half-life (12–19 min) with minimal plasma protein binding [77]. It rapidly achieves peak plasma concentrations and undergoes rapid widespread distribution throughout the body. It is primarily

hydrolyzed by serum peptidases into two metabolites, neither of which has any significant reversal activity. Both ciraparantag and its metabolites are recovered almost entirely in the urine 2 h after its administration.

The anticoagulant effect of ciraparantag can be monitored via whole blood clotting time (WBCT). Plasma-based coagulation assays are unsuitable for monitoring purpose because of binding of ciraparantag to contact pathway activators such as celite, kaolin, and in vitro anticoagulants such as citrate, EDTA, and heparin. An automated point of care coagulometer device is being developed for this purpose (as yet unlicensed) that will provide sensitive, accurate, and bedside measurement of WBCT and thus may facilitate its emergency use [80].

The most common potential adverse events of ciraparantag include periorbital and facial flushing, dysgeusia, headache, and cool sensation following IV injection. However, no procoagulant affects have been observed as measured by the laboratory values of D-dimer, prothrombin fragments 1.2, and TFPI levels. Phase 2 studies in healthy volunteers are currently in progress or have been completed and awaiting results, which will further pave the way for future phase 3 trials assessing the efficacy and safety of this promising agent in the clinical setting of major hemorrhage or urgent surgery [81–83].

Activated ^{super}Factor V

Activated ^{super}Factor V is an engineered activated protein C (APC)-resistant FVa-variant which utilizes drug-absorbing strategy for reversal of DOAC-associated bleeding. Normal FVa enhances the rate of thrombin generation in the prothrombinase complex by approximately 10,000-fold, but is rapidly inactivated by APC. Mutations of three APC cleavage sites (Arg506/306/679Gln) make SuperFVa resistant to APC inactivation. In addition, an engineered A2/A3 domain disulfide bond (Cys609-Cys1691) further enhances its specific activity [84]. Thus, SuperFVa's ability to both enhance the DOAC-compromised prothrombinase complex and APC-resistance provides a double advantage for inhibition of DOAC-associated bleeding. SuperFVa has been shown to reverse bleeding induced by FXaIs (rivaroxaban, apixaban), and the FIIa inhibitor dabigatran in Balb/c mice [85]. Further studies are needed to explore the class-independent prohemostatic activity of this promising universal DOACs reversal agent.

Protamine Alternatives

To avoid the unacceptable side effects associated with protamine administration, the search of various alternatives is on. Molecules like universal heparin reversal agent, Dex40-GTMAC3, cationically modified chitosan (HTCC2), cationically modified hydroxypropylcellulose (HPC-APTAMAC), and low molecular weight protamine are currently in the preclinical stage, while ciraparantag (as discussed above) is in the advanced clinical phase of approval [54].

2. Reversal of Antiplatelets

Traumatic or spontaneous bleeding especially in the form of ICH occurs in 10 to 30% of cases in patients on long-term antiplatelet therapy [86]. Antiplatelet therapy is independently associated with perioperative bleeding risk, transfusion requirements, increase in the size of ICH along with unfavorable functional outcome, and mortality in this patient population [87–89]. For patients on APAs, platelet function remains inhibited for a minimum of 96 hours after discontinuation of aspirin and for a minimum of 5–7 days after stopping $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel, and ticagrelor). Hence, to reduce the risk of bleeding, recent guidelines from the French Working Group on Perioperative Haemostasis (GIHP) and the French Study Group on Thrombosis and Haemostasis (GFHT) recommend a preoperative discontinuation period of 3 days for aspirin, 5 days for clopidogrel and ticagrelor, and 7 days for prasugrel, with the addition of 2 days for elective intracranial surgery, regardless of the APA [90]. However, for patients presenting with antiplatelet-associated ICH, no specific hemostatic therapy exists for emergency reversal of APAs [2, 91, 92].

The available guidelines from NCS/SCCM, British Committee for Standards in Haematology, and GIHP strongly recommend discontinuing APA immediately when ICH is present or suspected, considering the risk of hematoma expansion in a closed space [2, 91, 92]. Various other treatment options, including perioperative platelet transfusion, desmopressin administration, rFVIIa, and tranexamic acid, have been suggested to partially restore appropriate thrombogenesis, though with limited data for efficacy [Fig. 4] [2, 20, 91–93]. No evidence-based guidelines are currently available for $P2Y_{12}$ inhibitors or GP IIb/IIIa inhibitor-related ICH [2, 20, 91, 92]. In urgent cases, cautious delay in surgical intervention may be recommended to mitigate the residual antiplatelet effect of APAs, along with platelet function testing to guide perioperative platelet transfusion and surgical decisions that are mainly based on expert opinion. However, in emergent life-threatening situations, high-dose platelet transfusion, desmopressin, and rFVIIa may be considered. Sorbent hemadsorption is an option for ticagrelor reversal but has limited role in emergency settings [94].

Antiplatelet Reversal Agents

Platelet Transfusion

Normal platelet functioning is an integral component of effective clot formation. In neurosurgical patients, a platelet count of 100×10^9 cells/l or more is the minimum acceptable criteria for achieving effective hemostasis [91, 95]. For patients taking APAs and presenting with ICH, platelet transfusion has been suggested to neutralize APAs and improve primary homeostasis by replenishing functional platelets in the circulation. The British Committee for Standards in Haematology recommends therapeutic platelet transfusions in patients with TBI or spontaneous ICH to maintain the platelet count above 100×10^9 cells/l. (Class 2C) [91]. For urgent reversal of aspirin, platelets should be transfused at a standard dose of 0.5 to 0.7×10^{11} platelets per 10 kg of body weight [92]. Higher doses are proposed in patients treated with clopidogrel or prasugrel (at least double the standard dose and higher for prasugrel than for clopidogrel).

Perioperative platelet function testing has been recommended to specifically indicate dys-

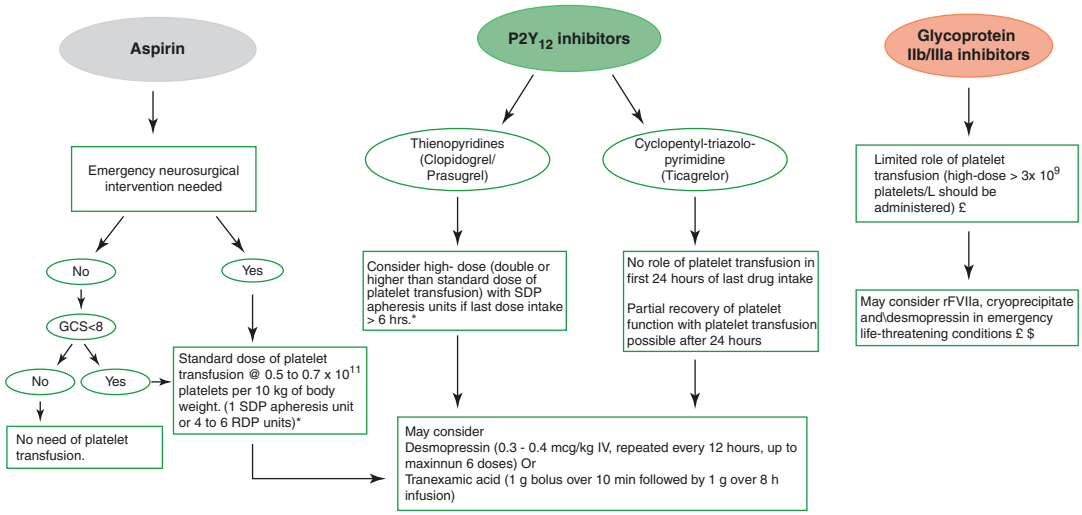

Fig. 4 Reversal strategies for antiplatelet agents in neurosciences. GCS, Glasgow Coma Score; SDP, single-donor platelet; RDP, random donor platelet; rFVIIa, recombinant factor VIIa. * Platelet testing is suggested prior to repeat platelet transfusion, if available and transfusion should be repeated only for those with persistently abnormal platelet function tests and/or ongoing bleeding. £ Dornbos D third, Nimjee SM. Reversal of Systemic Anticoagulants and Antiplatelet Therapeutics. Neurosurg Clin N Am. 2018 Oct;29(4):537–545. $ Wilbourn B, Harrison P, Mackie IJ, Liesner R, Machin SJ. Activation of platelets in whole blood by recombinant factor VIIa by a thrombin-dependent mechanism. Br J Haematol. 2003 Aug;122(4):651–661

function due to antiplatelet agents, in view of the proposed variability in on-treatment platelet reactivity and platelet function recovery timing [91, 92]. Use of bedside platelet function assays such as Platelet Mapping on TEG®6S (Haemonetics Corp., USA) and VerifyNow® (Instrumentation Laboratory Co., Bedford, MA, USA) can be used, to individually time the preoperative waiting period (in non-emergent stable cases) or to target perioperative platelet transfusion therapy [92]. However, the benefit of determining the discontinuation duration of the $P2Y_{12}$ inhibitor based on platelet function testing before neurosurgery has not been formally assessed.

Type of APA and the time since last intake are the two main factors that determine the neutralizing efficacy of platelet transfusion. Aspirin causes irreversible inhibition of cyclooxygenase, with a plasma half-life of 15–20 min. Thienopyridines (clopidogrel and prasugrel) bind irreversibly to the $P2Y_{12}$ receptor, existing as prodrug, and their active metabolites are relatively short-lived (30 min for clopidogrel and 4 h for prasugrel, respectively). In comparison, ticagrelor and its metabolite are reversible and directly active $P2Y_{12}$ inhibitors, with prolonged half-lives of 7 and 8.5 h, respectively. Hence in emergency situations with patient on a reversible inhibitor (i.e., ticagrelor) or on irreversible platelet inhibitor (aspirin, clopidogrel, or prasugrel) but with active metabolite still present in blood, the transfused "naïve" platelets also get inhibited, thus reducing the efficacy of platelet transfusion. Platelet transfusion is, thus, most effective in reversing the antiplatelet activity of clopidogrel and prasugrel if the time interval since the last intake of thienopyridine is more than 6 h [92].

Ticagrelor appears to be practically irreversible for up to 24 h after the last intake, with the possibility partial recovery at 24 to 48 h after administration [96]. Experimental data suggests that addition of human serum albumin might increase the reversal effect of platelet transfusion on ticagrelor [97]. Platelet transfusion has very limited role in patients with prior GPIIb/IIIa receptor inhibitors (abciximab, eptifibatide, or tirofiban) administration, as the transfused platelets are simply inhibited by circulating drug due to the rapid on/off pharmacokinetic properties of these small molecules.

In clinical practice, emergency platelet transfusion is the most extensively studied reversal strategy in antiplatelet-associated ICH. However, the literature to date provides inconclusive evidence as to the efficacy of platelet transfusion in limiting hematoma progression and survival benefit, particularly in nonoperative cases of antiplatelet-associated ICH [93, 98]. Xiaowei et al. demonstrated significant reduction in the incidence of rebleed and death in patients previously treated with aspirin monotherapy and transfused with previously frozen apheresis platelets before emergency craniotomy for acute hypertensive ICH [99]. The positive results led to the recommendation of platelet transfusion in antiplatelet-associated ICH by the NCS/SCCM. However, the proposed benefits of platelet transfusion on patient's outcome were called into question after the PATCH (platelet transfusion versus standard care after acute stroke due to spontaneous cerebral hemorrhage associated with antiplatelet therapy) trial revealed higher odds of death or disability at 3 months after platelet transfusion in nonoperative patients presenting with spontaneous ICH and Glasgow Coma Scores (GCS) ≥ 8 [93, 100].

The existing literature does not seem to favor empirical platelet transfusion in patients presenting with traumatic ICH and ongoing antiplatelet therapy. In a recent review of 12 studies on traumatic ICH in patients taking prehospital APAs (aspirin, dipyridamole, clopidogrel, ticagrelor, prasugrel, eptifibatide, or abciximab), Alvikas et al. observed no association between platelet transfusion and the risk of hematoma expansion, emergency surgical decompression, and death [98]. Furthermore, sensitivity analysis among studies with larger sample sizes revealed that though platelet transfusion reduced the risk of hematoma progression, it was associated with increased mortality, plausibly because of adverse reactions of platelet transfusion (hemolysis secondary to ABO incompatibility, anaphylaxis, bacterial sepsis, febrile non-hemolytic transfusion reaction, transmission of viral infections, and thrombosis). Immediate platelet transfusion is

unnecessary in blunt or mild TBI patients on chronic antiplatelet therapy who do not require immediate craniotomy [101]. However, these results cannot be extrapolated to the patients undergoing emergency neurosurgical interventions, where preprocedural platelet transfusion may still have some preventive role. In a recent study, Wu et al. explored the role of emergency surgery in patients with severe spontaneous ICH and receiving prior dual antiplatelet therapy and found it to be effective in improving patient's outcome [102]. Authors also observed that patients who received platelet transfusion had low rate of postoperative bleeding (1/11, $p = 0.312$), though the difference was not significant.

Thus, to summarize, platelet transfusion may be considered in ICH cases requiring neurosurgical intervention (though the quality of evidence for this is moderate), while it should be avoided in aspirin-treated cases that does not require urgent neurosurgery and presented with a GCS ≥ 8 on admission [2, 91, 92]. Further clinical trials are urgently needed to confirm the preventive effect of platelet transfusion on postoperative bleeding and functional recovery in the subset of ICH patients receiving pre-ICH dual antiplatelet therapy and requiring urgent neurosurgical intervention**.**

Desmopressin

Desmopressin is a synthetic analog of vasopressin that increases the plasma concentrations of vWF, factor VIII, and tissue plasminogen activator. vWF plays a major role in primary hemostasis by protecting FVIII from degradation, mediating platelet binding to the sub-endothelium at the site of vascular injury and promoting platelet aggregation. Thus, by increasing vWF levels, desmopressin may help to restore hemostasis in patients on antiplatelet therapy. Desmopressin is administered at a dose of 0.3–0.4 mcg/kg perfused in 100 mL of saline solution for 30 min, every 12 h for up to six doses [20]. It has quick onset of action (within 1 h), and effect lasts for 24 h. Current evidence provides weak evidence of higher platelet aggregation with desmopressin during aspirin monotherapy than during ADP-receptor inhibitor (clopidogrel, ticagrelor, prasugrel, or eptifbatide) treatment [103].

The NCS/SCCM guidelines provide conditional recommendation for a single dose of desmopressin (0.4 mcg/kg) in patients with ICH associated with aspirin/COX-1 inhibitors or ADP-receptor inhibitors and undergoing a neurosurgical procedure, though with low quality of evidence [2]. The recent GHIP guidelines do not recommend desmopressin in view of its poor efficacy in neutralizing the antiplatelet effects of APAs [92]. Recently, Andersen et al. investigated the effect of desmopressin on platelet function during antiplatelet therapy in patients undergoing non-cardiac surgery, patients with spontaneous or traumatic ICH, preclinical animal studies, and healthy volunteers [103]. In patients presenting with ICH, authors found an encouraging result with desmopressin administration resulting in improved bleeding time and increased platelet aggregation. Existing observational data, thus, suggests a possible effect of desmopressin in mitigating hematoma expansion, thus mandating future RCTs to support or refute the efficacy of desmopressin in antiplatelet-associated ICH.

DASH (Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage) trial is an ongoing multicenter phase-II RCT (started in year 2020) to assess the safety and efficacy of desmopressin for patients with antiplatelet-associated ICH [104]. In this trial, authors aim to include 50 patients with spontaneous antiplatelet drug-associated ICH, within 24 h of symptom onset, randomized (1:1) to receive IV desmopressin 20 micrograms or matching placebo. This is an ongoing feasibility trial, which will inform the design of a definitive trial. Adverse effects associated with the use of desmopressin include systemic vasodilation (with hypotension and reactive tachycardia), hyponatremia, hypervolemia, oliguria, and hyponatremic seizures, mandating close monitoring of serum sodium levels. An extensive literature review does not provide any evidence regarding increased incidence of thrombotic events in patients with ICH [103].

Tranexamic Acid

Tranexamic acid is an antifibrinolytic agent that is proposed to exert fibrin-clot stabilizing effect, thus contributing to hemostasis in antiplatelet-associated ICH, despite not having a direct platelet-enhancing effect. To date, tranexamic acid has been shown to be a safe, inexpensive, and effective hemostatic agent in reducing postoperative, traumatic, and postpartum hemorrhage bleeding, with decreased incidence of reoperations and reduced platelet/red blood cell transfusion requirements, with no significant increase in thromboembolic events or seizures [105]. Tranexamic acid is thus strongly recommended in cases of periprocedural or traumatic severe hemorrhages, whether the patient is on APA or not [92]. However, the results of recent trials (STOP-AUST and TICH-2) and meta-analysis of 14 RCTs assessing the efficacy of tranexamic acid in patients with ICH reveal lack of improvement in mortality and the poor functional outcomes in patients who received tranexamic acid, despite having a lower incidence of hematoma expansion and rebleeding [106–108]. Furthermore, the exploratory analysis of antiplatelet-associated ICH subgroup of the TICH-2 (tranexamic acid for hyperacute primary intracerebral hemorrhage) trial did not reveal significantly greater benefit of tranexamic acid (given 1 g as bolus in 10 min followed by an infusion of 1 g over 8 h) in reducing the risk of hematoma expansion in this subset of patients [108]. Larger RCTs are needed to further explore the effect of tranexamic acid on hematoma expansion in the antiplatelet group of ICH patients.

Recombinant Factor VIIa

rFVIIa accelerates thrombin generation and, hence, has the potential to improve hemostasis when platelet functions are compromised secondary to antiplatelet therapy. In vitro assessments of rFVIIa on ticagrelor reversal has revealed shortened coagulation times with rFVIIa using TEG with the platelet mapping device [109]. In clinical practice, rFVIIa (60 mcg/kg) has been shown to decrease ticagrelor-induced bleeding risk in a patient with ICH and requiring emergent neurosurgery, after failure of large volume platelet infusion to reverse ticagrelor-induced platelet inhibition [110]. However, the efficacy of such a therapy has not yet been evaluated in clinical trials and hence not recommended. In comparison to ticagrelor, no hemostatic effect of rFVIIa has been observed for clopidogrel or prasugrel.

Newer Agents in Pipeline

Human Monoclonal Antigen-Binding Fragment PB2452

PB2452 (former name MEDI2452) is a novel monoclonal antibody which binds to both ticagrelor and its active metabolite resulting in a rapid return of platelet aggregation. It binds to circulating ticagrelor and its metabolite with 100-fold higher affinity than ticagrelor's affinity for the $P2Y_{12}$ receptor. It has been evaluated successfully to reverse ticagrelor-induced bleeding in preclinical animal bleeding models, showing return to near normal levels of platelet aggregation within 60 min [111]. In the recent phase 1 trial in healthy volunteers, a bolus plus prolonged 16 h infusion regimen of 18 g of PB2452 provided immediate (within 5 min) reversal of ticagrelor, lasting for 20 to 24 h [112]. While it is currently not US FDA approved, future phase 2 and 3 studies are currently underway that to establish its role as a specific reversal agent for ticagrelor.

3. Reversal of Fibrinolytic Agents

Thrombolytic therapy with IV recombinant tissue plasminogen activator (rt-PA) or alteplase and tenecteplase (not FDA approved yet) is the mainstay for the early management of patients with acute ischemic stroke (AIS) [113]. Alteplase binds to fibrin within the thrombus and enhances the conversion of entrapped plasminogen to plasmin. Plasmin, in turn, degrades the cross-linked fibrin into fibrin split products, thus initiating local fibrinolysis. However, one of the most feared complication of IV thrombolytic therapy is 1–9% risk of secondary hemorrhages, including ICH [114, 115].

Hypofibrinogenemia (serum fibrinogen level ≤ 200 mg/dL), reduced plasminogen levels, longer half-life (15–20 min) of rt-PA, and prolongation of PT and aPTT have been attributed to fibrinolytic therapy-associated coagulopathy [116]. A decrease in serum fibrinogen level to <150 mg/dL has been identified as the sole risk factor for hematoma expansion in patients with thrombolysis-associated hemorrhage [117]. Despite being short acting, alteplase has a prolonged effect (≥ 24 hours) on fibrinogen levels in the circulation. Hence, an immediate reversal of rt-PA-induced coagulopathy may improve clinical outcomes in ICH patients. Fibrinogen level assessment and TEG allow rapid evaluation of hypofibrinogenemia to help identify patients at higher risk of rt-PA-induced coagulopathy.

To date, there is limited literature and guidance available for emergency reversal of rt-PA-treated patients with symptomatic ICH. Treatment options include fibrinogen supplementation with cryoprecipitate or fibrinogen concentrate, supplemental FFP or platelets, PCC, administration of vitamin K_1, and/or antifibrinolytics based on individual patient needs and as per institutional protocols [2, 113, 118]. Both FFP and cryoprecipitate have fibrinogen as their primary constituent. Fibrinogen concentrate offers an appealing alternative for immediate hemostasis in thrombolytic-associated ICH and may soon be incorporated as a first-line therapy in the updated guidelines. Potential for benefit with platelet, FFP, PCC, and vitamin K_1 is unclear except in patients with documented thrombocytopenia (platelets <100,000/μL) or patients on warfarin who may possibly benefit with these interventions [118].

In patients presenting with ICH, NCS/SCCM recommends immediate discontinuation of the thrombolytic agent and cryoprecipitate transfusion, if the thrombolytic drug was given within the last 24 h [2] [Fig. 5]. An alternative antifibrinolytic such as tranexamic acid or ε-aminocaproic acid may be considered if cryoprecipitate is unavailable or contraindicated. The recent AHA/American Stroke Association (ASA) guidelines, however, extend the use of

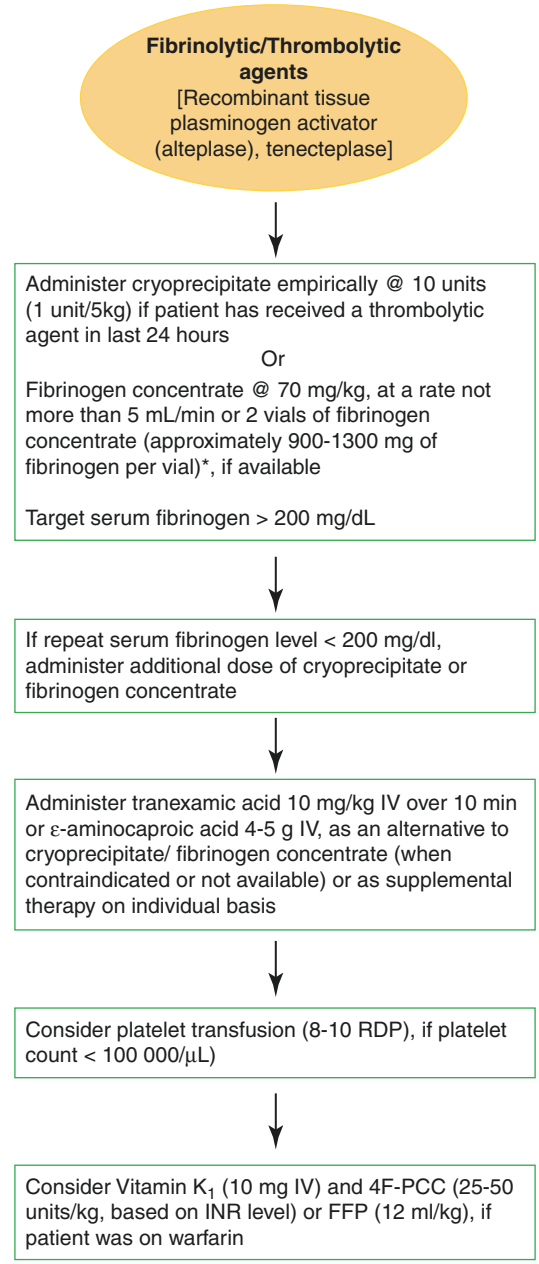

Fig. 5 Reversal strategies for fibrinolytic agents in neurosciences. IV, intravenous; RDP, random donor platelet, 4F-PCC, 4-factor prothrombin complex concentrate; INR, international normalized ratio, FFP, Fresh frozen plasma. * Barra ME, Feske SK, Sylvester KW, Ong C, Culbreth SE, Krause P, et al. Fibrinogen Concentrate for the Treatment of Thrombolysis-Associated Hemorrhage in Adult Ischemic Stroke Patients. Clin Appl Thromb Hemost. 2020 Jan-Dec;26:1076029620951867

cryoprecipitate and antifibrinolytic agents for alteplase reversal for up to 36 hours of its administration [113].

Fibrinolytic Reversal Agents

Cryoprecipitate

Cryoprecipitate is a cold insoluble protein fraction of FFP, consisting of fibrinogen, vWF, fibronectin, factor VIII, and factor XIII, stored at −20 °C. One infusion unit of cryoprecipitate (10–15 ml) has approximately 200–250 mg/unit of fibrinogen (minimum of 150 mg fibrinogen) and 50–500 units of factor VIII activity [119]. The recommended dose is 1 unit/5 kg (usually 10 units are given at a time) which will raise fibrinogen level by nearly 50 mg/dL [118].

Cryoprecipitate is often used as a first-line agent for thrombolytics reversal in ICH patients [2, 113, 118]. Based on the assessment of baseline fibrinogen levels, a repeat dose may be required to achieve a normal fibrinogen level of ≥150 mg/dL. Cryoprecipitate has certain limitations for its emergency use including the need for ABO matching, thawing of products prior to use, risk of transfusion reactions and TRALI (rarely reported), and potential risk of transmission of viral pathogens because of lack of pathogen inactivation [118].

Fibrinogen Concentrate

Purified human fibrinogen concentrate is a suitable alternative to cryoprecipitate for the repletion of serum fibrinogen in patients with post-thrombolysis hemorrhage [120]. Compared to cryoprecipitate, there is negligible risk for immunological reactions or pathogen transmission with fibrinogen concentrate. It is available as a lyophilized powder with approximately 900–1300 mg of fibrinogen per vial. It is stable for 8 h after reconstitution when stored at 20–25 °C and should be administered within this time period.

Its dosing and frequency of administration should be individualized based on the extent of bleeding, laboratory values of serum fibrinogen levels, target plasma fibrinogen level, and the clinical condition of the patient. When baseline serum fibrinogen levels are known, the dose is calculated based on the formula: [Target level (mg/dL)—measured level (mg/dL)]/1.7 (mg/dL per mg/kg body weight) [120]. However, if the baseline serum fibrinogen levels are unknown, it is dosed at 70 mg/kg body weight, at a rate not more than 5 mL/min. Fever and headache were the most common noted adverse reactions in clinical studies (at frequency > 1%), and the serious side effects included thrombotic and anaphylactic events. To date, there is a limited literature supporting its clinical safety and efficacy in increasing the serum fibrinogen levels in patients with post-thrombolysis ICH and hypofibrinogenemia, along with a low rate of thromboembolic events (0.05% −12.5%) (of uncertain onset) and no incidence of infusion-related or anaphylactic reactions [121, 122].

Antifibrinolytics (ε-Aminocaproic Acid and Tranexamic Acid)

Opposite to the molecular mechanism of action of alteplase, the antifibrinolytic agents competitively block the conversion of plasminogen to plasmin, thus preventing the break-up of fibrin and maintaining clot stability. Thus, antifibrinolytics directly counteract the action of rt-PA, making them an ideal agent for reversing the thrombolytic effects of rt-PA. Tranexamic aid also mitigates the effect of plasmin on degrading glycoprotein Ib receptors, ultimately leading to improved platelet function [123].

Antithrombotic reversal guidelines from NCS/SCCM and AHA/ASA guidelines for management of symptomatic ICH administration of IV alteplase for treatment of AIS recommend the use of antifibrinolytic agents particularly when blood products are contraindicated or declined by patient/family (as in Jehovah's Witness) or if cryoprecipitate is not available in a timely manner [2, 113, 118]. They are of particular benefit in emergency situations considering their easy availability and lack of reconstitution or thawing.

ε-Aminocaproic acid can be given as 4–5 g IV loading dose during the first hour followed by 1 g/hr. infusion for 8 hours [2, 113, 118]. However, there is limited evidence supporting

use of ε-aminocaproic acid in alteplase reversal [124]. Tranexamic acid is much preferred over ε-aminocaproic acid due to better efficacy to reduce blood loss and lesser risk of thrombosis. Tranexamic acid is usually administered at an initial loading dose of 1 gm IV push over 10 min followed by 1 g IV until bleeding is controlled (peak onset in 3 h) [113] or at a dose of 10 mg/kg, repeated 3–4 times/d [114, 118]. It has a half-life of 2 h and duration of action of 3 h after single dose. It is excreted renally and, therefore, may require dose adjustments in renal disease. It is a relatively safe alternative to cryoprecipitate with the main adverse reaction being an allergic reaction. However, moderate-to-high doses (approximately 100 mg/bolus and 10 mg/kg/h maintenance) have been potentially associated with neurological complications, including seizures, transient ischemic attack, and delirium [125]. Recent meta-analysis and literature reviews do not reveal increased risk of thrombotic events with tranexamic acid, irrespective of its dosing [126, 127]. Rather, a subgroup analysis of RCTs with low risk of bias revealed slightly lower-risk vascular occlusive events with tranexamic acid (RR 0.85 [0.73, 0.99]) compared to control or placebo group [128].

Conclusion

Intracranial hemorrhage is a devastating complication of the prophylactic or therapeutic administration of antithrombotic agents. Immediate discontinuation and reversal of the antithrombotic, along with general resuscitative measures, are highly critical during the first few hours to optimize patient's outcome. Once the patient has stabilized, the decision to discontinue and/or reverse and to reinstitute the antithrombotic agent is individualized on a case-to-case basis, weighing the benefit-risk ratio of supporting hemostasis and post-reversal thrombosis. A thorough understanding of the pharmacology and availability of all the reversal agents is thus of paramount importance for the practicing physicians in neurosciences.

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Part IX

Blood and Blood Products: General Considerations

Perioperative Assessment of Hemorrhagic Risk

Manikandan Sethuraman

Abstract

Perioperative bleeding is one of the major problems in neurosurgery. The incidence ranges from 25% in subarachnoid hemorrhage to as high as 41% in traumatic brain injuries. The consequences of perioperative bleeding vary from inadequate quantities of blood products availability, unnecessary reserving of blood leading to wastage, economic burden. Excessive use of allogenic blood is associated with complications such as infections, allergic reactions, coagulopathy, etc. Assessment of perioperative bleeding risk will help the surgical team to assess the blood requirements of the patient and the procedure and use of blood conservation techniques. Available literature shows that risk for perioperative bleeding includes factors related to patient, pathology, surgical technique, and other systemic illness such as anemia, hepatic and renal dysfunction, drug intake, etc. This chapter gives an overview of various risk factors to help the clinicians to understand, plan, and manage the perioperative bleeding.

Keywords

Hemorrhage risk · Neurosurgery · Spine surgeries · Coagulopathies · Perioperative transfusion · Allogenic transfusion

Introduction

Perioperative bleeding is one of the major problems in neurosurgery. The incidence varies in different types of surgeries and range from 25% in subarachnoid hemorrhage to as high as 41% in traumatic brain injuries [1].

The occurrence of intraoperative bleeding is not purely caused by the surgical procedure alone. The causes could be patient related, pathology related, and by intraoperative conditions including hemodynamics, vascular involvement, etc. Excessive perioperative bleeding and its management can be very challenging and needs appropriate planning. However, it can lead to management issues such as the availability of adequate quantities of blood products for transfusion, complications related to transfusion, intraoperative hemodynamic instability, and difficult operating conditions leading to increased morbidity and mortality. Hence the major concerns of perioperative bleeding are multi-factorial and can result in ICU and hospital stay, financial burden, morbidity, poor outcomes, etc.

M. Sethuraman (✉)
Division of Neuroanesthesia and Neurocritical Care, Department of Anaesthesiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India

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In addition, it was also found that there is excessive ordering and cross matching of blood in elective surgeries. It was noted that as high as 75% of the ordered blood were not utilized resulting in wastage [2]. A proper planning is necessary for the amount of blood required for each patient category based on the risk factors and establishment of formulation of maximum surgical blood order schedule (MSBOS) to prevent excessive ordering. Various centers use MSBOS to reduce the need for blood transfusion and to achieve effective utilization [3]. A proper preoperative assessment of the patients, planning, and preparation can reduce the perioperative bleeding. This chapter focuses on the various factors associated with increased risk of bleeding and helps in the preoperative preparation to reduce intraoperative bleeding complications.

Patient Factors

Patient related factors, which can be associated with increased perioperative bleeding, are age, American Society of Anesthesiologists (ASA) physical status, frailty, etc.

(a) *Age:* Age is an important factor for consideration for perioperative bleeding and transfusion requirements. Alterations in coagulation factor levels and activity has been observed in extremes of age [4, 5].

Patients at the extremes of age are prone to hemorrhage. Contributing risk factors are trauma, malignancy, comorbidities, and critical illness. Small children can have coagulation abnormalities due to immature coagulation factor production and various hereditary and acquired deficiencies. It was found that infants can have low levels of vitamin K-dependent clotting factors, reduced thrombin potential, and altered fibrinolytic pathway as well as prevention of intravascular coagulation leading to either bleeding or thromboembolic events [6].

Pediatric patients can undergo various neurosurgical procedures such as TBI, intracranial tumors, hemorrhage, epilepsy surgeries, craniofacial deformity correction, shunts, endoscopic surgeries, and spinal deformities such as scoliosis, etc. Pediatric tumors are generally large and highly vascular. Considering the higher amount of blood flow to the brain and immature coagulation system in children and pre-existing anemia, the risk of severe bleeding is high in children [7].

The incidence of massive bleeding involving more than one blood volume is high that necessitates massive transfusion [8]. Early preparation for transfusion must be ensured in pediatric patients [9]. Early administration of FFP rather than PRBC alone in children may help reduce the development of coagulopathy and worsening of bleeding.

The odds for transfusion in older adults have been found to be higher than young adults [10]. Elderly patients were found to have lower baseline hemoglobin levels and abnormalities of coagulation. Hence, transfusion requirements are higher in these patients [11, 12]. In addition to age, poor ASA grade, higher revised cardiac risk index (RCR), and frailty also increase the risk of bleeding and blood transfusion [13].

Abnormal Coagulation and Perioperative Hemorrhage

A normal coagulation factor levels, platelets number, and coagulation process are important in achieving adequate hemostasis. Alterations in the levels of coagulation factors, impaired coagulation cascade, and low platelet count ± activity can cause significant perioperative bleeding [14]. The causes of perioperative coagulopathy can be due to low levels of production as in liver dysfunction, hereditary and acquired factor deficiency like hemophilia, consumption of coagulation factors as in disseminated intravascular coagulation, (DIC) drug-induced inhibition (anticoagulation, anti-thrombotic agents), excessive fibrinolysis, systemic factors including dilutional coagulopathy, and electrolyte disturbances such as hypocalcemia, hypothermia, etc.

Patients with hereditary or acquired coagulopathies can present with CNS bleeding and may require neurosurgery. Fibrinogen, factor X and factor XIII deficiencies have shown to correlate strongly with severe bleeding [15, 16].

Thromboelastography guided management of blood products can help in the management of these patients.

Patients with liver disease like cirrhosis can undergo neurosurgical procedures especially that there is increased incidence of spontaneous ICH. The intraoperative bleeding may be excessive, and the severity of preoperative coagulation abnormality is assessed with Prothrombin time (PT), activated partial thromboplastin time (aPTT) monitoring [17]. Similarly, patients with chronic renal dysfunction may have low hemoglobin levels, coagulopathy, and their tolerance to the intraoperative bleeding may be limited [18, 19].

Various antiepileptic drugs administered in neurosurgical patients can alter the liver functions by different mechanisms causing varying degree of liver injury which can cause coagulation disorders [20]. Correction of coagulopathy and optimizing the liver function may be warranted before planning for surgery.

Preoperative intake of drugs such as anticoagulants, antiplatelets, and non-steroidal anti-inflammatory agents can impact the perioperative bleeding, postoperative hematoma formation in neurosurgical and spinal procedures. However, stopping the drugs may increase risk of perioperative thromboembolism. Heterogenicity exists in the management of patients taking anticoagulants for neurosurgery [21].

Recent studies have shown that continuation of aspirin daily did not increase the incidence of bleeding and transfusion compared to patients in whom the drug was stopped [22, 23]. Monotherapy with either clopidogrel or aspirin did not increase the risk of intracranial bleeding [24]. In contrast, prophylactic dual antiplatelet therapy with aspirin and clopidogrel has been shown to reduce the incidence of stroke, but significantly increase the risk of intracranial bleeding if given over one month [25]. Newer oral direct anticoagulants compared to warfarin were found to be safe in occurrence of ICH with reduced hematoma size, expansion as well as better outcome [26].

In contrast, a combination of either direct oral anticoagulant or warfarin with antiplatelet drugs increases the hemorrhagic risk two to threefold and needs to be taken care in perioperative period [27].

Abnormal Coagulation Tests and Bleeding

Patient undergoing major neurosurgical/spinal procedures undergo preoperative coagulation testing. Use of routine screening tests is a matter of debate as abnormal coagulation test was seen only in 1.8% in a large series of elective neurosurgical population. Moreover, history of previous bleeding and risk factors must be evaluated and considered for use of routine coagulation test screening and interpretation [28–30].

Sometimes, these tests may show abnormal values without obvious major medical conditions. In a large study of patients who underwent anterior spinal fusion, preoperative low platelet counts, prolonged aPTT, and high International normalized ratio (INR) were associated with increased bleeding needing blood transfusion. Hence, abnormal preoperative lab values of bleeding and coagulation testing is an independent risk factor for surgical and systemic perioperative complications [31, 32]. Controversy arises in preoperative administration of FFP in neurosurgical patients with prolonged INR. Studies have shown that prolonged INR <1.7 do not warrant preoperative FFP as the levels of coagulation factors were found to be normal [33].

Thromboelastography (TEG) is a method to test the coagulation status and provides better information on various stages of clotting process during bleeding compared to conventional test such as PT and aPTT [34]. R time measurement in TEG has been shown to be the better indicator of symptomatic intracranial bleeding compared to conventional test of coagulation screening in acute stroke patients receiving antiplatelet drugs [35]. TEG has been used to study the coagulation status in neurosurgical patients in the perioperative period. TEG has shown a state of hypercoagulability from skin incision to postoperative period in various neurosurgical population with illnesses such as tumors and aneurysms [36]. It was also found that TEG shows hypocoagulability in patients who had intracranial hematoma, indicating that TEG may be very useful in identifying patients at risk of bleeding and hematoma

[37]. Management of intraoperative bleeding during spine surgery using TEG-based techniques have shown more accurate identification of factor deficiencies and efficient management of blood product use, thereby reducing unnecessary products transfusion [38, 39].

Traumatic Brain Injury (TBI)

TBI is one of the major subsets of population needing neurosurgery. The most common causes are road traffic accidents and history of fall. The injury can manifest as bleeds (extradural, subdural, intraparenchymal, and intraventricular), contusions, diffuse axonal injury, and skull fractures. Patients arriving at emergency room may present with significant blood loss and hypotension. Perioperative bleeding can be significant due to ongoing blood loss, associated other injuries, preoperative loss of coagulation factors caused by activation of clotting, and dilutional coagulopathy due to resuscitation with large volumes of crystalloids and colloids.

Coagulopathy induced by brain injury is a well-established pathology now occurring in one out of three patients with TBI. It can occur in all age groups [40]. It is seen in up to 60% of severe TBI, while in mild injury the incidence is less (1%). The coagulopathy starts very early and can persists for many days following injury. Risk factors for coagulopathy development include Glasgow coma score (< 8), severe injury, use of fluids (>2,000 ml) in prehospital resuscitation, hypotension (<90 mm Hg), and age (> 75 years). The pathogenesis is thought to be due to the release of brain tissue factors in systemic circulation leading to activation of extrinsic pathway, intravascular coagulation, and enhanced fibrinolysis. The levels of fibrinogen have been found to be low and the D-dimer (cut off >500 ng/ml) has been seen in TBI coagulopathy. The clinical criteria for diagnosis include TBI associated with low platelet count (<100,000/cu mm), abnormal PT, and aPTT. TBI-induced coagulopathy has been shown to cause new onset secondary injury as well as poor outcome [41]. Surgical procedures in these TBI patients can lead to severe blood loss and transfusion requirement. Monitoring platelet counts, PT, and aPTT before surgical procedures and correction can reduce the need for blood transfusion. TEG and point of care coagulation monitoring can also be used to identify and manage the problem. Early recognition of low fibrinogen levels and administration of four-factor Prothrombin complex concentrate (PCC) has been shown to reduce the bleeding and blood requirements [42, 43].

Administration of tranexamic acid may be beneficial in these patients as its use has been shown to reduce the hematoma expansion and mortality compared to controls, but no difference in surgical interventions and neurological outcome [44]. Patients who are on treatment with antiplatelet drug or anticoagulants can sustain TBI. While routine use of platelet transfusion has not shown benefit on reducing hematoma expansion or bleeding, rapid reversal of anticoagulation using four-factor PCC, or FFP, cryoprecipitate may be instituted to prevent bleeding complications [45].

Patients with TBI may need transfusions especially RBCs during the ICU and hospital stay. Those needing surgical interventions may also need blood transfusions, including massive blood products use depending on the severity of injury. A study has shown that in females, the presence of anemia, coagulopathy, sepsis, bleeding, hypovolemic shock, other comorbid illnesses, and serious extracerebral trauma injuries were all significantly associated with RBC transfusion [46]. However, it must be borne in mind that using higher thresholds and RBC transfusions has been associated with poor outcomes.

Elective Neurosurgery

Elective neurosurgical procedures vary from spinal to intracranial locations.

Subarachnoid Hemorrhage (SAH) and AVMs

The management of patients presenting with subarachnoid hemorrhage (SAH) due to ruptured intracranial aneurysm can be challenging due to risk of rebleeding and high morbidity and mortality in untreated patients. Early surgery is warranted to prevent rebleed. SAH can lead to the development of anemia and coagulation abnormalities [47, 48]. Activation of both coagulation cascade and fibrinolytic system occurs in SAH and correlates with elevated D-dimer levels. The cause is thought to be due to microvascular injury and endothelial damage. The severity of the disturbances increases with grades of SAH, amount of blood in subarachnoid space, and correlates with poor outcome [49].

Anemia has been found to occur in 40–50% of SAH patients and correlated with peak of vasospasm. The mean decrease in Hb was about 3.0 g/dl. Anemia was associated with cerebral ischemia and an Hb levels are usually targeted to maintain at least a level of 10 g % to prevent cerebral ischemia. The development of anemia, the need to prevent cerebral ischemia in SAH, as well as coagulation abnormalities necessitate transfusion of blood products. It was noted that 25% of SAH patients may need packed red blood cells (PRBCs) in OT and two-thirds in intensive care unit [50].

Studies have evaluated the risk factors for bleeding during surgical clipping of aneurysms. Ten percent of SAH patients may need intraoperative transfusion. Factors contributing to the need are old age, female gender, aneurysm size >10 mm, preoperative low hemoglobin, intraventricular or intraparenchymal hematoma, and intraoperative rupture of aneurysms [51]. Factors such as clinical grade, location of aneurysms, associated comorbidities, and timing of surgery were not found to be significant for intraoperative transfusion [52].

Arteriovenous malformations (AVM) are another broad class of vascular disorders of the central nervous system in which surgical interventions for emergency evacuation of ICH/IVH to micro neurosurgery for excision of the AVMs are undertaken. Micro neurosurgery is undertaken for Spetzler-Ponce stage A and sometimes B. For the management of stage C AVMs, embolization or gamma knife is usually employed. The transfusion rate for microsurgery was reported to be at 7.1% [53]. Major bleeding (>1,000 ml or more than 2 L PRBC transfusion) during AVM resection was associated with poor outcome [54]. Although the available literature is limited on the risk factors for AVM bleeding and transfusion, a small compact nidus without deep seated venous drainage has good outcome, while large (>2.5 cm) diffuse nidus and deep venous drainage, intranidal aneurysm are associated with risks of hemorrhage and neurological deficits. Preoperative embolization of large AVMs before micro neurosurgery has been suggested to reduce the incidence of major bleeding intraoperatively [55].

Intracranial Space Occupying Lesions (SOL)

Various intracranial SOL may require surgical interventions. They range from various pathology such as tumors (benign, intermediate, malignant lesions), hematomas, vascular malformations, abscess, etc. The presentations also vary from acute, subacute, or chronic symptoms and signs. The diagnosis requires CT, MRI imaging. The location and size of the lesion and vascularity of the lesions and their relation to the blood vessels of the brain are relevant for the perioperative assessment of transfusion. *Hyper vascular tumors* are characterized by prominent tumor blush, enlarged feeders bilaterally, flow voids and prominent tumor draining veins in T2 weighted and perfusion images or dynamic susceptibility contrast techniques [56]. Preoperative hypervascularity assessment followed by preoperative microembolization of tumors has been shown to reduce the blood loss and improve resection [57]. Intracranial SOL is responsible for high incidence (32%) of transfusion compared to spinal and vascular procedures [58].

Among the SOL, meningioma and high-grade gliomas like glioblastoma multiforme, reoperations for recurrent tumors, usually cause more blood loss. In a retrospective analysis of one year data on elective primary brain tumors, 46% of patients had more than 20% blood loss. Of these, 2.4% needed massive blood loss. Blood loss has been shown to increase perioperative complications. The preoperative risk factors associated with blood loss were found to be female gender, presence of hypertension, tumor size (>5 cm), and vascularity of the tumor. Intraoperative factors include extended tumor approach, intraoperative colloid (>1,000 ml), and long operation time (> 300 min) [59]. With regard to meningioma, an increase of 1 cm in size was associated with 53% increase in rate of blood loss.

Spinal Cord Tumors

Various tumors of the spinal cord and vertebral column can be associated with severe blood loss.

Particularly, metastatic tumors of the spinal cord can be associated with severe blood loss. About 70% of symptomatic lesions are found in the thoracic region of the spine, and cord compression presents as the initial symptom in 5%–10% of patients. Studies have shown that open surgery is associated with more bleeding compared to minimally invasive techniques. The mean intraoperative blood loss in MISS group was lower than that in open surgery [60].

Spinal Instrumentation Surgeries

Various spine surgeries are performed for the correction of deformities, degenerative spine disease in different age groups. Laminectomy is one of the common spine surgeries performed nowadays as minimally invasive procedure where blood grouping and typing is adequate rather than additional cross matching. However, for more extensive procedures involving multiple levels, trauma, instrumentation, etc. transfusion requirements can be high. Autologous transfusion is practiced for spine surgeries and found to reduce allogenic blood requirements by 50% [61]. Nearly 80% of the autologous blood donated by patients who underwent simple laminectomies was wasted. However, the vast majority (70–90%) of patients who underwent fusion used their autologous blood. A substantial number of patients who underwent instrumented fusions (nearly 40%) required additional allogeneic blood transfusions despite predonation of blood [62]. Females, ASA 3, preoperative hemoglobin (≤136 g/L) and age older than 60 years increase the risk to be transfused in the postoperative period for degenerative conditions of the spine [63]. The use of tranexamic acid was associated with reduced transfusion rates in spine surgeries [64].

Estimation of perioperative blood loss is always challenging. Blood loss especially in spine surgery can be visible blood loss (VBL) and hidden blood loss (HBL). In a study on the lumber total interbody fusion, it was found that HBL is almost as twice as VBL even in minimally invasive surgery. The changes in hemoglobin values during surgery delta Hb 100 (Preoperative Hb-final Hb/Preoperative Hb) may be a better indicator of the estimate of the total blood loss [65].

Fusion surgeries for degenerative spine diseases are increasingly common, and the patients are old and may have coexisting diseases such as rheumatoid arthritis, diabetes, etc. The surgical technique can have impact on the blood loss. It was noted that patients undergoing posterior fusion (PLIF) had higher intraoperative blood loss compared to transforaminal interbody fusion (TLIF) [66]. In scoliosis correction, posterior or combine posteroanterior approach can lead to more blood loss than anterior approach. Various techniques have reduced the need for allogenic blood such as minimally invasive surgery, stages surgeries, used of antifibrinolytics like tranexamic acid, and the administration and application of cell savers [67].

Positioning in neurosurgery can impact the blood loss during surgery. In prone position of

Table 1. The various risk factors for perioperative hemorrhage in neurosurgery

SL No	Conditions	Risk factors
1	Patient related	Extremes of age, frailty, major surgery, poor ASA grade, higher revised cardiac risk index (RCR), and frailty [13]
2	Systemic factors	Anemia (Hb < 12 g%), prothrombin time (> 15 sec), INR (>1.7), low fibrinogen levels, platelet count (<1 lac), abnormal thromboelastography (low R, K, alpha angle, excessive fibrinolysis) Severe liver/renal dysfunction [17, 18, 34, 41] Hypothermia, hypocalcemia
3	Traumatic brain injury	Glasgow coma score (< 8), severe injury, use of fluids (>2,000 ml) in prehospital resuscitation, hypotension (<90 mm hg), and age (> 75 years), coagulopathy [41]
4	Intracranial space occupying lesions	Female gender, presence of hypertension, tumor size (>5 cm), vascularity of the tumor, Intraoperative factors include extended tumor approach, intraoperative colloid (>1,000 ml), and long operation time (> 300 min) [59] Hypervascular tumors by CT/MRI [56]
5	Subarachnoid hemorrhage	Old age, female gender, aneurysm size (>10 mm), preoperative low hemoglobin, intraventricular or intraparenchymal hematoma, intraoperative rupture of aneurysms [51]
6	Spine surgeries	Posterior approach, long segments (>4) osteotomies, age, anemia

spine surgery, neither mode (pressure vs. volume controlled) of mechanical ventilation nor the airway pressure were associated with intraoperative blood loss or need for allogeneic transfusion. Use of lung protective techniques can reduce the differences in blood loss previously observed between pressure and volume controlled ventilatory modes [68].

Pediatric Neurosurgery

Pediatric patients undergo various complex neurosurgeries such as craniofacial deformities, intracranial SOL, epilepsy surgeries, vascular malformations, correction of spinal deformities, trauma, etc. The use of autologous blood donation and cell salvage is limited in children. Tranexamic acid use has been shown to reduce the allogenic blood requirements in craniofacial and spine surgeries [69]. However, the need for allogenic blood and blood products is always present and sometimes more than one blood volume may be lost [70]. The identified risk factors for transfusion needs in pediatric neurosurgery include age (< 4 years), lower body weight, longer duration of surgery, and preoperative hemoglobin (<12.2 g/dl) [71].

Conclusion

The current knowledge on the perioperative hemorrhage in neurosurgery shows that risk factors are varied and multifactorial (Table 1). The presence of multiple factors increases the risk of allogenic transfusion requirements. It is also well documented that both anemia and blood transfusion have adverse consequences in neurosurgical patients. Although the well described methods to reduce the need for allogenic transfusion such as autologous blood transfusion and use of tranexamic acid have improved the scenario, they have not totally eliminated the need for allogenic blood especially in trauma, spinal deformity correction surgeries, and pediatric patients. Combining the effective way to reserve appropriate quantities of blood (maximum surgical blood ordering), use of blood conservation strategies, proper planning in patients at risk of bleeding, and staged surgical approach must be discussed among the stakeholders too as blood transfusion is associated with complications, poor outcomes, and increased hospital stay.

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Blood Salvage Techniques

Farzana Afroze, Andrea St Cyr, and Anirudh Gorti

Abstract

Anemia is common in critically ill neurosurgical patient populations, which can be detrimental to their neurological outcome. On the other hand, blood transfusion to treat anemia is not risk free and some of the risks range from acute and life threatening to causing chronic systemic issues. According to the current available literature, for neurologically injured populations the optimum hemoglobin concentration appears to be in the range of 9–11 g/dl. When deciding whether to transfuse red blood cells, one needs to consider overall risks and benefits of blood transfusion and those specific to individual patients. With recent advances in technology, there are several blood salvation strategies which have been successful for various surgical subspecialties including neurosurgery.

Keywords

Anemia · Blood transfusion · Cell salvage
Neurosurgery

F. Afroze (✉) · A. S. Cyr
Albany Medical Center, Albany, NY, USA
e-mail: afrozef@amc.edu

A. Gorti
University of Maryland Medical Center,
Baltimore, MD, USA

Introduction

Throughout all surgical populations, hemostasis and avoidance of anemia are crucially important for surgical success as well as patient outcomes. These concepts are particularly relevant to the neurosurgical population, as a relatively bloodless field is critically important during microscopic and other delicate intracranial procedures. Additionally, studies have shown that traumatic brain injury (TBI) patients are particularly sensitive to anemia. Hemorrhage is not uncommon in this population, and it is frequently necessary to provide blood to these patients. Transfusion of allogeneic blood products is fraught with number of risks and complications. Therefore, throughout the last century, several different mechanisms and compounds have been studied and utilized as blood salvage techniques.

American neurosurgeon Harvey Cushing published a landmark paper in 1911 outlining the "special reasons why the utmost precaution in anaesthetization, the gentlest methods of handling tissues, and the most accurate closure of wounds, accompanied by as painstaking haemostasis as possible, should be observed during the more difficult intracranial procedures [1]." These concepts were not universally accepted at the time, however, over the past century, a significant body of evidence has shown his premise to be true. Neurosurgical procedures are often performed on a microscopic level on particularly

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delicate tissues requiring, as Cushing noted, "painstaking haemostasis" to accurately identify and operate on critical structures. Additionally, bleeding and anemia in intracranial procedures is often substantial, with data showing the incidence of moderate to severe anemia (hematocrit <30%) in elective surgery to be 2.7% [2], with incidence as high as 50% in TBI patients, and 47% in patients with subarachnoid hemorrhage (SAH) [3].

Impact of Anemia on Brain

The impact of anemia on the brain is significant. The brain is a relatively small organ, constituting only 2% of total body weight, but has high metabolic rate and receiving 20–25% of cardiac output. The brain depends heavily on glucose and oxygen due to its high metabolic requirements. Reduction of oxygen availability to the brain in the form of cardiac arrest, systemic hypotension, or severe anemia can result in anoxic brain injury that ultimately leads to poor outcomes. Anemia is a common finding in TBI patients, as well as those undergoing other neurosurgical interventions. Many patients who are presenting for neurosurgical procedures tend to be critically ill due to TBI, SAH, shock, and chemotherapy and high dose steroid related adverse effects. In such critically ill patients, the etiology of anemia is usually multifactorial resulting from acute hemorrhage, inflammatory-mediated suppression of hematopoiesis, frequent phlebotomy and hemodilution from resuscitation [4]. The relevance and danger of anemia in the context of anoxic brain injury is directly tied to the delivery of oxygen. The delivery of oxygen equation is the following:

$$\text{Oxygen delivery} = \text{cerebral blood flow}\left(\text{CBF}\right) \times \text{oxygen content of the blood}\left(\text{CaO}_2\right)$$

Significance of Transfusion in Neurosurgical Patients

Delivery of oxygen is directly correlated with arterial oxygen concentration and cerebral blood flow. The cerebral blood flow is dictated by cardiac output (CO) and hemodynamic autoregulatory systems over a range of cerebral perfusion pressures (CPP) of 50 mmHg to 150 mmHg on a normal healthy person. CPP is determined by the difference between mean arterial pressure (MAP) and central venous pressure (CVP) or intracranial pressure (ICP), whichever is higher.

$$\text{CPP} = \text{MAP} - \text{CVP or ICP}\left(\text{whichever is higher}\right)$$

During periods of severe anemia, compensatory mechanisms include increasing cardiac output, preferential distribution of CO to the cerebral circulation, and cerebral vasodilation to increase CBF. In a healthy individual, the autoregulatory mechanisms function appropriately. However, in many neurosurgical patients, these autoregulatory mechanisms are altered. Consequently, the blood oxygen content becomes more important in managing concerns of hypoxic brain injury. The arterial oxygen concentration equation is the following:

$$\text{CaO}_2 = \left(1.34 \text{ x } \left[\text{Hb}\right] \text{x } \text{SaO}_2\right) + \left(0.023 \text{ x } \text{PaO}_2\right)$$

$$\text{CaO}_2 = \text{oxygen content of arterial blood}\left(\text{ml / dl blood}\right)$$

$$1.34 = \text{volume of oxygen bound to 1 gm of saturated hemoglobin}\left(\text{ml / g}\right)$$

$$\left[\text{Hb}\right] = \text{concentration of hemoglobin}\left(\text{g / L}\right)$$

$$\text{SaO}_2 = \text{percentage of hemoglobin fully saturated with oxygen}\left(\%\right)$$

$$0.023 = \text{solubility coefficient of oxygen in plasma}\left(\text{ml / dl / kPa}\right)$$

$$PaO_2 = \text{partial pressure of oxygen dissolved in arterial blood}\left(\text{kPa}\right)$$

As indicated by the equation, there are three factors that determine arterial blood oxygen concentration. The first and most important is the blood hemoglobin level. In a healthy brain with functioning compensatory mechanisms, hemoglobin concentrations of 5–6 g/dl will begin to show signs of cognitive dysfunction. In patients undergoing neurologic surgery without intact compensatory mechanisms, hemoglobin concentrations of 9–10 g/dl were associated with improved neurological outcomes and Hb of >11 g/dl was associated with reduced incidence of symptomatic cerebral vasospasm [4]. Alternatively, high hemoglobin concentrations can be detrimental as they result in increased blood viscosity and reduced CBF. The other two factors in the arterial oxygen content equation are oxygen saturation and partial pressure oxygen and both contributes very little to the overall final amount and often not used in estimating delivery of oxygen to the brain.

Transfusion in the neurosurgical population is frequently required to treat intraoperative anemia and maintain oxygen delivery to tissues. In one database study of neurosurgical cases from 2006 to 2011, 4.5% of all patients required transfusion, with that number rising to 5.4% in those undergoing intracranial surgical procedures [5]. These numbers can be even more dramatic when looking at particular surgical procedures, such as pediatric cranial vault reconstructions for craniosynostosis, with transfusion rates of up to 95% in infants under two years of age and 79% in children greater than 24 months [6].

Risks of Transfusion

Although anemia is harmful, normalizing Hb with allogenic red blood cell transfusion itself confers an increased risk of morbidity and mortality due to noninfectious and infectious causes. Blood transfusion is a very common practices in the hospitals and it was reported that, there were nearly 15 million whole blood and red blood cell units transfused in the United States alone in 2008 [7]. Over the time, blood storage and processing techniques have certainly improved, but there remain several risks associated with allogeneic blood cell transfusion. These include infectious, immunologic, and allergic reactions, as well as transfusion associated lung injury and circulatory overload [4]. The immunological reactions are more common than infectious causes and include—see Table 1 [8].

With advancement in blood screening technologies and highly sensitive testing to reduce

Table 1 Summary of immunological reaction due to red blood cell transfusion [8]

(1) Acute hemolytic anemia	Most common, acute, due to human error in cross matching or mismatch blood types
(2) Delayed hemolytic reaction	>24 h to 28 days, usually due to low or undetectable anti-Rh and anti-Kid antibodies
(3) Febrile nonhemolytic reaction	Most common (7%), due to release of inflammatory mediators from stored WBCs
(4) Allergic reaction	Caused by IgE anti-allergen antibodies from the donor or recipient
(5) Anaphylactic reaction	Rare, caused by IgA anti-plasma protein antibodies
(6) Post transfusion purpura	Extremely rare, due to antibodies directed against both the donor and recipient platelets
(7) Transfusion related acute lung injury (TRALI)	Within 6hr, similar to ARDS, related to donor antibodies interacting with recipient tissue antigen → release of inflammatory cytokines → capillary leak. Most common cause of transfusion related mortality reported by FDA [3]
(8) Transfusion-associated graft versus host disease	In immunodeficient patients, whose body failed to eliminate donor's T cells

the infectious window period that is the time between exposure to viral infection and ability of the blood test to detect the virus when the donor may be infectious although the test result is negative, blood transfusion is safer than ever before. With the current strategies in place, the risks of HIV and hepatitis C transmission through blood transfusion have been reduced to about 1 in 2 million, which is roughly the equivalent of the risk of getting struck by lightning [7]. However, contamination of stored blood products, especially platelets component which are stored at room temperature causing bacterial sepsis and immunosuppression predisposing to nosocomial infections are continues to be a major concern. At the same time, with the advent of emerging new infectious sources, transfusion—transmitted infection (TTI) continues to be a struggle for the twenty-first century. The number of the organisms found to be transmitted has drastically increased over the last 50–60 years. In 2009, some expert members of the American Association of Blood Bank (AABB) identified 68 infectious organisms that are capable of being transmitted by blood transfusion [8]. Other transmittable diseases, such as, Chagas disease (a parasitic disease caused by Trypanosoma cruzi), West Nile virus, prion transmissible agents (e.g., variant Creutzfeldt-Jakob (vCJD) disease, also known as the agent of mad cow disease) and Babesia species continue to pose risks for TTI [7, 8]. Some transmittable agents are more prevalent in certain county or geographic locations, for example, vCJD has a very low risk of transmission in North America but higher risk of transmission in the UK and Babesia has moderate risk for transmission in the USA but very low risk in Canada and Europe [8]. A division of U.S. Food and Drug Administration (FDA) continues to work on making blood transfusion safe and in recent years, testing for West Nile virus and Trypanosoma cruzi causing Chagas disease has been added to address those emerging transmissible disease threats from blood transfusion [7].

These risks of transmittable diseases increase for patients that have increased donor exposure, frequency of exposure, and with more transfusions over a short period of time as is the case with neurosurgical surgeries. Ultimately, the most effective way to prevent infectious risk is to stratify at-risk population and either temporarily or permanently exclude them from donation.

Patient Related Factors When Considering Blood Transfusion

Patient factors are also important to consider when discussing blood loss and transfusion, as patient refusal of blood products can result in an even greater need for blood salvage techniques intraoperatively. Refusal of blood product transfusion may be cultural, religious or patient preference. This includes Jehovah's Witnesses, one of the most well-known groups to hold beliefs against transfusion. Most Jehovah's Witnesses refuse whole blood and major blood components. The acceptance of minor blood components, albumin and individual blood factors are decided on an individual basis. When encountering a patient with refusal of transfusion, it is important to delve into the details regarding these individual components to determine patient preference. In the case of coagulopathy or hemorrhage, it may be vitally important to understand products that a patient is willing (or unwilling) to accept. The use of the blood salvage strategies discussed in this chapter are particularly relevant to those populations that refuse blood transfusion. In any instance where patient refusal occurs, except in the case of a minor, transfusion could be considered unethical and result in legal action.

Blood Salvation Strategies During Neurosurgical Procedures

Several strategies have been employed to minimize anemia and hemorrhage in all surgical populations intraoperatively. As studies have shown, the utilization of such techniques is of particular importance in neurosurgical populations given the high risk of perioperative anemia and continued questions surrounding transfusion risks and thresholds. In non-emergent scenarios, patient selection and preoperative preparation is the cru-

cial first step in minimizing blood loss. Blood salvation strategies start from preoperative planning and continue to postoperative period.

Preoperative Preparation

- Preoperative blood conservation strategies include correction of coagulopathy and preexisting iron deficiency anemia. Correction of iron deficiency anemia should occur preoperatively in elective procedures, with oral or IV iron supplementation depending on the length of time until the procedure.
- Medications that may need to be avoided perioperatively include NSAIDs and herbal supplements, such as garlic and ginseng, which can contribute to platelet dysfunction.
- It is important to withhold medications that may contribute to bleeding. Holding or reversing anticoagulation may be a crucial step in blood conservation when clinically feasible. Detailed information about types of anticoagulants and their reversal is beyond the scope of this chapter. However, the individual patient and their indication for anticoagulation should be considered and discussed with surgeons, cardiologists, and other specialists prior to holding or reversing any medications.
- The use of erythropoietin (EPO) preoperatively has also been studied, with meta-analyses showing reduced allogeneic RBC transfusions in cardiovascular and orthopedic surgical populations [9]. One retrospective study of 57 neurosurgical patients who received EPO matched with controls found similar rates of allogeneic red blood cell exposure between the groups [10], however, indicating that EPO may not be beneficial as a blood conservation strategy in neurosurgery. Additionally, EPO in TBI may have an increased risk of DVT and cardiovascular complications [10].
- Preoperative autologous donation (PAD) involves the patient donating their own blood several weeks prior to surgery to allow adequate time for erythropoiesis to occur. This donated blood could then be transfused autologously intraoperatively should significant bleeding occur. Studies of PAD (+/- EPO) in neurosurgery show no decreased risk of allogeneic transfusion, with iatrogenic anemia and increased transfusion requirements in the PAD group [11].

Intraoperative and Postoperative Considerations

To avoid the risks associated with allogeneic blood transfusion, several autologous techniques have been trialed with relatively limited evidence in neurosurgery, including acute normovolemic hemodilution (ANH), use of intraoperative cell salvage, intraoperative hemostasis techniques and continuous infusion of anti-fibrinolytic agents, such as Tranexamic acid (TXA) and aminocaproic acid (Amicar).

- Acute normovolemic hemodilution (ANH) involves the controlled removal of whole blood immediately prior to the surgical procedure, with the volume lost replaced by crystalloid or non-red cell solutions (i.e., albumin, etc.). This process allows the surgical operation to occur in the setting of a normal blood volume with a reduced red blood cell mass. Studies on the benefit of ANH in limiting allogeneic blood transfusion are mixed. In a prospective randomized study of patients undergoing excision of intracranial meningioma were evaluated for safety and effectiveness of ANH, where ANH was set to hematocrit of 30%. In this study, 100% of patients without ANH received homologous/allogenic blood transfusions compared to 25% with ANH and concluded that a target hematocrit to 30% with ANH is safe and effective in reduction of homologous blood transfusion [12]. Another study found ANH to be safe technique in patients undergoing cerebral aneurysm clipping for ruptured aneurysm, however found no significant difference in need for allogeneic blood products [13]. In certain patient populations, therefore, ANH

may be considered as a method of blood conservation, however evidence is limited.

- Use of cell salvage technique is one of the most versatile forms of intraoperative blood conservation methods. Cell salvage/scavenging is a type of autologous blood transfusion where the blood loss during surgery is collected in a sterile fashion directly from the surgical field in a separate apparatus, which is then washed and returned to the patient intravenously. This strategy is also not without risks and contraindications; however, it has been utilized in procedures across specialties where high blood loss is expected.

  Risks of cell salvage technique include the presence of foreign materials from the surgical field resulting in micro-embolisms, air embolism, bacterial contamination, dilutional coagulopathy with more than 3.5L autotransfusion [15] and electrolyte imbalance [14]. Some also quote the cost associated with cell salvage as a relatively contraindication to use. According to Chanda and colleagues, the cost of cell salvage technique is statistically comparable when greater than 500 ml of homologous red blood cell transfusion is necessary [15]. However, one must also consider the shortage of allogeneic blood products and other risks associated with homologous blood transfusion along with a discussion of the relative costs. There is little data available in the neurosurgery literature regarding intraoperative utilization of cell salvage method. Cataldi and colleagues in 1997 published that cell salvage method was safe in patients undergoing elective intracranial surgery, with 61% of their patient population received only autologous blood transfusions [16].

  The use of cell salvage in malignancy has largely been avoided due to concern for metastasis or recurrence. As a large proportion of neurosurgical procedures are related to malignancy, this raises the question of the utilization of cell salvage in this population. A review of relevant literature from 1973 to 2012 showed no evidence of an increased rate of metastasis or cancer recurrence and noted that leukoreduction filters are an effective method for removal of malignant cells [17]. Although not specific to neurosurgery, this article also draws attention to the risks associated with allogeneic blood transfusions in the oncologic population. Therefore, cell salvage should be considered in neurosurgical procedures where significant blood loss is anticipated; this includes oncological procedures after a detailed discussion of the potential risks with the surgeon and patient.
- Several mechanical techniques for maintaining hemostasis and limiting intraoperative blood loss have been employed throughout different specialties. In orthopedic surgery, pneumatic tourniquet application is a mainstay of hemostasis. Historically, tourniquet application has been utilized in neurosurgery, with Harvey Cushing detailing use of a tourniquet to decrease scalp bleeding in 1904 [18]. Additionally, an inflatable neck tourniquet was developed in 1984 to help prevent air embolism during sitting neurosurgical procedures, although not specifically related to blood loss [19]. Tourniquet use in neurosurgery as a means of blood conservation, however, is extremely limited given anatomy of neurosurgical operative sites. In addition to sitting craniotomies, unique patient positioning is not uncommon in neurosurgery and can contribute to both bleeding and blood conservation. Frequently, neurosurgeons will utilize a head up position in intracranial procedures for both surgical exposure and hemostasis, as well as to maintain a position that optimizes venous drainage. Another method of decreasing blood loss intraoperatively is permissive hypotension. This technique has been employed for decades in neurosurgery to decrease transfusion requirements. However, with advances in other conservation methods, permissive hypotension is no longer a popular method of decreasing bleeding due to concerns for cerebral and other end-organ ischemia. Some intracranial tumors can be vascular, which pose significant intraoperative blood loss during surgical resection. In such

cases, embolization of the feeding blood vessels is performed prior to the surgery to decrease intraoperative blood loss.

- Antifibrinolytics, such as, tranexamic acid (TXA) and aminocaproic acid (Amicar) have been utilized throughout multiple specialties to minimize allogeneic blood transfusions. Both TXA and Amicar have been used and studied widely in joint arthroplasty, cardiac, spine and trauma patients. In neurosurgery, data is most robust in TBI and craniosynostosis. In pediatric patients undergoing cranial vault reconstruction for craniosynostosis, the use of TXA significantly reduced perioperative blood loss and transfusion requirements [19]. In a meta-analysis from 2018, administering TXA in patients with TBI showed a "significant effect in reducing the risk of hematoma expansion and lowered the mortality rate when first bolus dose (1gm TXA) was administered within first 3hrs, but failed to decrease disability or independent and decrease the incidence of neurosurgery, vascular embolism and stroke [21]." Although, thromboembolic complications are one of the main concerns with the use of antifibrinolytics, the majority of neurosurgical data has not demonstrated increase in thrombosis. Similarly, a 4.1-fold increased risk of seizure has been reported with the use of high dose TXA in cardiac surgery [22]. However, a significant difference in rates of seizure has not been reported with the TXA use in neurosurgery.
- Several topical hemostatic agents have been developed and utilized by neurosurgeons. There are a wide range of products intended for topical use, many of which have been used intracranially. A study from 2008 with a rat model found that four topical agents (Arista, Avitene, FloSeal, and Surgicel) were effective in controlling bleeding in the majority of the intracranial lesions compared to the control group [23]. Additional human studies are necessary; however, these agents are generally considered safe.
- During perioperative period for neurosurgical patient, it is probably best to avoid medications that can affect coagulation, such as non-steroidal anti-inflammatory drugs (NSAIDs). In the current literature, there is inconclusive evidence regarding safety of use of ketorolac for elective neurosurgical surgeries, thus best to avoid till more data is available. In one study from Beijing, evaluated the safety of flurbiprofen, which is a NSAID and concluded that use of flurbiprofen during the surgery increased the risk for post-craniotomy intracranial hematoma requiring surgery [24].
- There is also conflicting evidence of use of synthetic colloids such as human albumin (HA) and hydroxyethyl starch (HES) during intracranial surgeries and their effects on anticoagulation. Li and colleagues evaluated the administration of both 5% HA and HES for elective intracranial tumor surgeries and concluded that HES affected coagulation at lower volumes with a more prominent effect on clot structure at the end of the surgery; although they also found that 5% HA decreased platelet aggregation but had a more potential volume effect than HES [25]. Further research is needed to clarify the safety and efficacy of the use of both type of synthetic colloids.

The use of blood conservation strategies is becoming increasingly necessary throughout all surgical specialties as blood bank shortages abound and many patients are hesitant to receive allogeneic blood products. This is particularly relevant in neurosurgery, where anemia and blood loss are common and alterations in autoregulatory mechanisms may occur. As outlined throughout this chapter, there are several techniques utilized for blood salvage, including prophylactic, mechanical and medicinal approaches. The decision to employ individual strategies should consider the unique factors specific to the case at hand and should involve a detailed discussion with the surgeon, the patient, and any relevant consultants.

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Blood Loss Estimation Techniques

Victoria Sokoliuk and Oksana Levchenko

Abstract

Blood loss estimation is a patient quality-of-care and patient-safety measure and requires a high degree of accuracy. Currently there is no practical, real-time blood loss estimation method for measuring blood loss. Techniques vary across specialties and institutions. The most popular technique is subjective visual estimation, followed by formula-based estimation, gravimetric-based estimation, and a novel approach that uses facial recognition technology to make calorimetric measurements of blood loss. In addition, physiological and vital signs monitoring can provide hemodynamic information suggesting hypovolemia due to blood loss. Blood loss estimation values are important in making patient treatment and transfusion decisions; therefore, an awareness of various estimation methods can improve perioperative patient care.

Keywords

Blood loss · Surgery · Blood transfusion
Gravimetric method · Triton system
Noninvasive monitoring · Perioperative care
Quality improvement

Introduction

Blood loss is an inevitable component of the perioperative environment and of surgical procedures. An accurate assessment of blood loss is important to recognize potential life-threatening hemorrhage and manage blood product replacement. Estimated operative blood loss (EBL) is used to guide perioperative care and serves as a quality marker. It is a critical metric and part of mandatory reporting in the brief operative note by Joint commission [1]. While an accurate assessment of blood loss in minor procedures is insignificant, procedures with expected major blood loss require reliable assessment to determine the necessity of allogeneic blood transfusion (ABT) for hemodynamic support. In cases with significant hemorrhage, anesthesiologists and surgeons are faced with the difficult decision of when and if ABT should take place [2]. Untreated acute perioperative anemia can result in end organ damage such as cardiac ischemia, neurological injury, kidney injury and death from hypovolemic shock [3, 4].

V. Sokoliuk (✉)
Albany Medical Center, Department of Anesthesiology, Albany, NY, USA
e-mail: sokoliv@amc.edu

O. Levchenko
Touro College of Osteopathic Medicine, Middletown, NY, USA

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The American Society of Anesthesiologists Task Force issued guidelines and recommendations on the importance of EBL monitoring while also noting deficiencies in measuring the impact of EBL on patient outcomes [5]. Prevention of major hemorrhage is critical; however, there are also many limitations to blood transfusions. Furthermore, transfusion itself can increase the risk of adverse clinical outcomes. In addition to cost and the availability of blood components and quality of the products, transfusions carry potential risks: hemolytic reactions, transfusion-related infections, transfusion-related acute lung injury and immunosuppression. In cancer patients, blood transfusion predicts disease progression and mortality. Estimated blood loss is included in surgical predictive models for postoperative morbidity and mortality; surgical Apgar score, pancreatic fistula risk score after Whipple procedures and P-Possum score for general surgery [6–8]. Blood loss can also predict long- term outcomes such as survival after colon cancer surgery and cancer recurrence rate after resection of hepatocellular carcinoma [9, 10].

Need for intraoperative blood transfusion is assessed based on the patient's hemodynamic stability, hemoglobin (Hb) and hematocrit (Hct) levels and the estimated blood loss. Even though surgical blood loss is a significant predictor of perioperative outcomes, studies have shown the estimation of surgical blood loss to be highly inaccurate [11–13]. There is currently no "gold standard" method to quantify perioperative blood loss. Hemoglobin values in the normovolemic patient can be helpful but they are confounded by factors that affect perioperative blood volume.

Fluid administration, anesthetic agents and insensible losses can alter accurate hemoglobin concentration and therefore alter the reflection of the extent of surgical blood loss. Accurate assessment is especially critical in the pediatric population since they have less hemodynamic reserve and transfusion is weight-based [14, 15]. Certain pediatric surgical procedures carry an especially high risk of unrecognized blood loss. Pediatric perioperative cardiac arrest is highest during craniosynostosis and pediatric scoliosis repair where hypovolemic shock secondary to unrecognized acute blood loss is a common cause [16–18].

Underestimation and overestimation can both lead to unrecognized blood loss and lead to inappropriate transfusion. Porous surfaces that absorb blood such as carpet, grass and gravel can lead to underestimation as high as two to three times the actual loss while clothing covered in blood can lead to two to three times the overestimation [19]. Though a universal adoption of a reproducible and practical method for evaluation of blood loss does not exist, EBL estimation is an important value for perioperative patient care [19, 20]. The provider should be familiar with the most common methods and new developments that are discussed in literature and used in practice.

Methods

Visual Estimation Technique

The oldest and most common blood loss estimation technique in practice is visual estimation. In most cases, EBL is determined by consensus of operating room (OR) personnel using visual estimation of blood loss available for inspection in suction canisters, gauze, drapes and OR floor. Though it is commonly used and is the most studied method, results from studies remain widely variable [19]. The method is biased towards overestimating modest quantities and underestimating significant quantities of blood loss [20, 21]. Blood can also be retained in non-visible regions such as in the retroperitoneal compartment and small hemothoraces [22].

A study by Rothermel and Lipman [13] was conducted to evaluate the visual estimation technique using OR simulations where known blood volumes were estimated by OR personnel. Provider specialties include anesthesiologists, surgeons, nurses and technicians. The simulations required participants to estimate three different combinations of blood and saline: a low volume, mid volume, and high volume. At this particular institution, all participants chosen for the study routinely participate in measuring

and agreeing to a final EBL. All participants ranked nurses as the most likely to provide accurate assessment. The results revealed that all estimations were inaccurate, with a 52% mean error for low volume; 61% for mid-volume; 85% for high volume. No specialty proved to be more consistent or accurate. The reported confidence level of a practitioner increased with more experience; however, the percent error tended to increase as well. The study concluded that visual estimation is unreliable and inaccurate, regardless of provider specialty, years or level of experience, which ranged between 1-43 years, or self-assessment of ability via a confidence scale [13].

Spectrophotometric

The spectrophotometric method is a laboratory-based technique that is considered a "benchmark" for assessment of EBL. The method was initially used to quantify postpartum blood loss. A measured amount of blood was collected from surgical sponges and suction canisters into bottles and poured unto absorbent material. The absorbed amount of blood was measured by a rapid method of automatic extraction and photometric measurement with alkaline hematin. The direct measurement of HgB within the samples resulted in an error rate of zero to 10%. Though a reliable method for quantifying blood loss, it is labor-intensive and still yields an error rate of up to 10%. Though frequently used in research as a standard for comparison of other blood loss estimation techniques, this method is not practical in daily intraoperative blood loss estimations [23].

Triton System

The importance and need for a more accurate blood loss estimation technique has led Gauss Surgical Inc, a medical equipment company, to the development of a novel FDA-cleared smartphone application (Triton System) on a tablet computer (iPad). Modeled after facial recognition technology, the application uses a unique algorithm called the Feature Extraction Technology (FET) image analysis system to make calculations based on captured images. This calorimetric technique is used to assist with canister estimation blood loss [24]. The user enters a manually recorded volume of fluid and uses the camera tablet to take photographs of used surgical gauze and canisters. The images are sent to a cloud-based computer server that processes photographic and geometric features of the image, automatically filtering out non-blood components mixed in the sponge and canister and normalizing for variations in room-lighting by calibrating to a color correction label attached to the canister. A Hb concentration is calculated and multiplied by the volume of the fluid which yields a Hb mass. The mass is divided by an entered preoperative Hb serum concentration, which results in an estimated volume of blood loss [25].

The new technique offers several advantages to standard laboratory tests. It is relatively easy to use, more time-efficient and avoids exposing staff to potentially contaminated body fluids. This novel Triton system has demonstrated that accurate, real-time estimation of blood loss may lead to early recognition of hemorrhage, earlier interventions, reduced blood transfusions and shortened length of stay for patients [24]. The method has been found to be accurate across many sponge types and lighting conditions and to be an accurate determinant of blood loss assessment in adult patients in real time [24, 25]. The device was also assessed for accuracy in pediatric patients with comparable results [15]. Triton is CE marked and has been adopted by over 50 hospitals in the US [26].

MAR

The MAR method was introduced by Merlin MA, Alter SM, and Rafeel B (hence, MAR) and was designed as a simple way to estimate a volume of blood to its surface area. The method suggests that the amount of blood volume that can be

covered with one fist by the provider is about 20 ml. The provider places the fist, palm up, approximately 2 inches above the blood pool. The number of side-by-side "fists" it takes to cover the blood pool multiplied by 20 ml provides the estimated volume. The estimation must be done on non-absorbent surfaces and the fist must be placed relatively close to the blood pool. When compared to visual estimation, this method increased the accuracy for large volume estimations. This still was not particularly accurate, underestimating a 750 ml blood pool by 20%. However, precision and accuracy are slightly improved, and the method is easy to use with rapid results [27].

Gravimetric

The gravimetric method is an indirect measurement of blood loss that is calculated by summing up the differences in weight of operating room materials before and after contamination with blood and/or fluid. The volume of blood within containers is estimated and normalized for any added fluids, such as those used for rinsing. Since the density of blood (1.06 g/ml) is similar to the density of water (1.00 g/ml), the blood loss is determined by assessing the weight difference, with every gram of weight equivocal to 1 ml blood loss. Meta analysis of data on this technique found higher correlation between studies as compared to the visual estimation technique, but still variable [19].

Direct Measurement

The direct measurement is a simple method that is usually used in the field of obstetrics and is useful for resource-limited areas. It is frequently used in combination with visual estimation [19]. A transparent collection bag is placed under a female's pelvis immediately after delivery of the baby but before delivery of the placenta, collecting blood mixed with amniotic fluid. The collection bag is calibrated with a scale that measures current blood loss [28].

Calculation Method

The calculation method has been suggested in response to a lack of accurate measurement via visual and gravimetric methods [22]. Modified over time to achieve more accurate and exact calculation, all methods still tend to overestimate blood loss at lower volumes [19]. There has been an extensive evolution of formulas documented in literature, however no establishment of a reference formula [22]. All calculation formulas depend on an estimation of the total blood volume of the patient. This is calculated using a combination of weight, build, height, and sex of the patient. The most common calculation formulas used to calculate blood volume are Moore, Nadler, and International Council for Standardization in Haematology (ICSH) [22]. Hematocrit-based formulas depend on the patient being euvolemic. This premise likely invalidates using these formulas in the intraoperative and perioperative period, at which points the patient has likely undergone volume replacement [22]. Formula-based methods are also limited by hidden blood loss, such as red blood cell (RBC) sequestration in non-circulating compartments like the spleen [29]. The formulas may be valid for research purposes but are less useful for making clinical decisions [22].

There are multiple blood loss estimation mathematical formulas. The most common and well-recognized formulas will be discussed. Ward et al. created a formula to resemble a clinical scenario of acute normovolemic hemodilution [30]. Brecher et al. used the formula developed by Ward but divided the surgical procedure into three phases, and calculated the blood loss for each phase, with a final sum. Bourke and Smith et al. used the natural logarithm of the ratio of the initial to final hematocrit, and Moore's formula for calculating blood volume [30]. Gross et al. built on Ward's formula but simplified the calculation for a more practical approach. Mercuriali calculation method assesses the preoperative hematocrit and fifth postoperative day hematocrit using Nadler's blood volume calculation and the volume of RBCs transfused [30]. The Camarasa method considers starting and

ending Hct values and volumes of blood that were transfused [22]. The Lopez-Picardo method modified the Camarasa formula via the International Council of Hematology (ICSH) criteria, which considers anthropometric data. The Hb difference method is widely used due to its simplicity, cost-effectiveness, and non-invasive approach. Gender, weight, and height are considered and Hb concentration is calculated before and after blood loss, assuming a normovolemic patient. This is one calculative method that actually underestimates blood loss. The majority of calculation-based blood estimation methods have a tendency to overestimate blood loss [30].

SbHb Monitoring

Continuous and noninvasive hemoglobin (SpHb) monitoring allows a physician to make a real-time decision on whether to continue transfusion. It can permit an immediate gauging of whether the transfusion has replenished hemoglobin to appropriate levels, preventing unnecessary RBC transfusion. Because this method avoids the need for laboratory assessment of Hb, a quick decision can be made whether to initiate transfusion. An advantage of SpHb monitoring is that it measures microcirculation (capillary blood) as opposed to macrocirculation (peripheral vein blood), which have different physiological responses to acute anemia. Rather than an absolute measurement, this method monitors the trend in a continuous, real-time fashion, thereby avoiding the lag-time in lab results. SpHb monitoring is cost-effective and could potentially reduce expenditures related to blood and transfusion related activities [31].

Physiologic Parameters Monitoring

New methods demonstrating early detection of hypovolemia that is undetected by more standard vital signs have been proposed. These include monitoring stroke volume using whole body biological impedance and quantifying venous circulating volume using photoplethysmography. The body's compensatory mechanisms (tachycardia and increase in the peripheral vascular resistance) can maintain blood pressure (BP) up to a 20-30% blood volume loss [32]. The body maintains perfusion well where a 25–35% blood loss is required before changes are evident in heart rate (HR) or BP [33]. Traditional vital signs, such as tachycardia and hypotension, tend to be better indicators of advanced stages of hypovolemia, at which point the body's ability to compensate has been surpassed, and is nearing circulatory compromise or hemodynamic collapse [32]. However, traditional vital signs lack sensitivity to detect lower percentages of hypovolemia and can be confounded by factors such as patient comorbidities and body habitus. Both arterial and venous waveforms have been studied to assess correlations with hypovolemia. Venous waveforms have been less studied than arterial waveforms, partly because wave amplitude in veins is very low, requiring better technology to sense and amplify the signals; however, that technology is now available [33]. New methods of monitoring for early signs of hypovolemia currently under investigation include the "NIVA prototype," photoplethysmography (PPG), and whole-body biological impedance such as continuous stroke volume (SV) monitoring (Fig. 1).

Non-Invasive Venous Waveform

The "NIVA device" proposed by Alvis et al. [33] detects venous waveform using Piezo-electric sensors, which is transformed to quantify the signal to an intravascular volume status. The sensor is placed on the skin over the venous complex on the volar aspect of the wrist. A control box on the device contains an amplifier, an analogue-to-digital converter, microcontroller, and an SD card. The sensors measure a pulse rate which is converted into a "NIVA value," a numerical representation of intravascular volume. In a study done in porcine and human models, NIVA value's ability to detect hypovolemia was compared to changes in vital signs. The NIVA value was found to be able to detect blood loss of about 8%-10%. This is significantly lower than the amount needed to affect vital signs changes which was at 25–35% blood loss. An advantage of non-invasive venous waveform analysis is that

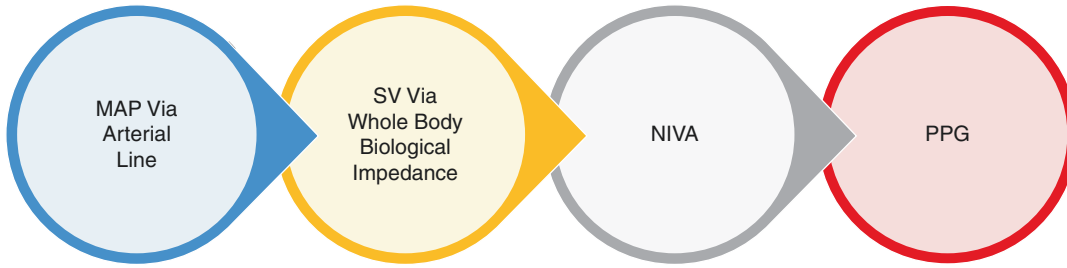

Fig. 1 Comparison of the sensitivities of advanced physiological modalities in detecting hypovolemia (as compared to standard vital sign monitoring). (*MAP* Mean Arterial Pressure, *SV* Stroke Volume, *NIVA* Noninvasive Venous Waveform Analysis, *PPG* Photoplethysmography)

it can be used as a point-of-care tool to accurately and sensitively detect early blood loss [33].

Photoplethysmography and Arterial Blood Pressure

A proof-of-concept study performed by Chen et al. [21] studied photoplethysmography (PPG) and invasive arterial blood pressure (ABP) as a method of continuously monitoring vital signs and quantifying blood loss volume. PPG is a noninvasive signal that uses a pleth variability index and amplitude modulations that can detect local intravascular volume changes. Variations in PPG amplitude correlate with changes in circulating blood volume, and area under the PPG waveform correlates to stroke volume. This method could offer a more accurate estimation than previously used hematocrit-based formulas. Invasive arterial blood pressure has been a gold-standard but has poor sensitivity considering physiologic compensatory responses. Heart rate and blood oxygen saturation also have low sensitivity, as well as specificity, for blood loss. The PPG model was very sensitive at "capturing the early physiologic response" at low blood volume loss in the early stage of bleeding, especially when coupled with ABG measurements [21].

Whole Body Biological Impedance/ Stroke Volume Monitoring

Another new method for detecting hypovolemia is the use of whole-body biological impedance technology to continuously monitor SV at bedside. Whole body biological impedance technology has been shown to be reliable in bedside hemodynamic monitoring and is used in a variety of scenarios, particularly in the intensive critical care setting [34]. Stroke volume can be used as a physiological parameter for the early detection of acute hemorrhage. Continuous noninvasive monitoring of SV has been shown to be significantly more sensitive than traditional vital signs at detecting acute blood loss [32, 33]. Based on previous findings that the first hemodynamic response to hemorrhage is a reduction in cardiac preload, followed by decrease in stroke volume, in a study by Epstein et al. [32], the researchers investigated the ability of SV monitoring to detect blood volume loss. Adult males donated a standard amount of blood and the changes in SV and cardiac output (CO) were monitored. The results showed that SV monitoring was able to accurately detect 8–9% of total blood volume loss.

Conclusion

Prevention and treatment of major perioperative hemorrhage is an integral aspect of perioperative practice for anesthesiologists and surgeons. Clinical guidelines emphasize on the importance of accurate blood loss assessment and its impact on quality of patient care and long-term outcomes [5]. There are many blood loss estimation techniques reported in clinical use and in practice (Table 1). Measuring blood loss is complex with research suggesting that all blood loss estimation techniques carry a high rate of inaccuracy. As these estimations are used to make patient treatment and transfusion decisions, clinicians should consider the universal adoption of a practical and reproducible method for blood loss evaluation. The newer methods can assist in accurate monitoring of potentially bleeding patients and with early identification of hemorrhage. More sensi-

Table 1 Key aspects and comparison of estimated blood loss (EBL) techniques

EBL estimation method	Key aspects	Advantages	Disadvantages
Visual Estimation (VAS)	Most common method	Easy to use No specific training required	Highly inaccurate, regardless of years of experience, position, or speciality
Gravimetric	EBL calculated based on premise that 1g blood equals 1ml blood	Easy to use Minimal training required	Assumes density of blood is equal to water (blood is slightly denser) Variable accuracy, better than VAS
Spectrophotometric	Benchmark method, "gold-standard"	Most accurate Used as a standard for comparison	Laboratory-base Time-consuming Error rate up to 10%
MAR	One fist = 20 ml blood	Easy to use Minimal training required	Requires non-absorbent surface Underestimates large volumes
Direct Measurement	Used in obstetrics, bag under pelvis directly collects blood	Easy to use Best for resource-limited areas	Inevitable amniotic fluid increases inaccurate blood volume
Triton System	Innovative approach uses facial recognition technology	Higher accuracy, comparable results to Spectrophotometric method	Complex training, requires iPad tablet with mobile applications and WiFi weigh-scale
Calculation	Mathematical Formulations	Considers anthropometric data such as body surface area and sex, thereby increasing reliability	Time-consuming and complex Overestimates blood loss
SbHb Monitoring	Non-invasive continuous Hb monitoring	Allows for real-time patient data, no lag in time	Prone to artifact and interference
Vital Signs Monitoring	Standard blood pressure, heart rate and pulse oximetry monitoring	Equipment readily available, real-time patient data	Detects only severe hypovolemia Multiple confounding factors
Physiological Parameters	Advanced monitoring using venous and arterial waveforms, and SV	PPG, NIVA, and whole-body biological impedance highly sensitive in detecting low percentage of hypovolemia	Complex training to set up and interpret data collecting systems

Hb hemoglobin, *SbHb* continuous and noninvasive hemoglobin, *PPG* photoplethysmography, *NIVA* non-invasive venous waveform analysis, *SV* stroke volume

tive physiological parameters for monitoring blood loss is an area of focus in current research and can aid in improving morbidity and mortality associated with perioperative care.

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Monitoring Anticoagulation

Kavitha Jayaram

Abstract

Monitoring coagulation is recommended only in specific situation, especially if standardised tests are available, which serves multiple purposes such as efficacy, assess bleeding, use of antidotes, and aid in drug selection. Coagulation assays may provide qualitative or quantitative assessment of the drug used. Laboratory measurements are dependent on several patient factors such as age, time when the last dose was taken, half-life and other factors affecting pharmacokinetics for the appropriate interpretation of the test results. Clinical monitoring along with noncoagulation laboratory monitoring also play a major role in many patient scenarios. This chapter gives information on the physiology, pharmacology and monitoring of anticoagulation.

Keywords

Anticoagulant · Antiplatelet agent · Laboratory assessment · Perioperative care · Direct-acting oral anticoagulant · Monitoring Heparin · Dabigatran · Rivaroxaban · Apixaban

K. Jayaram (✉)
Nizams Institute of Medical Sciences, Hyderabad, India

Introduction

Anticoagulants and antiplatelets are being increasingly used nowadays with higher incidence of comorbid conditions and risk of thromboembolism. Elderly patients who chronically use these kinds of drugs present themselves to the anesthesiologists for both elective and emergency procedures. Intracranial hemorrhage (ICH) risk in patients with atrial fibrillation is high compared with other patients. Also, they have higher risk for falls and for ischemic strokes along with ICH. Although the incidence of ICH did not vary with warfarin, more severe hemorrhagic events and higher 30-day mortality are present in patients on warfarin compared to those without warfarin [1].

With a huge leap in the life expectancy, patients consuming antiplatelets or anticoagulants attending the preanesthetic check-up or emergency room has become a regular scenario in most hospitals. In case of elective procedures, these patients are properly evaluated using laboratory monitoring methods from which various bridging therapy are decided. Even in emergency, some simple means of evaluation are asked for antiplatelets and vitamin K antagonists to reverse them.

We have many direct-acting oral anticoagulants (DOAC) with better safety profile and reversibility. With the increasing use of DOACs in place of older parenteral drugs and Vitamin K

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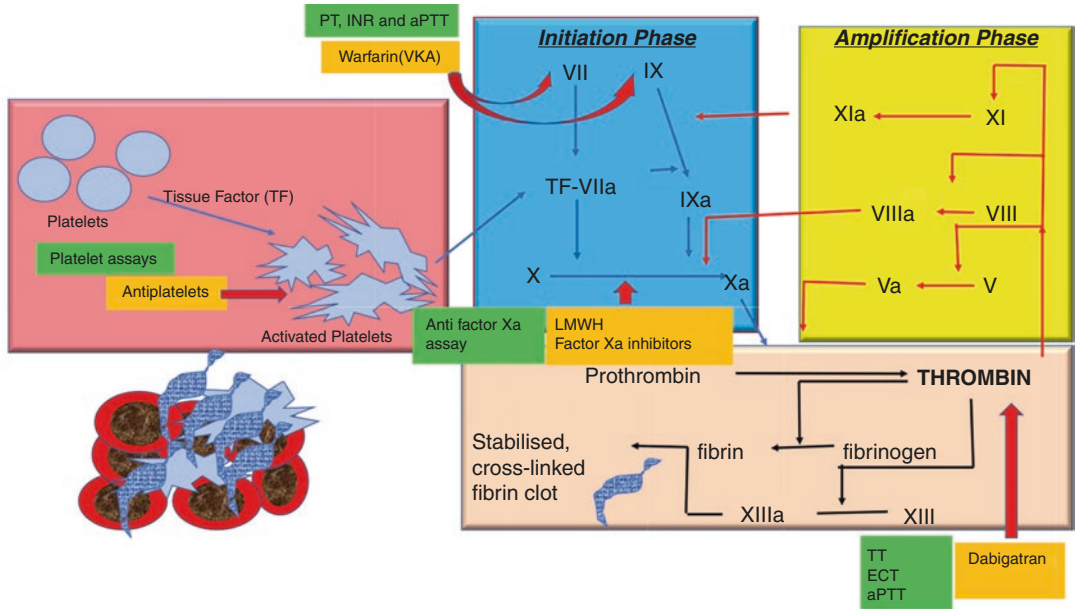

Fig. 1 Hemostasis with drugs and monitoring

antagonists, patients under these drugs will be exposed to different clinical scenarios which would warrant intervention. In trauma and perioperative setting, there are increasing concerns with respect to management. Although it is claimed that no regular monitoring of the DOACs is needed, laboratory monitoring is relevant in certain circumstances such as prior to surgery, urgent invasive procedures, major bleeding, suspected overdose, to confirm reversal, trauma, in patients with malabsorption, to assess patient compliance and so on [2]. There are several uses of monitoring coagulation such as assessment of anticoagulation, bleeding potential and in drug selection decisions [2]. It is also useful in ensuring efficacy when there is history of non-adherence, drug interaction with cytochrome P450, etc. [2].

Hemostasis: Physiology

Hemostasis is a complex process involving interaction between platelets, endothelial cells, blood flow and shear stress, coagulation cascade and fibrinolysis [3]. There are basically two reactions. Primary hemostasis provides immediate seal by von Willebrand factor-induced platelet adhesion and fibrinogen-induced platelet aggregation. Secondary hemostasis is the reinforcement of the platelet aggregate by clot formation which is a battery of reactions involving conversion of non-activated coagulation factors into active forms which ultimately generates fibrin. These two processes are closely related and properly regulated (Fig. 1).

A disruption in vascular endothelium triggers the platelets which are discoid in shape to spherical with pseudopodia. These platelets get attached to subendothelial collagen with von Willebrand factor and surface glycoprotein receptors. After this phenomena called adhesion, ADP, histamine, serotonin, TXA2 and several other contents are released from platelets. Platelet aggregation occurs via GPIIb/IIIa receptors which causes platelet-platelet bridging, and this forms the hemostatic plug. This initiates coagulation by releasing coagulation factors present in stored vesicles due to exposure of negatively charged phospholipids from the surface. Traditionally, coagulation cascade starts, and it can be of two pathways, intrinsic and extrinsic, which converge into common pathway in vitro.

In vivo, there are three phases: (1) initiation phase is the TF pathway – where TF exposed on

the cell surface interacts with preformed FVIIa; (2) amplification phase – involves FV and FVIII; and (3) propagation phase – involves FXI, XII, and VIII. This is the intrinsic pathway. The contact factors such as FXII, prekallikrein, and high-molecular-weight kininogen affect the PTT, but not in vivo. Thrombin is thus constantly produced in small quantities and are regulated by natural anticoagulants (antithrombin, protein C and S, and TF pathway inhibitor [TFPI]). The cross-linked fibrin thrombi are dissolved by plasmin which is derived from plasminogen acted on by tissue plasminogen activator.

Hemostasis Pharmacology

Generally, these drugs can be divided into drugs affecting action of platelets and drugs inhibiting coagulation cascade (Table 1).

Drugs Inhibiting Platelet Activity

Aspirin

Aspirin acetylates cyclo-oxygenase in platelets irreversibly and prevents thromboxane and prostaglandin production. Prothrombin concentrations are also reduced when aspirin is consumed in large doses. The most widely tested antiplatelet regimen was medium dose aspirin which is 75–325 mg per day. This therapy was sufficient to reduce about 1/3 of myocardial infarction, stroke and vascular death. Early aspirin therapy in patients with ischemic stroke has reduced the early mortality by 1% in 19,000 patients according to the International Stroke trial. But a few trials showed 1–2% incidence of gastrointestinal or cerebral hemorrhage following aspirin therapy.

Adenosine Di Phosphate Inhibitors

Clopidogrel, a thienopyridine derivative, acts by blocking ADP-induced platelet activation pathway. Platelet activation because of shear stress is prevented by clopidogrel, which is not inhibited by aspirin. Prasugrel and Ticagrelor are other ADP inhibitors available. Ticagrelor causes reversible inhibition, while on platelets the effects are not reversible and discontinuation of drug for at least 5–7 days before surgery is essential. In emergencies, high dose of aprotinin reduced the bleeding times.

Platelet Glycoprotein IIb/IIIa Antagonists

Expression of glycoprotein IIb/IIIa receptors on the surface of the platelets at the end of activation of platelets is essential for adherence of platelets to fibrin, other platelets, or the endothelium. Antagonism of these receptors therefore blocks the final common pathway of platelet function. Apart from anti-platelet activity, these antagonists decrease thrombin concentrations to act as anticoagulants. Abciximab and peptide inhibitors such as lamifiban, eptifibatide, tirofiban belong to this group. All of them produce thrombocytopenia and lead to increased perioperative bleeding. Abciximab has longer duration of action up to 48 h, while with eptifibatide, bleeding time normalises 1 h after stopping the drug. If patients on this treatment bleed, platelet transfusion is advised.

Drugs Which Inhibit Coagulation Cascade

Vitamin K Antagonists: Warfarin

Warfarin, a coumarin derivative, inhibits vitamin K synthesis and thus limits coagulation factors that are vitamin K dependent (factors II, VII. IX, X and protein C and S). It is available in enteral formulation only with 100% bioavailability. Patients receiving warfarin will be fully anticoagulated only after three days as prothrombin has longer half-life than other factors. Warfarin is almost entirely metabolised in liver, thus exposing it to several drug interactions. The anticoagulant effects can be monitored using prothrombin time (PT) and International normalised ratio (INR). This is the measure of extrinsic coagulation pathway. When a patient on warfarin is posted for elective surgery, we need to stop warfarin at least 5–7 days prior to surgery and monitor for INR.

Table 1 Summary of pharmacology of Hemostasis

	Antiplatelets	Unfractionated heparin	LMWH	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Platelets and its receptors	Antithrombin III	Factor Xa and thrombin	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Prodrug	Yes	No	No	Yes	No	No	No
Half life	7–9 h	1 h	4–7 h	12–17 h	5–9: healthy individuals 11–13: elderly	8–15: healthy individuals	10–14
Metabolism	Liver, P450	Liver	No	Conjugation	CYP-dependent and independent mechanism	CYP-dependent mechanism (25%)	CYP-dependent and independent mechanism
Elimination	50% kidney	In Urine	Kidney	80% renal	33% unchanged via the kidney	27% renal	50% renal
Available studies	CURE [27] CREDO [28]	Multiple old trials	ADVANCE -2 [18]	RE-LY [29]	ROCKET AF [30, 31]	ARISTOTLE [32] ADVANCE -2 [18]	ENGAGE AFTIMI [33]
Emergency reversal	NA	Protamine	Protamine to some extent	Idarucizumab	Andexanet alfa	Charcoal PCC	Charcoal PCC
Tests available	LTA VASP Verify Now TEG ROTEM	aPTT ACT	Ami Factor Xa assay	TT dTT ECT	Anti factor Xa assay Plasma drug concentration	Anti factor Xa assay Plasma drug concentration	Anti factor Xa assay Plasma drug concentration

Unfractionated Heparin

Unfractionated heparin has a molecular weight of 15,000–18,000 Da [4]. Heparin acts by binding reversibly with antithrombin III (AT III), and it also accelerates the function of coagulation factors XII, XI, X, IX, plasmin and thrombin. Heparin inhibits platelet activation by fibrin, and it also causes thrombocytopenia (Heparin-induced thrombocytopenia). The other complication of long-term use of heparin is osteoporosis. Unfractionated heparin is routinely monitored using activated partial thromboplastin time (aPTT).

Low Molecular Weight Heparin (LMWH)

LMWH has a molecular weight of 2,000–10,000 Da. They act by inhibition of factor Xa rather than thrombin [4]. Their interaction with platelets is very less and therefore have less bleeding tendency. Because of their longer half-life, single maintenance dose for prophylaxis is recommended. LMWH has replaced unfractionated heparins in the management of thromboembolic disorders as they have significantly lower incidence of hemorrhagic complications. Monitoring of LMWH does not require aPTT and in case of suspected overdose, direct factor Xa assays are useful.

Direct-Acting Oral Anticoagulants

Dabigatran

Dabigatran is primarily a direct thrombin inhibitor and it inhibits both free thrombin and fibrin bound thrombin. The action is reversible and does not need antithrombin [2]. Dabigatran etexilate is a prodrug with rapid onset of action and few drug interactions. According to a recent meta-analysis, Dabigatran provides benefit in the prevention of stroke, systemic embolism, and mortality when compared with antiplatelets and placebo without increased intracranial or extracranial hemorrhage [5]. Within 3 h after oral dose, the drug achieves peak plasma concentration and maximal anticoagulant effect. During this time, the maximum effect on coagulation parameters also occurs with Dabigatran. Thus, sample collection for monitoring the effect of Dabigatran should be timed to the last dose. All the routine coagulations assays are prolonged except prothrombin time, because of the thrombin-mediated conversion of fibrinogen to fibrin with Dabigatran. In case of high risk of bleeding, a specific antidote, Idarucizumab, may be given as it binds to Dabigatran; or hemodialysis can be done for removal. Measurement of level of anticoagulation is mandatory prior to any of these procedures to determine the amount of medication present.

Rivaroxaban, Apixaban and Edoxaban

These are direct inhibitors of factor Xa, found as complex with factor Va and are independent of antithrombin [6]. The maximal effect of rivaroxaban and apixaban is at 3 h after drug, while it is achieved at 2 h after edoxaban. Out of the DOACs, rivaroxaban shows the highest effect on prothrombin time (PT), followed by edoxaban and then apixaban, but different PT reagents have shown variation in sensitivity to these drugs. The prolongation of PT by rivaroxaban is concentration dependent and depends on the reagent used. For apixaban, PT is not the test recommended for quantifying plasma drug concentrations or relative intensity of anticoagulation at therapeutic concentrations as PT may be normal. Unlike Dabigatran, Rivaroxaban, Apixaban cannot be dialysed because of their higher plasma protein binding capacity. For edoxaban, within 2 h, PT and aPTT are prolonged, but for routinely assessing anticoagulant effect, these tests have modest effect and variability.

Monitoring

Indications for Monitoring

During perioperative handling of patients' anticoagulant therapy, multiple factors must be considered such as indication, risk of thromboembolism and risk of perioperative bleeding. The decision to be taken includes continuation of anticoagulation therapy and perioperative pause and bridging therapy. In case of emergencies such as bleeding, thrombosis, urgent invasive procedures and

thrombolysis, physicians aim to identify the levels of drugs. Administration of antidotes or reversal agents during emergencies also warrants assessment of level of coagulation. In acute ischemic stroke for patients requiring thrombolysis, assessing plasma concentrations of DOACs are recommended for considering r-tPA. Routine monitoring of coagulation for elective procedures is not required if we follow the window periods of stopping drugs according to the risk of procedure. For patients with altered pharmacokinetics due to multiple factors or in cases where window period is not sure, laboratory approach is recommended, especially for interventions with high risk of bleeding (Table 2).

Monitoring the Antiplatelets

Platelet function assays determine the efficacy of the drug, its sensitivity, compliance of the patient, timing of emergency or urgent surgery. Platelet function assays also have an important role in minimising the side effects of overtreatment or under treatment. To balance the risks and benefits of antiplatelets and to tailor the antiplatelet therapy, platelet activation and aggregation are assessed in platelet function testing.

Light Transmittance Aggregometry

Light transmittance aggregometry is the gold standard in platelet function testing. But it is not used in daily practice due to lack of standardisation, spurious platelet activation and complexity of the test. Light transmittance aggregometry quantifies the final common pathway of platelet aggregation through GPIIb/IIIa-dependent bridging [7, 8]. Turbidometric optical detection method is used in the quantification of response to agonists. Agonists such as epinephrine, collagen, arachidonic acid, thrombin receptor activating peptide or ristocetin are added to induce platelet aggregation. After this, the sample becomes translucent and the transmittance of light is increased. Despite limitations, it still provides prognostic information.

Vasodilator-Stimulated Phosphoprotein Phosphorylation Assay (VASP)

This flow cytometric test measures P2Y12 receptor inhibition indirectly. Intracellular fluorescently labeled antibodies are used against phosphorylated vasodilator-stimulated phosphoprotein (VASP). In resting conditions, the VASP protein is unphosphorylated and cyclic adenosine monophosphate (cAMP) cascade regulates its phosphorylation. When P2Y21 receptor is stimulated by ADP, it reduces cAMP levels via prostaglandin E1 activation. If VASP phosphorylation is still persistent, it correlates with P2Y21 inhibition [7]. Skilled personnel and specialised equipment are required for this procedure and has variability in results.

Table 2 Laboratory monitoring and assays for DOACs

Assay	Direct thrombin inhibitors		Factor Xa inhibitors	
	Sensitivity	Interpretation	Sensitivity	Interpretation
Activated partial thromboplastin time (aPTT)	Low	Qualitative assessment	Low	Not useful
Prothrombin time (PT)	Low	Not suitable	Low	Qualitative assessment if specific reagents used
Thrombin time (TT)	Highly (over) sensitive	Qualitative assessment	N/A	N/A
Dilute thrombin time (dTT)	Sensitive	Quantitative assessment	N/A	N/A
Ecarin clotting time (ECA)	Sensitive	Quantitative assessment	N/A	N/A
Anti-factor Xa assay	N/A	Still being determined	High	N/A
Prothrombinase induced clotting time (PiCT)	Low	Quantitative assessment	Sensitive	Quantitative assessment if calibrated to specific drug
Plasma drug concentration	Sensitive	N/A	Sensitive	Still being determined
		Still being determined		Quantitative assessment
		Quantitative assessment		

Whole Blood Impedance Aggregometry

Whole Blood Impedance Aggregometry is used for analysing platelet inhibition during P2Y21 inhibitor treatment using adenosine di phosphate (ADP) multiplate analyser. This multiplate device uses citrated whole blood and when activated platelets attach and coat the electrodes where there is an increase in electrical impedance which is measured in aggregation units. In this test, platelet agonists are added manually, and it is a rapid and comprehensive test. This test is also useful to prognosticate clopidogrel treated patients.

VerifyNow

VerifyNow is the simple and most reliable method for evaluating P2Y21 inhibitors such as clopidogrel, prasugrel and ticagrelor. There is not enough evidence to support whether this assay improved clinical outcomes when used to guide therapy [7].

VerifyNow uses single use catridge that contains different wells which contain fibrinogen coated beads, chrome plated mixing ball and a platelet agonist. It uses anticoagulated whole blood for detection of platelet aggregation by turbidometry. Because of fibrinogen coated beads and platelet agonists, activated platelets bind to other platelets and aggregation occurs between platelets and beads. There is a subsequent reduction in turbidity and increase in the transmittance of light. For aspirin, P2Y21 inhibitor and GIIb/IIIa inhibitors, VerifyNow assays are available [7, 8].

Platelet Function Analyzer-100 (PFA-100)

This rapid, reproducible and standardised point of care test is a screening tool for qualitative assessment of platelet defects [7, 9]. It lacks sensitivity and specificity for aspirin and P2Y21 inhibitors [7]. The system has a capillary, sample reservoir and an aperture with a membrane coated with agonists such as collagen, epinephrine or ADP. When citrated blood is aspirated through a disposable catridge, functional platelets which meet the membrane are activated; and they aggregate at the aperture.

Viscoelastic Tests: Thromboelastography (TEG)/ Rotational Thromboelastometry (ROTEM)

Viscoelastic tests measure dynamic changes of hemostasis in clot formation using whole blood. The blood is kept in a cup that has a pin suspended which is connected to a computer [10]. In ROTEM technology, an oscillating pin is used to measure the resistance that occurs during clot formation, which is interpreted as a curve. This curve describes the dynamic changes from clot initiation to clot termination. The difference in TEG is that the cup is in oscillation during clot formation and when the movement detects the change in resistance, clot formation is achieved. Both are rapid tests used in the assessment of platelet inhibition as well as for evaluating drug sensitivity and efficacy [10].

When unfractionated heparin is present, paired samples of TEG and ROTEM can be used for hemostasis assessment with or without heparinase. If there is difference in R or clotting time in comparison with the two tests, then heparin resistance can be resolved. During the perioperative period for transfusion management, these tests are used.

Another additional technology in TEG which uses arachidonic acid and ADP for agonists is platelet mapping. This mapping compares standard TEG results by combination of snake venom and ADP which is a weak platelet agonist.

Thromboxane Assay

For assessing the platelet, the inhibitory activity of aspirin thromboxane can be measured. The two methods available are: serum TXB2 and urinary 11-dehydro TXB2. There are alternative techniques which use arachidonic acid to stimulate platelets and use any of the available platelet function tests (TEG, VerifyNow aspirin test, impedance platelet aggregometry). The major limitations of these techniques are the exact mimic of in vivo situation is not possible due to absence of pathological shear and endothelium. The primary goal of all these assays is to help guide the choice of antiplatelet therapy and the use of bridging therapy in perioperative period to prevent complications.

Monitoring Anticoagulants

Prothrombin Time/INR

Prothrombin time evaluates the extrinsic, final common pathway and measures the function of clotting factors I, II, V, VII and X. This is the most common test for monitoring anticoagulation therapy with warfarin. This test is performed when a suspension of tissue thromboplastin and calcium chloride is added to platelet poor plasma. The time to form fibrin clot is called the prothrombin time. Different tissue thromboplastin agents have different sensitivities, hence there is variability in PT. To standardise the PT, INR was used which is the ratio of patient PT to mean normal PT multiplied by International Sensitivity Index (ISI). ISI is the value assigned to the PT reagent when compared with a WHO reference standard.

Plasma of patients using chronic warfarin therapy was used to standardise INR and is not appropriate to use in medical conditions in which clotting factors which are not vitamin K dependent are also affected. INR is not a test for DOAC therapy, as there is ISI which is specific for vitamin K antagonists. For every individual drugs in DOAC, determination of ISI is needed.

Direct thrombin inhibitor, Dabigatran, causes prolongation of PT but has poor sensitivity with variations as per the reagent used. Higher concentrations of Dabigatran, or more than the therapeutic range, have more influence on PT. Prior to the interpretation of results, it is reasonable to understand the fact that depending on the thromboplastin agent used, sensitivity of the assay varies.

Factor Xa inhibitors have concentration dependent PT levels with more pronounced effect at supratherapeutic concentrations [2]. Rivaroxaban in therapeutic concentrations has relatively weak effect on PT. However, the presence of normal PT does not exclude anticoagulant levels that are of clinical significance. However, meaningful results can be demonstrated if performed with specific reagents used such as PT Neoplastin plus (Siemens, Marburg, Germany), RecombiPlasTin2G (Instrumentation laboratory) and STA- NeoplastinCl+/Neoplastin R (Diagnostica Stago) [2]. For monitoring, apixaban PT, INR, and aPTT tests are not ideal; however, a normal PT value represents no activity of apixaban and is more useful when other tests are not available [2]. The prolongation of PT is small with therapeutic doses of apixaban and edoxaban, and it is also variable. Sensitive reagents such as TriniCLOT PT Excel S, STA- Neoplastin R can be useful for the assessing plasma concentrations of edoxaban [2]. Use of INR will not correct this variation, hence not recommended for factor Xa inhibitors (rivaroxaban> edoxaban> > apixaban).

Activated Partial Thromboplastin Time (aPTT)

This assay is based on plasma for clot formation, usually used for monitoring unfractionated heparin. An aPTT assesses intrinsic pathway by contact activation including contact factors (fXII, prekallikrein, fXI, fIX and fVIII levels) [3]. The PTT test is conducted by mixing citrated plasma with silica, calcium and a synthetic phospholipid (ellagic acid), to initialise clot formation. The clot can be detected by optical and mechanical methods. Optical density is used in optical method, while movement or oscillations is used in mechanical method. As the fibrin is formed, oscillation or movement slows down and this time PTT is measured. Also known as activated PTT, it is so named because coagulation is enhanced using surface activating agent such as kaolin or silica.

Dabigatran affects intrinsic pathway primarily and so prolongs aPTT than PT. It can be useful as a qualitative assessment for Dabigatran levels with moderate correlation [2]. The influence of Dabigatran on aPTT can be plotted in a curvilinear fashion as it has no sensitivity at supratherapeutic levels [2]. Hence, higher concentrations of the drug may be underestimated, and overdose assessment is significantly problematic. A normal aPTT does not exclude clinically relevant Dabigatran activity.

The aPTT is not a sensitive test for factor Xa inhibitors. The aPTT is influenced to a large

extent by different reagents used and also by the individual drug. Within normal therapeutic range, both apixaban and edoxaban prolonged aPTT, but variability was high. Hence, this test cannot be used for qualitative or quantitative evaluation of factor Xa inhibitors. This is because of multiple reasons such as the variability of reagents used, insensitivity, no standardisation across the laboratories and low concentration with paradoxical responses.

Activated Clotting Time (ACT)

To assess the anticoagulant effect of unfractionated heparin ACT, a whole blood test is used [11]. In this test, a whole blood is added to a tube which has a surface activator (either kaolin or diatomaceous earth), which stimulates clot formation by contact activation pathway. This is a clot-based assay which measures the movement of a magnet placed in the tube as and when the clot is formed or changed in the velocity of the mobility reduced by the clots. The time is measured in seconds from the fibrin formation in the tube. The factors that can prolong ACT include hemodilution, platelet counts and functionality, hypothermia, and coagulation factor deficiencies and are independent of UFH usage.

Thrombin Clotting Time (TT)

Thrombin time measures the functional assay of thrombin in plasma, and in this test thrombin agent converts fibrinogen to fibrin [12]. This test is very sensitive to inhibitory effects of heparin or direct thrombin inhibitors on thrombin. TT is a widely available test and often used for qualitative assessment rather than quantitative. Normal thrombin time definitely excludes Dabigatran because TT is sensitive to Dabigatran [13]. However, this assay is overly sensitive to Dabigatran levels and can be prolonged even in the presence of insignificant Dabigatran levels [14]. Many studies [6] recommend aPTT along with TT before elective surgery in patients who are using Dabigatran. Factor Xa inhibitors have been shown to have no effect on TT [15].

Dilute Thrombin Time (dTT)

The dTT is a coagulation which uses dilute plasma to measure coagulation and is thus more useful test than the sensitive TT. Various assays to measure dTT are Hemoclot, Technoview, and Hemosil. The dose relationship of dTT with Dabigatran is linear and accurately predicts anticoagulation intensity. Whenever available, this test is suited for quantitative assessment of anticoagulant intensity of Dabigatran. If dTT is normal, then it represents that there is no clinically relevant anticoagulation. Some dTT tests are available even for low range of concentrations without much of modifications (e.g. HemoSILDTI and STA-ECA II); but some still require a dedicated test (e.g. Hemoclot Thrombin Inhibitor LOW) [16]. In this Hemoclot Thrombin Inhibitor LOW, another procedure is adapted which uses lower dilutions of blood sample. On the other hand, the HemoSIL Direct thrombin inhibitor (DTI) is accurate even with wide a range of concentration (from <50 to 500 ng/mL) without much change in methodologies and calibration curves.

Ecarin Clotting Time (ECT) or Chromogenic Assay (ECA)

Ecarin-based assays provide measures of Dabigatran activity directly by checking the thrombin generation [16]. In this assay, prothrombin is converted to meizothrombin, an intermediate compound by snake venom ecarin. Dabigatran directly inhibits this meizothrombin in a dose-dependent manner [17]. The ECT assay is not approved by regulatory bodies, and useful when specific kits and standards are absent. ECT is precise and sensitive in patients taking Dabigatran as it shows linear response and concentration dependent. Direct factor Xa inhibitors such as rivaroxaban, apixaban, edoxaban have no effect on ECT.

Dabigatran plasma concentrations can be accurately measured by chromogenic assay in low and normal range. Ecarin assays may be valuable when there is concomitant administra-

tion of heparin, although they are not sensitive to heparins (like changing therapy from heparins to Dabigatran etexilate or vice versa) [16].

Prothrombinase-Induced Clotting Time (PiCT)

The PiCT assay consists of factor Xa, phospholipids, and an enzyme activator for factor V [12]. PiCT also has concentration dependent relation with direct thrombin inhibitors but without acceptable sensitivity. Only rivaroxaban has sensitive response with PiCT which has been demonstrated (correlation coefficient = 0.9663) [7]. Still the test requires some refinements in view of its paradoxical effect with low doses of rivaroxaban (shortening of PiCT) so that it could be used for assessing anticoagulant activity [18]. Other drugs of the same group such as apixaban and edoxaban have not been studied with PiCT [15].

Anti-Factor Xa Assay

In this assay, factor Xa tagged to a chromophore is added to plasma containing factor Xa substrate like heparin. The chromophore will be cleaved by factor Xa when a color change occurs which is directly proportional to concentration of factor Xa. Calibration of this test for specific anticoagulant is essential and usage of other uncalibrated anticoagulant agents cannot be performed. Each of these standard assays must be calibrated for a specific anticoagulant and cannot be used to assess the anticoagulation effect of other agents not previously calibrated. Most of the healthcare setting do not have such standardised assay calibrated for individual DOACs. Dabigatran has no effect on anti-factor Xa assay because its mechanism of action is direct thrombin inhibition.

The anticoagulant effect of rivaroxaban, edoxaban, and apixaban as assessed by chromogenic assay is concentration dependent, sensitive, precise and accurate [19, 20]. Important practical considerations that influence the results of the test include the timing of the sampling and standardisation of the assays. The understanding of expected time to maximum and trough levels of the drugs is essential for the interpretation of the test results. Extremes of plasma concentrations can be measured with precision with acceptable variations among the laboratories [21]. Specific Xaban levels can be measured by using the anti-Xa test calibrated for that xaban of interest [21]. These specific tests are available in special laboratories and not in all times of the day or week. In emergency situations, heparin assays calibrated with UFH or LMWH have been used to screen the clinically significant levels of these DOACs as per studies [22]. These heparin assays are non-specific, with no differentiation between heparin and anti-Xa DOACs, but could help clinicians in situations when proper history is unavailable.

Inhibition of exogenous factor Xa can also be measured by a clot-based anti-Xa assay where heparin is used as catalyst to inactivate factor Xa. These tests are quantitative measures of drug concentration and the intensity of drug action (which is qualitative) cannot be measured. Hyperbilirubinemia can influence anti-Xa heparin assay [11]. Anti-Xa assays provides the amount of inhibition, not levels of thrombin and fibrin which can be generated from the patient. This understanding is essential in the management of patients in extracorporeal support. Highly prothrombotic patients might continue to be prothrombotic despite heparin in therapeutic range according to anti-Xa levels. In such cases, titration of anticoagulation should be based on amount of thrombin and fibrin formation rather than Xa inhibition.

Dilute Russell's Viper Venom Time (dRVVT)

The dilute Russell's Viper Venom Time (dRVVT) is a promising assay which can be performed on all coagulometers [2]. In this test, factor X is activated and the formation of prothrombinase complex is triggered. According to available data, this test provides estimation of anticoagulation intensity with any DOAC, even in sub-therapeutic range of plasma levels without the requirement of any calibrators. Clinical utility of this test should be confirmed by further studies as it is less widely available than anti-Xa chromogenic assays or TT [2].

Plasma Drug Concentrations

Measurement of plasma concentrations for individual DOACs can be performed using liquid

chromatography-tandem mass spectrometry (LC-MS) [23]. Although it is a gold standard coagulation test, it is not practical to use this test by laboratories. Hence, this test is commonly used for validation of other assays for various anticoagulants. Implementation of mass spectrometry in clinical laboratories is being argued because of cost, performance and reliability.

Laboratory Safety Monitoring

Dose Adjustments for Renal Insufficiency

In severe cases of renal insufficiency, UFH is opted over LMWH. Monitoring of renal function routinely is essential for patients on DOACs to avoid complications from thromboembolism and bleeding. Among the DOACs Dabigatran, up to 80% of active metabolite is eliminated through kidney. Other DOACs have much lesser elimination through kidney than Dabigatran, Rivaroxaban - 67%, apixaban - 33%, and edoxaban - 50%. The estimation of GFR based on creatinine clearance can be used for dosing DOACs. This titration is also useful when patient is posted for elective or emergency surgery to assess the level of drug present in the blood.

Dosing in Hepatic Impairment

Assessment of liver function (such as aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, PT, and INR) and calculating Child-Pugh scores at baseline are essential for appropriate treatment with DOACs. All the DOACs have hepatic metabolism except Dabigatran which is excreted primarily through kidney. Depending upon certain patient related factors such as comorbidities and concomitant medications, testing frequency can be adjusted. When there is a high risk of hepatic dysfunction, patients should be monitored at least once in six months.

Available Recommendations

Delaying intervention or administration of antidote can cause life threatening bleeding, such as intraventricular or intracranial bleed, emergency surgery like major aneurysm surgery. Neutralisation of the effect of anticoagulant should be on emergency basis rather than waiting for test results.

According to the American Society of Hematology (ASH) 2019 guidelines for major neurosurgical procedures, patients should undergo mechanical prophylaxis for thrombosis [24]. If the patient belongs to high-risk category for thrombus formation such as prolonged immobility following surgery, pharmacological prophylaxis is recommended. This pharmacological prophylaxis is in the form of LMWH than unfractionated heparin [24].

All traumatic brain injury (TBI) patients who were on oral anticoagulants and normal CT scan during admission, who cannot be assessed with neurological examination, need to repeat CT within 6–24 h [22]. For patients on warfarin, if the CT scan shows a positive result in TBI, it is recommended to maintain INR of <1.5. In patients on DOACs with TBI, TT or dTT, it is recommended to rule out Dabigatran anticoagulation. In case of rivaraxaban, apixaban and edoxaban, the anti-factor Xa assay calibrated using LMWH or specific to drug is recommended. In case of antiplatelets, there is no clear recommendation if desmopressin, tranexamic acid or platelet transfusion will reverse the progression of ICH or improve neurologic outcome. These are few recommendations from Austrian consensus statement for monitoring and managing TBI in patients on anticoagulants [22].

For intravenous thrombolysis with r-tPA in cases of acute ischemic stroke, the recommended cut-off plasma concentrations of DOACs are 10, 50, 100 ng/ml for apixaban, Dabigatran and rivaroxaban respectively after risk benefit assessment on individual basis [25]. One study recommended the concentration of rivaroxaban as <20 (or 30 ng/mL) for intravenous thrombolysis [26]. When the plasma concentrations of >100 ng/ml preclude the possibility of intravenous thrombolysis, it can still be considered in concentrations between 20 and 100 ng/ml [26]. In case of intracranial artery occlusion on rivaroxaban, the recommendations are intravenous thrombolysis plus

endovascular treatment for plasma levels of ≤100 ng/mL or endovascular treatment alone for plasma levels of 100 ng/mL. For this study, the measurement of plasma levels of rivaroxaban enabled intravenous thrombolysis in one third of patients who would otherwise be ineligible for the treatment [26]. No bleeding were reported in this study [26], and hence future studies should be set up to investigate this approach.

Conclusion

Management of patients receiving anticoagulants in the perioperative period is a serious issue requiring appropriate guidelines. The availability of specific coagulation tests which are accurate with better turnaround time (ideally less than 20 min) is the need of the hour. Recommendations and guidelines development could be possible only with appropriate laboratory backup and further studies.

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Conflicts of Interest Nil.

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Adjunct Therapies to Minimize Blood Loss

Luis Fernando Botero and Mauricio Giraldo

Abstract

The neurosurgical patient is exposed to high blood loss due to the lesions to be operated on and the duration of the surgeries. Reducing anemia and perioperative bleeding avoids complications, improves outcomes, and reduces costs. To achieve this objective, in addition to the strategies of increasing the hemoglobin level with iron and erythropoietin, and blood saving with PABD, acute normovolemic and hypervolemic hemodilution, cell salvage (cell saver), there are additional therapies and strategies that can be performed by the anesthesiologist and surgeon during the perioperative process. Conditions that may increase the risk of intraoperative and postoperative bleeding such as comorbidities, medications, and herbal medicine are detected and corrected preoperatively; the anesthetic management with the correct position of the patient, temperature adequacy, acid-base and electrolyte status, choice of anesthetic technique, hemodynamic and ventilation management; strategies with antifibrinolytics and hemostatics such as tranexamic acid, desmopressin, factor concentrates and sealants; and the rationalization of blood sampling and patient-side coagulation analysis methods, points of care (POCs), such as viscoelastic methods (VHAs) with rapid information for timely decision making make perioperative bleeding less. On the other hand, the surgical preparation of the patient, the number of surgeons, experience, and the decisions, devices, and techniques to be used are also determining factors that together with the others described try to achieve the goal of minimizing perioperative bleeding and thus better outcomes.

Keywords

Patient blood management (PBM) · Acute normovolemic hemodilution (ANH) Preoperative autologous blood donation (PABD) · Cell saver (CS) · Direct oral anticoagulants (DOACs) · Tranexamic acid (TXA) · Antifibrinolytics · Topical

L. F. Botero (✉)
Anesthesiology Universidad Pontificia Bolivariana (UPB), Bogotá, Colombia

Neuroanesthesia Coordinator Neurological Institute of Colombia, Medellin, Colombia

Anesthesiologist Clinica Las Americas, Medellin, Colombia

Neurofunctional Surgery Group Specialized Centers Hospital San Vicente de Paul, Rionegro, Colombia

UPB and CES University, Medellin, Colombia
e-mail: luis.botero@neurologico.org.co

M. Giraldo
Western University and Schulich Medicine and Dentistry School, Anesthesiologist London Health Science Centre, London, ON, Canada

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hemostatic agents · Viscoelastic hemostatic assays (VHAs) · Points of care (POC) Removal blood · Embolization · Prone position · Spinal surgery · Brain surgery

Introduction

The care and conservation of a patient's own blood are critical, as recognized by the World Health Organization (WHO) in the patient blood management (PBM) strategy. The PBM is an evidence-based, patient-centered systematic approach aiming to improve patient care and judicious use of blood products [1, 2]. Up to 20% of all blood transfusions are inappropriate or not supported by guidelines, increasing the risk of adverse events and unfavorable outcomes after transfusions [3].

Blood management and its adverse effects cost over 10 billion USD per year [4]. Therefore, optimizing patient safety and increase the cost-effectiveness of blood loss and blood management is of the utmost importance [5].

In children, even minimum losses are significant. However, the compensatory capacity is tremendously effective at maintaining stable hemodynamic parameters but can be suddenly overwhelmed, leading to physiological deterioration and circulatory collapse. Up to 12% of all cardiac arrests in pediatric patients are secondary to hypovolemia, 50% of which were not detected due to underestimating blood losses. Meanwhile, the mortality rate due to blood transfusions is two per 100,000 blood product units and are related to transfusion-associated circulatory overload (TACO), transfusion-related lung injury (TRALI), transfusion-transmitted infection (TTI), transfusion-related immunomodulation (TRIM), and hemolysis [6].

The American Medical Association and the Joint Commission stated that allogeneic blood transfusions (ABT) are one of the pillars of unnecessary procedures, in which the benefit is minimal, yet the patient is exposed to risks [7]. Hospitals must encourage practitioners to follow the indications for a blood transfusion and emphasize reducing perioperative blood loss and other adverse events [8].

Minimizing blood losses and optimizing surgical and anesthesia techniques are a crucial component of PBM. The strategy's effectiveness is evidenced by the improvement in patient outcomes, the reduction in the complications rate, and the cost-effectiveness reports. These are currently endorsed by WHO, positioning these strategies as the standard of care and reducing the use of packed red cells by 20% in the past ten years [9, 10].

In addition to blood-conservation strategies (such as screening and correction of coagulation imbalances, preoperative autologous blood donation [PABD], acute normovolemic hemodilution [ANH], cell saver, and others), which we will discuss elsewhere in this book, it is necessary to implement other measures to minimize perioperative blood losses in the neurosurgical patient. This chapter will initially describe general blood-saving strategies.

Preoperative Autologous Blood Donation (PABD)

This strategy aims to conserve and store the patient's blood and does not affect intraoperative bleeding. The patient receives his or her own blood during surgery. According to health status, patients may donate up to three blood units, which can be stored for up to 42 days (an optimizing additive must be available) before a scheduled elective surgery. Oral iron supplements and erythropoietin (EPO) are routinely prescribed to prevent anemia. This donation takes place in a facility that also handles regular blood donors [11].

PABD has limited evidence on its cost-effectiveness and safety, and thus it is rarely used. PABD may be unavailable to patients with comorbidities, including anemia, which would decrease blood quality and the donation size [12].

Administration of EPO before PABD increases patient eligibility. However, it does not reduce the number of ABT or the incidence of adverse events [13].

In children, the complications of PABD are three times higher than in adults (17.3% vs. 6.0%) and may include hypotension, anxiety, surgery delay, and IV access problems [14]. PABD is indicated in children with expected losses of over 20% of their estimated blood volume (EBV). Eligibility guidelines also include children >35 kg, >10 years old, and with Hemoglobin (Hb) >11 g/dL. Other centers establish a minimum weight of 20 kg for a 6–10 mL/kg blood donation [15].

Acute Normovolemic Hemodilution (ANH)

ANH entails removing whole blood from a patient shortly after induction of anesthesia, with the maintaining normovolemia using crystalloid and/or colloid replacement fluids. The patient's hematocrit is reduced, and tissue oxygenation is improved thanks to decreased viscosity [16, 17].

At the conclusion of the operation, the stored autologous blood is returned to the patient within 4–6 h, after which the coagulation factors' effectiveness would be decreased. Some studies suggest ANH is more cost-effective than a cell saver and can reduce ABT rates [18, 19]. Noticeably, when ANH and salvaged blood units are available, the salvaged units must be administered first [17].

In spinal surgery, patients that do not undergo ANH have a higher ABT rate than those who undergo ANH (37% vs. 79%, 28% vs. 79%) [20].

This technique could be useful in older children or those with multiple antibodies that are difficult to crossmatch. In younger children, however, ANH may cause hemodynamic instability and anemia. Hypervolemic hemodilution may be acceptable using 15 mL/kg of colloid without blood removal [6]. Observational data suggests ANH is clinically acceptable in children [21].

Blood-saving strategies, such as PABD, EPO, and ANH may help to avoid allogeneic transfusions during scoliosis surgery [8].

Cell Saver (CS)

Cell saver (CS) is a red blood cell salvage strategy that ultimately reduces red cell mass loss. CS uses a dedicated double-lumen suction device to collect blood from the operative field. The salvaged blood is stored with an anticoagulant solution, and it is then washed, filtered, and returned to the patient. The final product does not contain coagulation factors, platelets, or plasma. A caveat of CS is that high-pressure suction may cause turbulent flow and hemolysis [22]. However, a unit of allogeneic blood can cost between 1600 and 2400 USD, compared to a 240 to 512 USD per unit with a functioning CS, making the CS an attractive and cost-effective option [23].

CS is common in major orthopedic and cardiovascular surgery, especially when blood losses of >1,000 mL are expected [24]. When using CS, the risk of transfusion may be reduced by 38%, saving around 68% of allogeneic red blood cells per patient, making CS a cost-effective method [18]. In spinal surgery, CS reduces blood losses and up to 47.3% of perioperative ABT, representing about one unit of allogeneic blood per case. CS may increase the surgical time by 0.9% but reduces the risk of infection and adverse reactions to transfusions [25].

In children, CS decreases the ABT rate in craniosynostosis and spinal fusion surgeries of over 6 h. Compared to PABD, it is more cost-effective, without increasing the risk of infection [26, 27]. Nevertheless, the use of CS in children is limited, as most of the blood loss is left in the gauzes in the surgical field and not in the collection canister [28]. CS use is currently limited in children >10 kg, and when volume losses of >40% are expected [29]. Noticeably, there are continuous autotransfusion systems (CATS) equipped for suction and autotransfusion of low volumes (>30 mL), which are particularly useful in patients of <10 Kg [30].

The use of salvaged cells that contain malignant cells remains controversial. In these cases, the use of a leukoreduction filter is indicated, and the salvaged cells must be irradiated

(50 Gy) to minimize the content of malignant cells. A recent systematic review found no association between using a leukoreduction filter and the risk of tumoral dissemination or metastasis [31]. It is also essential to prevent contamination with bone, urine, alcohol, soaps, hydrogen peroxide, hemostatic agents, and other contaminants [32].

CS does not affect mortality outcomes, re-exploration for bleeding, infection, wound complication, myocardial infarction, thrombosis, stroke, or length of hospital stay [32].

In addition to the above topicals aimed at preserving blood volume and the best possible hemoglobin level in the neurosurgical patient, there are more and no less important strategies to minimize blood loss as discussed below.

Identification and Bleeding Risk Management

This strategy relates to the medications or antiaggregants and anticoagulants normally prescribed to the patient. These medications pose a risk of postoperative bleeding. In neurosurgery, patients may also have an increased risk of hemorrhage and hematoma expansion. Risk prevention includes recognizing and optimizing the pharmacological treatment to minimize bleeding.

Before an elective procedure, it is vital to detect any factors that may increase intraoperative bleeding and optimize the coagulation status. When there is no time to correct coagulation times, it is essential to detect any alteration in these parameters to monitor blood losses carefully. The lack of a reliable clinical history may increase intraoperative bleeding.

A detailed family history-oriented to coagulation disorders, previous history of postoperative bleeding or trauma, metrorrhagia, anticoagulant medications, or herbal medication must be carefully obtained from the patient [33].

For patients taking oral anticoagulants, it is necessary to determine the risk-benefit of restarting the medication after surgery (Strong recommendation, moderate quality of evidence) [34]. In elective surgery, the interruption of the medication depends on the cardiac risk factors and the intraoperative hemorrhage risk. In neurosurgery, however, halting the medication is usually recommended due to the high risk of hemorrhage in an enclosed space. Aspirin and ticagrelor should be stopped 3–5 days before surgery, clopidogrel 5 days before surgery, and prasugrel 7 days before surgery [35].

It is essential to know the last dose of anticoagulant, renal function, age, and other concurrent medications, to estimate the plasma concentration of the anticoagulant so the intervention can proceed. (Strong recommendation, high quality of evidence) [34].

In a patient with normal renal function and creatinine clearance (CrCl) >80 mL/min for dabigatran or ≥30 mL/mon for rivaroxaban, edoxaban, or apixaban; the medication must be discontinued 48 h before a neurosurgical procedure (major surgery or major blood loss expected) [36].

However, in patients with renal failure or if the patient took the medication on the day of the surgery, the procedure must be delayed between 48 to 96 h depending on the renal function, intraoperative bleeding risk, and the specific anticoagulant [36].

The antidepressants selective serotonin reuptake inhibitors (SSRI) by reducing intraplatelet serotonin alter platelet functionality [37]. Discontinuation or replacement with other medications should be accompanied by psychiatric assessment in elective patients given the implications for the patient's well-being. Valproic acid can also alter coagulation by altering platelet aggregation. It may respond to desmopressin administration by improving coagulation when faced with unexplained bleeding [38].

Careful Hemostasis and Surgical Technique

Several bleeding-reduction strategies have been proposed, including endoscopic surgery, percutaneous procedures, cell blood salvage (Cell saver), ANH, and the antifibrinolytic agents [39].

Infiltrating the incision site with epinephrine dilutions (as a vasoconstrictor, epinephrine 1:200,000 or less) may decrease bleeding during the incision [40]. On the other hand, the use of bipolar and monopolar, have little evidence supporting its use to reduce intraoperative blood loss [41]. See below (diathermy).

In spinal surgery, excessive bleeding is a frequent perioperative complication, with a prevalence of 0.85%. Excessive bleeding and the increase of the surgical and anesthetic time lead to an increased rate of blood transfusions, non-neurological complications; [42] while increasing the risk of postoperative infection. The number of intervened levels, number of inserted pins, surgery length, and Cobb's angle are correlated to blood loss. As such, male gender, Risser's sign (higher), preoperative Cobb's angle (>50°), preoperative kyphosis, premenstrual stage, osteotomy number, surgical approach, and stage of the pin insertion into the peduncle are correlated to higher blood loss. Blood losses are lower when a second surgeon is present (2003 vs. 5278 mL), or with a more experienced surgeon (1013 mL vs. 2042 mL). Concerning surgical time, time is shortened with two surgeons (5 h vs 7.6 h) [43].

Percutaneous procedures are superior in terms of blood sparing, postoperative pain, surgical time, hospital stay, and incision length, but they have no impact on the radiology results or the complication rates compared to open procedures [44].

Diathermy: The Radiofrequency Bipolar Hemostatic Sealer (RBHS) applies radiofrequency to irrigated saline to generate hemostatic tissue closure. It delivers water-cooled energy to maintain a tissue temperature < 100 C. The use of radiofrequency can reduce type I and III collagen fibers in the walls of arteries and veins. Standard electrocautery does not decrease the bleeding coming from the bone since this tissue has very low electrical conductivity. It has been shown that RBHS in spinal surgery decreases intraoperative bleeding (up to 57%) and therefore also decreases transfusions, surgery time, LOS and costs without increasing the risk of infection [45, 46].

Drains may increase postoperative losses [47]. There is no benefit compared to not placing a drain [48]. They might be useful as postoperative bleeding receptacles, and the blood collected could be reinfused into the patient, thus minimizing blood losses [49].

Blood-Sparing Anesthesia Strategies

Position

For spinal surgery while in a prone position, the abdomen must be free, without extrinsic pressure, to facilitate the venous return and decrease venous pressure in the surgical site, the mass effect, and the surgical bleeding [50, 51].

The spinal venous system (VVS, Batson plexus) has the capacity to store 20 times the volume of the contributing arteries [52]. This plexus is connected to the superior and inferior vena cava, creating connections with the intrathoracic hemiazygos and the intra-abdominal lumbar veins. The VVS will also connect with the subcutaneous veins in the thorax and abdomen, the vertebral veins in the neck, and the sacral venous plexus. The VVS does not have valves, so the pressure and flux direction in the spinal canal and the intracranial pressure (ICP) depend on the intra-abdominal pressure (IAP) and the intrathoracic pressure (ITP) [53, 54].

Proper positioning and high-quality equipment are required to keep the IAP and ITP low, diminishing the risk of medullar congestion [51, 53]. Ideally, the pelvic support should rest on the iliac crest, to prevent pressure transmission to the abdomen (Fig. 1) [55, 56]. It is also likely that a kneeling position will generate less pressure on the pulmonary pressure variables, and therefore, will cause less pressure as it not compressing the VVS [57].

Interestingly, when the surgical site is located above the myocardium it may contribute to reducing intraoperative bleeding [59].

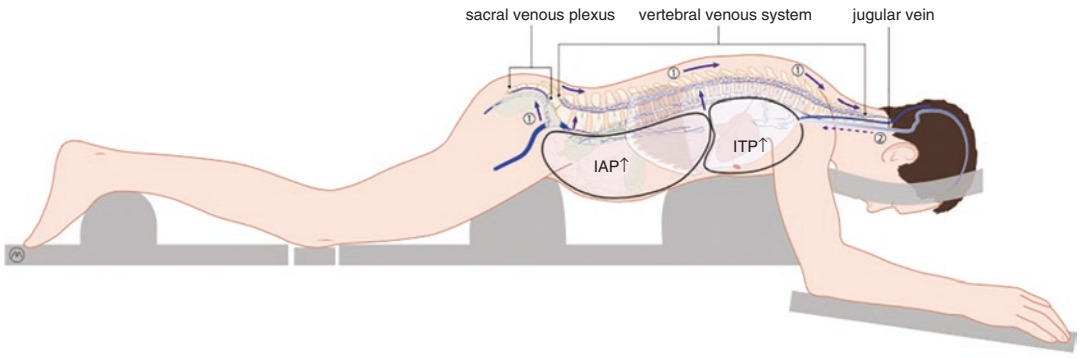

Fig. 1 Effects of increased AIP. In the first pathway, can cause backflow through the sacral venous plexus and the vertebral venous into the spinal canal. This can cause congestion of venous blood in the spinal canal and can cause flow of venous blood into the brain. In the second pathway, an increase in IAP can cause an increase in ITP (intrathoracic pressure) which in turn results in a back pressure on the jugular veins and decreases the drainage of the CSF and the venous blood. Drawing made by Medical Visuals in collaboration with Dr. Paul Depauw [58]

Hypotension

Although hypotension could help minimize bleeding, hypoperfusion is a constant risk. For preexisting conditions, including cardiovascular, cerebrovascular, and renal, a mean arterial pressure (MAP) < 65 mmHg increases the risk of complications [60].

However, the minimum MAP allowed should be set according to the functional state of the patient and the length of time that the patient will stays at that MAP.

Mild risk: MAP <80 mmHg > 10 min, <70 mmHg, <10 min.

Moderate risk: MAP <60 to 65 mmHg for >5 min, <50 mmHg for any duration.

High risk: MAP <65 mmHg for 20 min, <50 mmHg for >5 min, any exposure to <40 mmHg [61].

MAP must be projected in the Willis circle, with the understanding that for each centimeter of head elevation over the horizontal, the pressure will diminish 1.35 mmHg [62]. However, in cases of large intradural tumors, it is recommended that the MAP is kept >85 mmHg, to keep the cerebral perfusion [63].

Ventilation: Hypercapnia and increased intrathoracic pressure may increase blood losses during surgery [64].

Induced cerebral vasoconstriction may avoid blood losses [65].

PEEP values below 10 cm H_2O have shown minimal effects on CBF [66].

And compared to zero PEEP strategies, it was not associated with increased bleeding in liver surgery [67].

However, it has been found that it does increase central venous pressure significantly, especially at PEEP of 4 to 8 cm H_2O [68].

This could increase the pressure and volume of the spinal venous system being a factor of increased bleeding in spinal surgeries as mentioned above.

Anesthetic Techniques

A prospective randomized trial comparing the use of sevoflurane vs. the use of propofol in spinal surgeries where the MAP was reduced by 15%, the sevoflurane group exhibited more bleeding (315 ± 99 mL vs. 106 ± 59 mL), but the propofol group presented significantly more paraspinal blood flow. This may be due to the selective vasodilating effects of each agent [69].

Sevofluorane seems to generate alteration of coagulation by suppression of thromboxane A2 formation. It may be necessary to be attentive to the serum levels of lidocaine when it is administered in IV infusion since it could alter platelet functionality [70].

The use of magnesium seems to decrease IBL, but that would not be related to its hemodynamic effects [71].

Spinal anesthesia for spinal surgery has not been shown to decrease bleeding when compared to general anesthesia [72].

Epidural anesthesia may decrease bleeding in sacral sarcoma resection when compared to general anesthesia, leading to savings of up to one unit of transfusion [73].

Normothermia, Hypocalcemia, and Acidosis

Acidosis, hypocalcemia, and hypothermia alter coagulation, as they initially alter platelet function [74]. At pH <7.2, platelet dysfunction is evident [75].

At temperatures below 35 °C, the platelet function and the enzymatic function of the coagulation factors are altered. For every 1 °C drop in temperature, blood losses are increased by 16%, and the relative risk for transfusion is increased by 22%. Rajagopalan S, - [76] Serum calcium must also be kept between 1.1–1.3 mmol/L [77].

Hemostatic Agents

Three hemostatic agents as antifibrinolytics might be used to reduce perioperative blood losses: tranexamic acid (TXA) [78], ε-aminocaproic acid (EACA) [79], and aprotinin, which is no longer used due to its adverse effects.

Tranexamic Acid (TXA)

TXA exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules, thus limiting plasmin, which normally degrades fibrin [80].

TXA has been proven to reduce blood losses in over a third of all surgical procedures including spinal, trauma, urologic, OB/GYN, and cardiac surgery [81]. This strategy has helped reduce the rate of blood transfusions by 39–69% [82].

Intravenously administered TXA is usually given in a loading dose followed by an infusion [83]. In the CRASH-IBS study (The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage) and others, 133 patients received TXA in a 1-g loading dose, followed by an infusion of 1 g over 8 h, showing a non-significative reduction of hematoma growth, with a mortality rate of 10% vs. 17.5% in the placebo group. The TXA group had a better overall outcome than the placebo group (45% vs. 58%, OR 0.57) [81, 84]. The effect of tranexamic acid in a similar group of patients with traumatic brain injury (TBI), TXA does not offer an advantage regarding surgery requirements, mortality, extracranial surgery, or the risk of an unfavorable Glasgow Outcome Scale (GOS).

Considering that the hemostatic responses are similar between surgery and trauma, it can be inferred that the use of TXA during surgery should decrease overall mortality [64].

TXA IV is an efficient hemostatic agent in spinal surgery, but it can also be administered as a topical agent (tTXA). This has been used at doses no lower than 20 mg/kg and has not been associated with venous thrombosis or pulmonary embolism. With this agent, it is possible to decrease blood losses by 29% and decrease the need for transfusion by up to 45% in spinal, urologic, otolaryngology, and cardiothoracic surgery. It may also decrease postoperative bleeding, drain blood loss, operating time, hospital stay, and may preserve the levels of hemoglobin. Additionally, blood losses do not seem to increase with tTXA when compared to the control groups (TXA IV and placebo) [85].

Some studies have also found a better safety profile for topical administration than when it is administered as an IV [86].

The combination of tTXA and IV TXA may be more effective than only administering one of the two, exhibiting advantages in reducing bleeding, Hb, and the need for ABT, without

increasing the rate of thromboembolic complications [87].

In base skull surgeries [88], cervical column surgery [89], y craniosynostosis Reduced perioperative blood loss the use of TXA in a loading dose of 15 mg/kg and then infusion of 100 mg/h until surgical site closure decreases intra- and postoperative bleeding compared with the control group. The use of a loading dose may also decrease the use of frozen fresh plasma (FFP) [90] and its adverse events [91]. There is no difference in seizures or thromboembolism between the compared groups [89, 92, 93].

The European Society of Anaesthesiology recommends the use of TXA to prevent bleeding during major surgery, or to treat bleeding secondary to fibrinolysis (20–25 mg/Kg) (Recommendation Level 1B) [84].

During a craniosynostosis procedure, blood loss can be over 100% of the entire volemia, particularly in children younger than 18 months, weight <10 kg with craniofacial syndromes and multiple sutures [94].

TXA has decreased total blood losses by 18 mL/kg during the postoperative period and by 52 mL/kg when accounting for the intraoperative and postoperative periods. Reduced perioperative blood loss.

High TXA loading doses (50 mg/kg) in craniosynostosis are not superior to standard 10 mg/kg doses, when evaluating blood losses and transfusion rates [95]. Doses may be adjusted between 10–20 mg/kg, with additional doses in the intraoperative and postoperative period [96].

The effect of TXA on vascular or brain parenchyma surgery has not been conclusive, but there are a few cases that report reduced blood loss and improved hemostasis in hemangioma resection surgery [97].

Additionally, the efficacy of red blood cell salvaging by CS is improved by TXA [98].

More studies are necessary to determine the impact of TXA in brain surgery [99].

ε-Aminocaproic Acid, EACA

At loading doses of 100 mg/kg, and with maintenance doses of 10 mg/kg/h until closure [100] or until after 8 h [101], EACA decreases perioperative bleeding, due to a more significant effect on the postoperative blood loss, when analyzing the Hemovac drains. No additional complications were associated to the use of a EACA loading dose.

When comparing TXA and EACA in spinal surgery, there are no differences in intraoperative blood losses (IBL). However, in the TXA group the number of ABT and the change in INR were lower, and the fibrinogen levels were higher during the postoperative period [102].

Desmopressin

Desmopressin (1-deamino-8-d-arginine vasopressin, DDAVP), is a synthetic analog of vasopressin, which releases factor VIII from the von Willebrand factor of the endothelial cells, and the tissue plasminogen activator (tPA). This is used to treat or prevent bleeding in patients with von Willebrand type I, hemophilia, and platelet dysfunction in uremia [103].

The usual dose is 0.3 mg/kg IV or SC. The decrease bleeding time can be seen within 60 min and is maintained for almost 24 h. DDAVP is indicated in drug-secondary platelet dysfunction, uremia, von Willebrand's, and aortic stenosis [104]. The effect on the platelets apparently remains for 3 h [105].

DDAVP has also been associated to a decreased requirement for ABT in Hemophilia A or BSe, when it is not possible to administer a factor infusion. In acquired hemophilia, and Glanzmann's thrombasthenia, the risk of thromboembolism may be increased [106].

Administering DDAVP during cardiac surgery reduces blood losses and transfusion requirements. This effect, however, is not consistent or non-verifiable in other type of procedures [104].

In intracranial bleeding, platelet transfusions are not recommended unless surgery is indicated [107]. DDAVP is suggested for trauma patients and intracranial hemorrhage exposed to antiplatelet therapy. These recommendations, however, have a low level of evidence [108, 74, 107].

Different from the concentrated platelet transfusion, DDAVP cannot transmit infectious agents. Some adverse effects include hypertension, facial blushing, and hyponatremia, which is particularly risky for patients with increased ICP [108, 109].

The Neurocritical Care Society recommends a DDAVP dose of 0.4 mg for aspirin-related ICH, cyclooxygenase-1 inhibitors or inhibitors of the adenosine biphosphate [107].

DDAVP may have a biochemical benefit over the platelet function in humans and animals receiving aspirin therapy, but there are no studies that support DDAVP use as a blood-sparing method [110].

Coagulation Factor Concentrates

Fibrinogen is essential in hemostasis. Hypofibrinogenemia is the first manifestation of coagulation factor depletion in situations of heavy bleeding. Its levels should be above 1.5 to 2.0 g/L. Early detection is desirable to initiate correction and avoid further blood loss. VHAs through ROTEM provide this information quickly. The administration of Fibrinogen Concentrate restores levels more efficiently, as fresh frozen plasma has very low levels of fibrinogen and large amounts would have to be given to reach levels of at least 2.0 g/L. Equally important is the monitoring of Factor XIII where a detection of as low as 60% may suggest replacement with FXIII concentrate. Prothrombin complex concentrates (PCC) are used according to the circumstance and within strict algorithms [111].

Topical Hemostatic Agents

These agents are used as coadjuvants for hemostasis. There are two classes: the physical and the biological (fibrin sealant). The former will activate local platelets and the extrinsic pathway, aiding clot formation. The latter increases hemostasis by containing the fibrin sealant, and may include the use of thrombin gel, and TXA [112].

- The fibrin or biological sealants (fibrinogen and thrombin) promote the reactions of the coagulation cascade through fibrinogen, thrombin and TXA. The physical sealant activates local platelets and the extrinsic pathway, favoring the thrombus formation. Some studies demonstrate that these methods are not effective to decrease bleeding nor transfusion rate [113]. On the other hand, other studies demonstrate that a fibrin sealant decreases relative exposure up to 54% for an autologous transfusion [114]. A recent systematic review shows a decrease in bleeding and transfusions in orthopedic surgery [115].

The absorbable gelatin sponges (Gelfoam, Baxter, CA) can absorb 10x their weight and seals the bleeding site. Microfibrillar collagen (i.e., Avitene; Davol RI) facilitates platelet aggregation and adhesion without affecting the coagulation cascade. Oxidized cellulose (i.e., Surgicel; Ethicon, NJ) creates an acidic environment that will react with blood and precipitates clot formation. They are effective when a functional coagulation cascade is also available [116].

An example of fibrin sealant is Tisseel (Baxter, IL), which liberates fibrin and induces clot formation. It is used to treat and prevent cerebrospinal fluid (CSF) in open or endoscopic skull base surgery [116].

Other sealants are Floseal (Baxter, IL) and Surgiflo (Ethicon, NJ), made of a gelatin-thrombin matrix. They are composed by bovine

gelatin that facilitates the sealing and thrombin that processes fibrinogen into fibrin, forming a stable clot, in the presence of factor XIII. It is useful for the endoscopic approach, as it can be easily applied in a small space [116–118]. However, it must be used judiciously as it may induce cerebral edema and increases the risk of complete vascular occlusion [114]. When using a gelatin-thrombin matrix, there is the possibility of allergic reactions and reactive granuloma [116, 119].

Bone wax (a combination of bees' wax and paraffin) may be used to control bleeding over a bone with no collapsible vessels. It is also used in the bleeding edges of the sphenoid during the pterygoid craniotomy, and the clivus [116].

Human thrombin was not inferior to bovine thrombin as a hemostatic agent, and does not generate antibodies against factor V, as bovine thrombin does [79].

The evidence that suggests these agents may significantly reduce bleeding during surgery is weak [120, 121]. However, the American Society of Anesthesiology (ASA), recommends the use of topical hemostatic agents as the fibrin sealant or thrombin in patients with excessive bleeding *American Society* [122].

TESTS (Point-of-Care Testing)

Viscoelastic analyses (VHA), such as thromboelastography, (TEG, Haemonetics, Braintre, MA, USA) and the rotational thromboelastography (ROTEM, Team International, Basel, Switzerland) give out quick, detailed information regarding the status of the coagulation cascade, and can guide the therapeutic approach. A recent meta-analysis examined the potential of these tests to reduce the need for blood products and mortality rates [123].

VHA measure changes in the tensile strength of the clot, presenting information on the state and altered phase of coagulation within 10–20 min, to guide the administration of blood products or medication to correct altered coagulation status [124, 125].

The VHA allows the treating physician to make an objective assessment of the coagulation state of the patient, determining the need for a transfusion [126].

Conventional lab tests may not be convenient, as the time to results is long (40–90 min)-*Haas T,* and the specific factors deficiencies may not be evident when evaluating PT, TP, and PTT, as the coagulation factor levels need to be less than 50% of normal values to be evident on the tests. TEG or ROTEM, however, may detect subtle abnormalities earlier in the disease [127].

Intracranial surgery has been associated with a higher incidence of coagulation problems, hemorrhage, and postoperative hematomas than other general surgery procedures [128].

In patients with brain tumors and TBI [129, 130], is it possible to find hypo- and hypercoagulability, increasing the risk of thromboembolic events, disseminated intravascular coagulation, and hemorrhages [131, 132]. There is activation of the coagulations cascade due to the release of tissue factor (TF) from the tumor [130]. Fibrinogen and platelets get depleted, leading to bleeding [133].

In dilutional coagulopathy, there is dilution and expenditure of the coagulation factors, affecting thrombin generation. The severity of fibrinolysis depends on the blood loss, and the amount and type of replacement fluid. Fibrinogen is the first compromised factor [134]. The depletion on platelet count appears when the patient as lost at least 1x of his volemia [135].

The correction of coagulopathy in a patient with TBI or a different condition that requires neurosurgery, must be performed in a timely manner to decrease intra- and postoperative bleeding. VHA permit early detection of hypo- or hypercoagulability states [136]. Transfusion algorithms based on POC facilitate the real-time identification of coagulopathies, so that any decision and treatment is targeting a specific alteration, leading to a reduction in blood losses and ABT. In urgent situations, when the patient has been treated with DOACs, VHA may be useful to control bleeding [137, 138]. These methods are fast, reliable, and have shown to decrease platelet

and plasma transfusions in craniosynostosis and spinal surgery [139, 140].

There is a strong recommendation, based on moderate quality evidence suggesting traditional methods for monitoring the hemostatic values of neocritical patients. A similar recommendation exists for TEG and ROTEM to identify and monitor anticoagulation therapy [34].

A Cochrane analysis showed low evidence (most studies were done in cardiac surgery) that using TEG or ROTEM to guide transfusions in patients with active bleeding will improve outcomes, mortality rates, and transfusion rates [141].

However, while coagulopathy has decreased the need for ABT, but has not had an effect on mortality or re-exploration due to bleeding, stroke, ventilation time, or hospital stay [141].

In neurosurgical oncology, platelet count is routinely close to 100,000/μL. Real-time information would facilitate the surgery, avoid further platelet depletion and other risky situations [142].

These techniques appear to decrease mortality rate and intraoperative transfusion rate, but the quality of the evidence is low. The European Society of Anaesthesiology recommend VHA to monitor (Grade IIC, weak recommendation with low evidence quality) [84]. The National Institute for Health and Care Excellence (NICE) in the UK finds them acceptable for cardiac surgery [143].

The results in the SEER evaluation (sonic estimation of elasticity via resonance) seem to be correlated with the ROTEM [144].

Sampling

Minimize the iatrogenic blood loss. Loss of blood can be minimized by being more rational with the current sample approach, Microfluidics, high frequency, and others are more effective at conserving red cell mass, reaching a reduction of 47% [145].

The improvement in patient detection is slow, as HB and Hto decrease little by little during the pre- or postoperative period. In a UK study, increased its public hospitals committed to a "diminishing sampling," seeking to reduce unnecessary blood losses [146].

Repeated testing may lose blood volumes of 454–1,000 mL during the post- intraoperative period. More volume lost through samples indicates a longer hospital stay, which derives into further increasing the amount of blood lost through blood samples [147].

An arterial line is more common in chronically or critically ill patients and allows for repeated pressure yet requires multiple tests per day. Low. If the equipment is set to return the leftover sample back to the patients, it can reduce cell mass loss by up to 25% [148].

Transcutaneous methods of Hb measurement should be used whenever possible, although this method represents limitations when used concurrently with a vasopressor therapy [149].

Several measures should be put in place:

1. Test only when absolutely necessary.
2. Reduce volume and frequency of each sample.
3. Using pediatric vials.
4. Use the appropriate sample container.
5. Optimize hemostasis.
6. Make point-of-care testing available.
7. Educate and implement checklists [150].

Embolization

In meningiomas, surgical morbidity and mortality are 30 and 4%, respectively. In older patients, it can reach 48 and 6.6%, respectively [151].

Many meningiomas obtain some vascular flux from intra and extracranial circuits, and the resection results in a significant blood loss (up to 2.2 L) [152].

In some cases, preparatory embolization of some lesions of the nervous system and spinal cord may be a correct approach to decrease blood loss and facilitating tumoral resection [153].

The embolization should be performed 24–72 h before surgery to achieve an adequate thrombosis while avoiding recanalization [154]. Other authors

recommend that the surgery is scheduled no more than 24 h after embolization [155].

Embolization is effective when the irrigating vessels can be completely occluded, although this procedure is risky. The external carotid branches are approached unless the patient has any contraindications for this procedure, such as a direct anastomosis between the ophthalmic and the meningeal arteries [156]. Conservative methods are more appropriate to avoid branches of the internal carotid arteries, using different devices or particles according to each patient's anatomy [157].

A meningioma is a good candidate for embolization when presenting with high vascularity, or when irrigating tumor vessels are out of reach, size, and a connection with the external carotid artery, limited localized edema, compromise of dural sinuses and cranial structures, and proximity to eloquent zones [158].

For some meningiomas, embolization is a viable option according to size and location. For tumors located in the base of the skull larger than 2 cm, the study sequence would go as follows:

1. Image location
2. Anterior fossa: High likelihood of embolization failure
3. Posterior, middle fossa, and tentorium. Angiography to examine surrounding vessels and make a therapeutic decision:
   (a) The vascular peduncle is accessible
   (b) No vascular anastomosis
   (c) No collateral circulation to other normal structures

When all three conditions are met, embolization can proceed [156].

Embolization has many advantages, including better lesion visualization, increased efficacy and safety during decompression of the neuronal elements, and a broader view of the surgical field, allowing for prolonged procedures. However, there is always a risk of neurologic injury [159].

The benefits are measured through better or high lesion resectability, decreased surgical time, and saving blood components, although the technique and materials used also affect these parameters. The side effects of the lesion resection tend to be the same as the non-embolized group [160].

Some spinal tumors may be susceptible to embolization, but the description of the techniques is not commonly found in literature [161].

Peripheral vascular disease and a history of stroke are contraindications for the procedure.

Hemangioblastomas (HB) are commonly located in the cerebellum (up to 72%) and the spinal cord (up to 44%). One-third of all patients with HB also have Von Hippel Lindau Syndrome (VHL) [162].

Some HB might be susceptible to embolization, including those >3 cm, with defined blood vessels, and not eligible for surgery [163]. However, the results are contradictory. HB embolization may increase postoperative bleeding (8.4% vs. 1.6%), and consequently, increase the transfusion rates (15.3% vs. 0.51), and the postoperative complications. Several studies concluded that preoperative embolization is not recommended, as the outcomes do not improve but the risks increase significantly. It is not currently recommended as a standard care [164].

Due to the lack of randomized controlled trials, it is challenging to make a recommendation regarding the use and indications of embolization. The related complications risk and overall cost have limited its use.

Minimize Postoperative Blood Loss

The risk of bleeding from the gastrointestinal tract may occur during the perioperative period, so prophylaxis would decrease the risk of blood loss for this reason [50, 165].

Keeping each of these therapies in mind as an important part of the management of the patient who is bleeding or at risk of bleeding, coupled with interdisciplinary collaboration and teamwork during the perioperative period will lead to the best hemoglobin level and therefore better outcomes.

The following Table 1 summarizes the above topics related to the goal of minimizing blood loss in the neurosurgical patient.

Table 1 Strategies and elements concerning adjunctive therapies to minimize blood loss in the perioperative neurosurgical patient

Adjunct therapies to minimize blood loss			
ETAPA	Strategy	Elements	Observations
PREOPERATIVE Preoperative **v**	1. Identify the risk of bleeding	Comorbidities and antecedents Antiaggregants Anticoagulants Herbal medicine Other medicaments Type surgery Location and anatomy of injury	Bleeding history DOCs – SSRI- Valproic acid? Spinal – Brain surgery- duration? Adjacent or compromises vascular structures?
	2. Evaluate acid-base status and Ca^{+}	Correction hypocalcemia management of acidosis	pH >7.2 Ca^{+}: 1.1–1.3 nmol/L
	3. Minimize blood sampling	Strict indication Consider frequency, volume and containers	Neonatal containers?
	4. Advance anesthesia-surgical planning	Check surgical devices	RBHS (spinal surgery) Suction—CS
		Surgical technique	Endoscopic technique? Percutaneous technique?
		Verify antifibrinolytic drugs and sealants.	TXA – EACA Physical -biological
		Frames or supports suitable for prone position. Suitable operating table	Consider adapting for obese
		Devices to prevent hypothermia	Order Prewarming normothermia
	5. Consider possible embolization	Communication with multidisciplinary team	Depending on the lesion

(continued)

Table 1 (continued)

Adjunct therapies to minimize blood loss			
ETAPA	Strategy	Elements	Observations
INTROPERATIVE INTRAOPERATIVE d	1. Checklist	Position Laterality. Devices - surgical equipment - surgical technique - medications - coagulation monitoring.	Jackson, Wlson or Relton- Hall frames
	2. Ensure adequate position	Prone. Abdomen free. No abdominal compression. Support on the ASISs Avoid obstruction to cerebral venous drainage	Caution in obese patient
	3. Minimize incisional bleeding	LA infiltration with epinephrine	Avoid intravascular injection or overdose
	4. Decrease bleeding on dissection	Use of electrosurgical sealant indicated	RBHS (spinal surgery)
	5. To maintain normothermia	Temperature monitoring and control	Thermometer Thermal blankets
	6. To provide acid-base stability	Arterial gases – CA+	
	7. Surgeon's team	Ideal two surgeons (spinal surgery) Experienced surgeon	
	8. MAP control	Hypotension with adequate perfusion Consider lower limits of MAP and duration times Avoid elevation of MAP. In dissection	
	9. Adequate ventilation	EtCO2 management	PEEP?
	10. Consider anesthetic technique	TIVA vs sevoflurane	Sevoflurane may alter clotting Conductive in spinal surgery?
	11. Hemostatic - Antifibrinolytic agents	TXA – EACA - DDAVP	TXA with more evidence and more used
	12. Bleed site sealants	Physical - Biological	
	13. Coagulation monitoring and control	Standard Methods- POCs - VHAs	Timely therapy
	11. Minimize blood removal	Strict indication Consider frequency, volume and containers	To consider neonatal containers
	12. Avoid drains.		
POSTOPERATIVE	Prevent and recover bleeding	Acute upper gastrointestinal bleeding prophylaxis	Recover and infuse content. CS strategy
		If drains.	
		Avoid unnecessary blood sampling	

DOACs Direct oral Anticoagulants, *RBHS* Radiofrequency bipolar hemostatic sealer, *CS* Cell saver, *MAP* Medium Arterial Pressure, *TIVA* Total Intravenous Anesthesia, *TXA* Tranexamic acid, *EACA* ε-aminocaproic acid, *DDAVP* 1-deamino-8-d-arginine vasopressin, *POCs* Points of Care, *VHAs* Viscoelastic Hemostatic Assays

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Part X

Blood and Blood Products: Special Considerations

Management of Patients on Anticoagulants and Antiplatelets in Neurosurgery

Qi Yang, Stephanie A. Zyck, Grahame Gould, Reza Gorji, and Fenghua Li

Abstract

For patients on antiplatelet and anticoagulation therapy undergoing neurosurgical intervention, appropriate management of administration and reversal is critical in protecting them from hemorrhagic injuries and minimizing risks of thromboembolic events. Although treatment for patients will differ based on individual co-morbidities, illness condition, and urgency/invasiveness of procedures, a generalized guideline can be established to serve as the backbone for anticoagulation management in neurosurgical patients. In this chapter, we seek to examine the pharmacologic properties of some commonly used anticoagulation/antiplatelet agents, determine the timing to stop and restart antithrombotic therapy based on type of procedure and risk of thrombosis in the patient, and evaluate the suitable reversal therapy given the urgency of procedure and anticoagulant dosing.

Keywords

Neurosurgery · Neurointerventional procedure · Anticoagulants · Antiplatelets · Antithrombotic therapy

General Consideration of Neurosurgical Patients on Antithrombotic Therapy

Management of neurosurgical patients receiving antithrombotic therapy, including anticoagulants and antiplatelets, is challenging due to the complexity of antithrombotic therapy and increased types of new agents used today. Knowledge of anticoagulants and antiplatelets is critical in the management of neurosurgical patients receiving therapies. To properly manage antithrombotic therapy, the following questions should be explored. First, when is the optimal time to stop antithrombotic therapy prior to neurosurgery? Second, should bridging therapy be considered to minimize the interruption of antithrombotic therapy in patients with high thromboembolic risk? Third, when is it safe to reinstitute antithrombotic therapy after craniotomy to reduce thromboembolic complications? Fourth, considering the increase in risk of venous thromboembolism (VTE) after elective and emergency neurosurgery, particularly that of brain tumor resection, when is it safe to

Q. Yang · R. Gorji · F. Li (✉)
Department of Anesthesiology, SUNY Upstate Medical University, Syracuse, NY, USA
e-mail: lif@upstate.edu

S. A. Zyck · G. Gould
Department of Neurosurgery, SUNY Upstate Medical University, Syracuse, NY, USA

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initiate postoperative chemoprophylaxis of VTE in neurosurgical patients without prior antithrombotic therapy? Fifth, how are antithrombotic therapy reversed during emergency intracranial surgery? Lastly, how should antithrombotic therapy be managed in patients undergoing endovascular procedures when there is a need for perioperative anticoagulation? To answer the above, timing of preoperative discontinuation of antithrombotic therapy for elective surgery should be based on the individual agent's pharmacologic profile and the patient's risk of thromboembolic events during the period of antithrombotic therapy interruption. Appropriate and rapid reversal of antithrombotic therapy during emergency surgery and intracranial bleeding is critical in improving patient outcomes. The time to restart antithrombotic therapy after surgery depends on the postoperative bleeding risk of neurosurgical procedures and any underlying medical conditions which may place the patient at high thromboembolic risk. The risk of causing or worsening intracranial bleeding must be balanced against the risk of morbidity and mortality of VTE.

Characteristics of Common Anticoagulants and Antiplatelets

Anticoagulants

Anticoagulants function by inhibition of specific pathways of the coagulation cascade that occurs after platelet aggregation, resulting in prevention of coagulation and prolonging clotting time. They are indicated in thromboembolic disease such atrial fibrillation, coronary artery disease, ischemic stroke, deep vein thrombosis, mechanical heart valves, and cardiopulmonary bypass. Anticoagulants come in intravenous, subcutaneous, and oral formulations, with increased bleeding risk proportional to reduced thromboembolic risk. Oral anticoagulants are most commonly used. For certain agents, monitoring of plasma level/activity and reversal agents are available (Table 1).

Vitamin K Antagonist (VKA)

Vitamin K antagonists function by inhibition of the vitamin K dependent coagulation factors (II, VII, IX, and X), which require carboxylation by

Table 1 Commonly encountered antithrombotics in neurosurgery and their route of administration, half-life, and reversal agent

Class	Agents	Route	Half-life	Reversal
Vitamin K antagonist	Warfarin	Oral	20–60 h	Vit K/PCC/FFP
Heparin and derivative	Unfractionated heparin	IV/SubQ	60–90 min	Protamine
Low molecular weight heparin	Dalteparin	IV/SubQ	2–4 h	Protamine
	Enoxaparin	SubQ	3–6 h	Protamine
Synthetic pentasaccharide factor Xa inhibitor	Fondaparinux	SubQ	17–21 h	PCC
Direct thrombin inhibitors (univalent)	Argatroban	IV	40 min	PCC
	Dabigatran	Oral	12–17 h	Idarucizumab
Direct factor Xa inhibitor	Rivaroxaban	Oral	5–9 h	PCC/Adnexanet Alfa
	Apixaban	Oral	8–15 h	PCC/Adnexanet Alfa
Cox inhibitor	Aspirin	Oral	15–20 min	[a]Platelet/desmopressin
PDE inhibitor	Cilostazol	Oral	11 h	[a]Platelet/desmopressin
Protease-activated receptor inhibitor	Vorapaxar	Oral	5–13 days	[a]Platelet/desmopressin
P2Y12 inhibitor	Clopidogrel	Oral	6 h	[a]Platelet/desmopressin
	Ticagrelor	Oral	7–9 h	[a]Platelet/desmopressin
	Cangrelor	IV	3–6 min	
GPIIb/IIIa inhibitor	Abciximab	IV	10–30 min	[a]Platelet/desmopressin
	Eptifibatide	IV	~2.5 h	[a]Platelet/desmopressin
	Tirofiban	IV	2 h	[a]Platelet/desmopressin

[a]May consider use

vitamin K to achieve full procoagulant activity [1]. In a similar manner, anticoagulant proteins C, S, and Z are also affected by VKA, which results in a transient procoagulant phase during the start of VKA therapy, initially increasing the risk of acute thrombotic events. A well-known example of a VKA is warfarin, which is highly absorbed from the gastrointestinal tract with peak concentration at about 90 min. Other examples of VKA include acenocoumarol, phenprocoumon, and fluindione. VKA activity can be monitored by prothrombin time and international normalization ratio (PT/INR) assay, which is routinely obtained to maintain the patient in therapeutic range. Reversal of the agent includes stopping the VKA, which may take days to return the patient to a normal level, or by the administration of IV/oral vitamin K, fresh frozen plasma, prothrombin complex concentrates, and recombinant activated factor VII based on urgency of reversal. Side effects for the drug, aside from increased risk of bleeding, include acute thrombosis, skin necrosis, and limb gangrene.

Heparin and Derivatives

Heparin binds to antithrombin and causes a conformational change that results in rapid inhibition of factor IIa (thrombin), Xa, IXa, XIa, and XIIa [2]. At higher doses, it inactivates thrombin by binding to heparin cofactor II. When used at supratherapeutic doses, it also exerts anticoagulation effects by binding to factor IXa. Heparin is administered by either an IV or subcutaneous route, based on indication. On introduction to the bloodstream, it binds to plasma proteins, endothelial cells, and macrophages, resulting in variable and unpredictable pharmacokinetics. Its effect is, therefore, monitored by partial thromboplastin time (aPPT) to be kept in therapeutic range. When used in higher doses intraoperatively, is monitored by activated clotting time (ACT). Other than risk of hemorrhage, heparin has possible complications of heparin induced thrombocytopenia (HIT) and osteoporosis. Heparin is often used in bridging therapy, deep vein thrombosis prevention, and intraoperative neurointerventional and neurovascular procedures.

Low molecular weight heparin (LMWH) is derived from depolymerization of unfractionated heparin and is about one third of heparin's molecular weight. Drugs in this class include dalteparin, enoxaparin, nadroparin, and tinzaparin, which differ in pharmacokinetics and should not be interchanged [2]. The anticoagulation effect is achieved through binding of antithrombin, as well as anti-Xa/anti-IIa activity. Compared to heparin, LMWH has decreased thrombin inactivation and decreased binding to plasma protein; therefore, it has the benefit of more predictable pharmacokinetics, less incidence of HIT, and decreased bone loss. Clearance of LMWH is dictated by renal function and is prolonged in renal failure patients. Although monitoring is not necessary, anti-Xa levels can be obtained for evaluation in obese, renal impaired, and/or pregnant patients. LMWH is often used in preoperative bridging therapy and postoperative DVT prophylaxis.

Synthetic Pentasaccharide Factor Xa Inhibitors

Drugs in this class include fondaparinux, idraparinux, and idrabiotaparinux. They are synthetic pentasaccharides derived from heparin fragments. Compared with heparin, they have increased affinity for antithrombin and a longer half-life (17 h) [2]. These agents bind to antithrombin and cause a conformational change that enhances inhibition of factor Xa, but do not directly affect antithrombin inhibition of thrombin. Synthetic pentasaccharide factor Xa inhibitors bind minimally to plasma protein, can be used in HIT patients, and can be given as a daily dose without routine monitoring. If needed, anti-Xa assays can be used to determine their activity levels.

Direct Thrombin Inhibitors

Unlike indirect thrombin inhibitors (heparin, LMWH, and VKA), which require binding to antithrombin for effect, direct thrombin inhibitors bind to the active site of thrombin and function directly [1]. Direct thrombin inhibitors are classified as either univalent (binds only to cata-

lytic site of thrombin) or bivalent (binds to catalytic site and fibrin binding site). Univalent drugs include dabigatran, argatroban, inogatran, and melagatran. Dabigatran is a pro-drug that is converted to its active form by esterase-mediated hydrolysis in the plasma and liver. It is excreted mainly by route of the kidney. Dabigatran, in its main active form in plasma, is a rapid-acting competitive and reversible direct inhibitor of thrombin. This agent further blocks thrombin-mediated conversion of fibrinogen to fibrin, feedback activation of coagulation, and platelet activation. Its peak onset of action is in 2 h. Argatroban acts as a competitive inhibitor of thrombin by reversibly binding to thrombin's active site. It is administered intravenously, is metabolized by the liver, and should be used with caution in liver failure patients. It can be safely used in renal impairment and HIT patients. Dosing is adjusted and monitored by aPPT [3].

Bivalent drugs of this class include hirudin, bivalirudin, lepirudin, and desirudin. Hirudin is derived from the salivary glands of leeches [2]. It binds irreversibly to thrombin and is administered by an IV or subcutaneous route. The therapeutic dose is adjusted and monitored by aPPT, and when used in higher doses during cardiopulmonary bypass, it is adjusted and monitored by ecarin clotting time (ECT) [3].

There is no direct reversal to most direct thrombin inhibitors, although prothrombin complex concentrate, fresh frozen plasma, and recombinant factor VIIa can be utilized to decrease the anticoagulation effects of these agents. Dialysis with polymethyl-methyl acrylate membranes can be used to remove hirudin from the system. Dabigatran can be reversed by idarucizumab, which works by binding to free and thrombin-bound forms of dabigatran to nullify its effects [4].

Factor Xa Inhibitors

Direct factor Xa inhibitors function directly on factor Xa in the coagulation cascade. Compared to VKA, heparin, and LMWH, they have a quick onset/offset, reduced need for bridging therapy, less potential for drug-drug interaction, and relatively stable anticoagulation response that makes routine monitoring unnecessary [5]. Drugs in this class include rivaroxaban, apixaban, edoxaban, and betrixaban. Reversal agents for direct factor Xa inhibitors include andexanet alfa, which is an inactive factor Xa that binds to inhibitors and works in two to five min.

Antiplatelet Agents

Antiplatelets function in the prevention of clot formation by inhibiting the process of platelet activation, adhesion, release, and/or aggregation. They are often used in combination with aspirin in dual antiplatelet therapy for greater effect than either single agent. They are indicated in patients with risk of arterial thrombosis such as in cases of stroke, cardiac surgery, stable/unstable angina, and intravascular stent placement.

Irreversible Cyclooxygenase (COX) Inhibitors

Aspirin is one of the irreversible cyclooxygenase inhibitors, and functions by acetylation of a serine unit on the COX enzyme channel. This action prevents substrate access and permanently inactivates Cox-1 and Cox-2, which subsequently inhibits the prostanoid biosynthesis pathway. At a low dose of 81 milligrams, aspirin works on inhibiting platelet function through Cox-1 [5]. When a higher dose of aspirin is utilized, this drug acts on Cox-2 and produces physiologic changes of pain control and inflammation. Aspirin is absorbed in the stomach and upper intestine, with a peak time of around 30–40 min. When taken in the enteric coated form, peak plasma time can take up to 3–4 h. This drug has a half-life of 15–20 min and is quickly cleared, but as an irreversible inhibitor, aspirin's effect lasts up to the entire lifetime of the platelet, which is usually 7–10 days [5].

Adenosine Diphosphate (ADP) Receptor Inhibitors

ADP receptor antagonists inhibit platelet function at the P2Y1 and P2Y12 receptors. The former initiates platelet response and the latter promotes it [6]. Function at either one or both

receptors will cause an antiplatelet effect. Drugs in this class include cangrelor, clopidogrel, prasugrel, and ticlopidine. Clopidogrel is a thienopyridine and is one of the most commonly used agents. It requires metabolism by hepatic cytochrome P450 to its active metabolite, which then irreversibly affects P2Y12, reducing platelet function in a dose dependent fashion for the lifetime of the platelet for 7–10 days [6]. Similar to aspirin, return of platelet function happens in seven days. Clopidogrel is often used with aspirin as dual antiplatelet therapy for increased effectiveness in patients undergoing acute myocardial infarction or undergoing percutaneous coronary intervention [5].

Glycoprotein (GP) IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors are agents that bind to the fibrinogen and von Willebrand factor glycoprotein receptors on platelet plasma membranes, thus preventing platelet activation and adherence [7]. Drugs in this class include abciximab, tirofiban, and eptifibatide, which are utilized intravenously. Abciximab is composed of murine monoclonal antibody that blocks GP IIb/IIIa, with onset of action in 10 min, maximum effect in 30 min, and duration for 72 h. Abciximab differs from the other two in that it does not require dosing reduction for renally impaired patients [7]. One of the major side effects, aside from hemorrhaging, includes thrombocytopenia, and it is recommended to obtain a platelet count 2–4 h after initiation of treatment.

Management of Patients on Anticoagulants and Antiplatelets for Elective Neurosurgery

Coagulation derangements, such as those frequently seen in patients with chronic subdural hematomas, are risk factors in patients undergoing elective neurosurgical procedures. A brain injured patient who has coagulopathy will also face heightened morbidity and mortality [8]. Despite what seems an obvious clinical scenario, there is lack of strong concrete evidence associating coagulation and mortality in patients with intracranial hemorrhage [9]. In general, antithrombotic therapy should be stopped before any elective neurosurgery because of the risk of devastating consequences from intracranial bleeding. However, finding a balance between the risk of thromboembolic events and the risk of perioperative intracranial bleeding must be considered during perioperative care of neurosurgical patients.

(1) Optimal Time to Stop the Antithrombotic Therapy Prior to Surgery

Anticoagulants

Vitamin-K Antagonist: Warfarin is typically held for a period of five days before surgery. PT/INR should be rechecked and confirmed to be normal in patients with liver and kidney diseases before surgery.

Factor Xa Inhibitors: Rivaroxaban, apixaban, and edoxaban are recommended to be withheld three days (72 h) prior to elective surgery [10–12].

Direct Thrombin Inhibitor: Dabigatran can be stopped three days before surgery in patients with normal kidney function. In patients with renal dysfunction with creatinine clearance less than 80 ml/min, dabigatran can be held longer, anywhere up to five days [12].

Antiplatelets

Aspirin (ASA): Aspirin is widely used for primary and secondary prevention of ischemic stroke and cardiovascular events. It is usually administered orally at a dosage of 81–325 mg daily. ASA can be stopped five days prior to elective neurosurgical cases [13]. However, Dornbos D and Nimjee SM recommend withholding ASA for 7–10 days before elective neurosurgery because of its irreversible inhibition for life-span platelet function [14]. In patients with moyamoya or carotid artery disease requiring revascularization surgery, ASA should be continued because of high risk of ischemic stroke.

ADP/P2Y12 Inhibitors: ADP inhibitors need to be discontinued for at least five days for clopi-

dogrel and ticagrelor and seven days for prasugrel prior to elective neurosurgery [15, 16]. Ticlopidine, which is discontinued in the United States, should be held for at least seven days before surgery [17, 18]. Patients on dual antiplatelet therapy after a recent cardiac stent placement should defer elective surgery until stent thrombosis risk is significantly reduced. A recommendation from cardiology on optimum timing to stop antiplatelets therapy is imperative in decision-making.

(2) Preoperative Bridging of Anticoagulation

As mentioned previously, when anticoagulation is paused, the risk of thrombotic events needs to be considered. Patients with a mechanical heart valve, non-valvular atrial fibrillation with higher CHA_2DS_2-VASc scores >5, recent ischemic stroke, deep venous thromboembolism, and pulmonary embolism are at high risk of thromboembolism [15].

Bridging therapy is recommended for patients who were on vitamin K-antagonists that are at a high thromboembolic risk [15, 19]. Douketis and co-investigators recently reported that in patients with atrial fibrillation, non-bridging anticoagulation was inferior to peri-operative bridging with LMWH for prevention of arterial thromboembolism and decreased risk of major bleeding [20]. Patients at a low risk for hemorrhagic complications resulting from the neurosurgical procedure can begin bridging therapy with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) at 36 h after the last dose of warfarin. Patients at a high risk for hemorrhagic complications should be kept off of all medications for 48–72 h before instituting a similar bridge. Each group should receive the last infusion 6–12 h before surgery, and a half dose is recommended for patients on LMWH [21]. The preferred bridging agent is LMWH due to ease of use and decreased overall cost. LMWH can be used safely in the outpatient setting, benefitting patients and providers. When a proper bridge protocol is followed, the rate of peri-operative hemorrhaging is ≤5% [22].

Direct acting anticoagulants need no bridging therapy, as their duration of action is relatively short (one of their distinct advantages) [15]. This seems to be a safe approach to take in non-neurosurgical patients at high risk of bleeding [23].

(3) Restarting Anticoagulants and Antiplatelets After Neurosurgery

Anticoagulants: The prospective peri-operative enoxaparin cohort trial (PROSPECT) recommended that after major cranial and spinal surgery, re-institution of a therapeutic dose of UFH or LMWH should be delayed for 48 to 72 h after hemostasis has been secured [24]. There is a lack of prospective studies in restarting direct oral anticoagulants (DOACs) in neurosurgical patients. There are multiple studies recommending restarting DOACs 2–3 days postoperatively [10, 25]. One group recommends risk stratification as a guideline to restarting DOACs. Validations of such approaches are currently lacking in neurosurgical patients [26, 27]. Our approach is to discuss these issues preoperatively with the neurosurgeon but also with hematology consultations. Patients undergoing neurosurgical procedures who are at high risk of thrombosis need aggressive reestablishment of DOACs.

Patient who received warfarin preoperatively and required bridging therapy may restart warfarin based on the bleeding risk of the procedure. In low-risk patients, the current recommendation is to restart warfarin 24 h postoperatively with concurrent UFH or LMWH bridge. In patients with high risk for hemorrhage, warfarin is recommended to be restarted 48–72 h postoperatively with concurrent bridge therapy as early as possible [21].

Antiplatelets: Aspirin and other antiplatelet drugs like clopidogrel begin their antiplatelet effects quickly and within hours of administration. There are no set protocols available on when to safely resume antiplatelets postoperatively. Spencer DA et al. [21] recommended waiting five days postoperatively or until the individual surgeon feels the bleeding risk is acceptable.

Postoperative Deep Venous Thrombosis and Pulmonary Embolism Prophylaxis

Venous thromboembolism (VTE), which includes both deep vein thrombosis and pulmonary embolism, is a common cause of morbidity in neurosurgical patients. Most neurosurgical patients, such as those with gliomas, are at high risk of postoperative venous thromboembolism [28, 29]. Appropriate prophylaxis with pneumatic compression devices, graduated compression stockings, and pharmacologic prophylaxis can significantly decrease complication rates. LMWH or UFH within 24 h after a craniotomy is the current guideline for DVT prophylaxis [30]. There is good evidence that shows the safety of DVT prophylaxis in patients undergoing craniotomy for brain tumors [31]. For intracranial hemorrhages, there is no clear consensus in the literature on the optimal timing of starting DVT prophylaxis. However, data suggests that there is no statistically significant increased risk of a new post-operative hemorrhage with starting chemical DVT prophylaxis with subcutaneous heparin in patients with ICH within 24-hours post-procedure [32]. For patients with SAH, the current recommendation by the Neurocritical Care Society is to start DVT prophylaxis in all patients with UFH except in cases of ruptured and unsecured aneurysms. Furthermore, 24 h after securing the aneurysm, DVT prophylaxis with UFH is recommended [30].

Management of Patients on Anticoagulants and Antiplatelets for Emergency Neurosurgery

Patients with antithrombotic therapy may require emergency craniotomy due to traumatic brain injury or other brain pathologies such as hemorrhages. Antithrombotic therapy itself can lead to life threatening intracranial hemorrhages (ICHs) [33–35] that necessitate emergency evacuation of intracranial blood. In addition to immediate discontinuation of anticoagulation, reversal and correction of anticoagulation is paramount in neurosurgical emergencies. This is true especially in ICHs to prevent hematoma expansion and intraoperative bleeding that lead to further brain tissue damage. The reversal agent of choice is based on the type of antithrombotic therapy, which can be obtained from the patient's past medical history or from coagulation studies.

Vitamin-K antagonists: Vitamin-K antagonists such as warfarin are associated with hematoma expansion and worsened patient outcome in ICH [36, 37]. Prompt reversal can be achieved by several treatment approaches to target an INR < 1.4 [38]. Prothrombin complex concentrates (PCCs) such as 4-factor PCC and activated PCC are very effective and should be the first line reversal agent if the INR > 1.4 [38, 39]. PCC dosing should be weight-based and varies according to admission INR and type of PCC used. For example, 25 units/kg for INR 2–4, 35 units/kg for INR 4–6, 50 units/kg for INR > 6, with maximal dose of 5000 units, have been proven to be effective [40]. For INR between 1.4–1.9, 25 units/kg of PCCs is recommended [38]. Repeat testing of the INR needs to be done soon after PCC administration and serially every 6–8 h for the next 24–48 h. Subsequent treatment should be guided by a follow-up INR, with consideration given to the fact that repeat PCC dosing may lead to increased thrombotic complications and risk of DIC. If the repeat INR is still elevated more than 1.4 within the first 24–48 h after initial PCC dosing, correction with fresh frozen plasma (FFP) is suggested. If PCCs are not available or contraindicated, FFP dosing at 10–15 ml/kg IV along with one dose of vitamin K 10 mg IV are recommended. Vitamin K takes 6–24 h to correct INR, and a dose of 10 mg IV should be given as soon as possible to ensure durable reversal of INR.

Un-fractioned heparin: Protamine is the antidote for heparin. It must be given by slow IV infusion because rapid infusion of protamine may cause severe hypotension. If heparin is intravenously administered for 30 min, 1 mg of protamine should be given for every 100 units of heparin. If heparin is given within 30 min to 120 min prior, then 0.5 mg of protamine should be given for every 100 units of heparin. If the

most recent dose of heparin was administered greater than 2 h prior, 0.25 mg for protamine maybe given for every 100 unit of a heparin [14, 38]. No reversal is needed if more than 4 h have passed. Prophylactic subcutaneous heparin is not routinely reversed. However, reversal of prophylactic subcutaneous heparin should be considered if the aPTT is significantly prolonged.

Low-molecular-Weight-Heparin (LMWH): LMWH has anti-factor Xa and IIa activity and includes enoxaparin, dalteparin, nadroparin, and tinzaparin. Protamine is an effective reversal agent in emergency neurosurgery if a patient receives therapeutic doses of LMWH. The protamine dosing depends on the timing of the most recent LMWH dose. LMWH administered with 8 h can be treated with 1 mg of protamine for every 1 mg of enoxaparin or 100 U of dalteparin/nadroparin/tinzaparin up to maximal single dose of 50 mg. If LMWH was given within 8–12 h, a dose of 0.5 mg of protamine per 1 mg of enoxaparin or 100 U of dalteparin/nadroparin/tinzaparin should be administered [14, 38]. After 3–5 half-lives have elapsed, protamine is probably not needed.

Fondaparinux: Fondaparinux is the only pentasaccharide available in the United States. Fondaparinux binds antithrombin and potentiates its inhibition of free factor Xa. Administration of aPCC (20 IU/kg) can reverse fondaparinux's effect. If aPCC is contraindicated or not available, we suggest administration of rFVIIa (90 mcg/kg) [14, 38, 41, 42].

Direct thrombin inhibitors (DTI): Direct thrombin inhibitors include dabigatran, argatroban, and bivalirudin. Out of the above, dabigatran is the only oral DTI. Dabigatran administered within 3–5 half-lives should be reversed. Idarucizumab is an anti-dabigatran monoclonal antibody fragment and is used to reverse dabigatran during emergency surgery. It can reverse effect of dabigatran within minutes and lasts for 24 h; when there is a risk of ongoing bleeding, a second dose may be required [43–45]. The dose of idarucizumab is 5 g, which can be administered intravenously in two divided doses. If idarucizumab is not available, aPCC or 4-factor PCC at a dose of 50 units/kg can be administered. Bivalirudin and argatroban have no antidotes, and aPCC or 4-factor PCC at a dose of 50 units/kg can be attempted.

Oral Direct Factor Xa inhibitors (Apixaban, Rivaroxaban, and Endoxaban): PCC has been shown to immediately and completely reverse the anticoagulation effect of factor X inhibitors. The dose of PCC is 50 IU/kg as an intravenous bolus. Andexanet alfa, a modified factor Xa decoy protein, is effective in reversing factor Xa inhibitors [46, 47] and its use was approved by the FDA in 2018. Andexanet dosing depends on the last factor Xa inhibitor dose and timing of last dose being administered. If patients received a lower dose of factor Xa inhibitor (e.g., apixaban $\leq$5 mg, rivaroxaban $\leq$10 mg) or if 8 h or more have elapsed since the last dose of factor Xa inhibitor, a low dose is given as 400 mg IV bolus administered at a rate of approximately 30 mg/minute, followed within 2 min by an IV infusion of 4 mg/minute for up to 120 min. If patients received higher dose of factor Xa inhibitor (e.g., apixaban $\geq$5 mg, rivaroxaban $\geq$10 mg) or unknown dose with 8 h of last dose administered, then a higher dose is given as 800 mg IV bolus administered at a rate of ~30 mg/minute, followed within 2 min by an IV infusion of 8 mg/minute for up to 120 min.

Antiplatelet Agents: There are no antidotes for antiplatelet agents. Although controversy exists, platelet transfusion and desmopressin infusion are recommended to reverse antiplatelet effects during emergency neurosurgery [40, 48]. For patients on Cox inhibitors such as aspirin, thromboxane inhibitors such as dipyridamole, PDE inhibitors like cilostazol, and protease-activated receptor inhibitors like vorapaxar, one unit of pooled platelet can be transfused and desmopressin at dose of 0.3 μg/kg can be administered intravenously within 30 min. For P2Y12 inhibitors such as clopidogrel and GpIIb/IIIa inhibitors like abciximab, transfusion of 2 units of pooled platelets in addition to infusion of desmopressin at dose of 0.3 μg/kg may be used. Platelet transfusion is of little use if patients are on eptifibatide and tirofiban [49].

Management of Patients for Neurointerventional Procedures

Effective antithrombotic therapy during neurointerventional procedures requires a careful balance between risk of bleeding and thromboembolic complications. This principle applies for all neurointerventions, including diagnostic cerebral angiograms, ruptured and unruptured aneurysm coiling, vascular malformation embolization, intracranial and extracranial stent placement, and mechanical thrombectomy for ischemic stroke. Diagnostic cerebral angiography, often performed for treatment planning prior to interventional procedures, carries approximately a 0.5% risk of permanent neurologic complications [50] and 23% risk of silent embolic infarcts on magnetic resonance imaging [51]. For interventions, risk of thromboembolism is higher. For example, one review found an 8–10% incidence of thromboembolism in patients undergoing coil embolization of cerebral aneurysms [52]. Intracranial and extracranial stent placement causes vessel wall damage, alteration of flow, and introduction of a foreign body that further increases thrombogenicity. Preventive measures should therefore always be taken to prevent thromboembolic complications while considering individual patient and procedure-specific risk factors for both bleeding and thrombosis.

(1) Heparin Use in Neurointerventional Procedures

While many anticoagulant medications are used in varying circumstances, unfractionated heparin is the standard medication given during neurointerventions due to its short half-life, intravenous route of administration, and availability of protamine as an antidote when rapid reversal is needed. Heparin is also typically mixed with saline and used for continuous flush of indwelling catheters to minimize risk of blood stasis and clot formation. Because of its unpredictable plasma protein binding and distribution, it does require laboratory monitoring for frequent dose adjustment. Activated clotting time (ACT) and partial thromboplastin time (PTT) are both useful for monitoring this therapeutic effect, as previously described. However, point of care ACT testing is performed with whole blood, while PTT levels are performed from citrated plasma, making ACT more suitable during neurointerventional procedures.

For neurointerventional procedures using heparin, baseline ACT levels are obtained at the start of the procedure where therapeutic anticoagulation is anticipated. A weight-based heparin bolus of 70–100 U/kg is given after access is obtained, with serial ACT measurements every 30 minutes and redosing of heparin as needed. The target ACT is typically 250–300 s or twice the baseline value. Several decisions regarding periprocedural anticoagulation depend on the indication for the intervention, individual bleeding risk, and interventionalist preference. During coil embolization of acutely ruptured aneurysms, for example, some interventionalists withhold anticoagulation until the first coil is in place, others give the first heparin bolus prior to intracranial placement of the guide catheter, and others do not routinely use any systemic anticoagulation. Consideration of recent cranial procedures, such as craniotomy or external ventricular drain placement, can help inform decisions on heparin use. In cases of acute intra-procedural hemorrhaging, heparin must be rapidly reversed with protamine administration. For patients who have heparin induced thrombocytopenia or other heparin intolerance, argatroban has been demonstrated to be a reasonable alternative [53].

(2) Antiplatelets Therapy in Neurointerventional Procedures

Antiplatelet therapy, although not typically beneficial during diagnostic angiograms [54], has an important role in neurovascular interventions. For intracranial and extracranial stent placement, dual antiplatelet therapy remains the standard of care. This, like many other treatment paradigms in neurointerventional surgery, was initially extrapolated from the cardiac literature [53]. Aspirin and clopidogrel is the most common

combination in current use. This regimen is ideally started seven days prior to any elective neurointervention requiring stent placement. For cases in which the procedure must be performed urgently, loading doses of 600 mg clopidogrel and 650 mg aspirin are given approximately 6 h prior to the procedure to reach a more rapid antiplatelet effect [55]. Platelet inhibition in response to clopidogrel is highly variable amongst individuals. Platelet function testing with P2Y12 assays, performed at baseline and after antiplatelet administration, guides the choice and dosing of subsequent antiplatelet agents with a goal of at least 50% platelet inhibition. Despite some controversies over the routine use of P2Y12 testing for neuroendovascular procedures, most practitioners use the assay to adjust antiplatelet therapy prior to performing flow-diversion procedures using low-porosity stents. When there is a poor therapeutic response to clopidogrel, prasugrel and ticagrelor are viable alternatives [55]. For emergency intra-procedural initiation of antiplatelet treatment, such as with emergent carotid stenting during mechanical thrombectomy, cangrelor is a useful intravenous P2Y12 inhibitor [56]. Other specific circumstances may also warrant antiplatelet use, including vessel dissection, intraluminal thrombus, or the presence of coil or device herniation into the parent artery following aneurysm embolization.

(3) Antithrombotic Therapy During Endovascular Treatment

Thromboembolic complications that occur during endovascular treatment, such as a vessel occlusion or partially occlusive thrombus, require treatment that selectively lyses the clot without increasing bleeding from the vascular lesion being treated. Local intra-arterial infusion of fibrinolytic drugs such as alteplase (tPA) or urokinase have been described for this purpose due to their selectivity for clot-associated fibrin. One series of 19 patients undergoing endovascular aneurysm coiling receiving local intra-arterial urokinase infusion for a thromboembolic complication had 74% partial or complete recanalization [57]. While this treatment is effective for thrombolysis, the risk of hemorrhaging is significant [57, 58].

Glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors are generally thought to be safer than fibrinolytics for selective intra-arterial thrombolytic infusions and more potent that P2Y12 inhibitors. These intravenous antiplatelet drugs block the glycoprotein IIb/IIIa receptors that are involved in the final steps of platelet aggregation with fibrin and other clotting factors. They are thought to prevent aggregation of hyperacute clots encountered during neurointerventions without disrupting more subacute thrombi already stabilized with fibrin [59]. Several series using abciximab, a GP IIb/IIIa inhibitor that is no longer available in the United States, either as an intravenous or local intra-arterial infusion, suggest that it is highly effective at clot dissolution with a lower rate of hemorrhagic complications than fibrinolytic infusions [60, 61]. Other GP IIb/IIIa inhibitors, such as eptifibatide and tirofiban, are widely available and should be familiar to the practicing neuroendovascular team.

For the reasons mentioned above, antiplatelet and anticoagulant medications are an essential part of neuroendovascular surgery before, during, and after interventions. Adequate procedural preparation includes familiarity with the dosing and rapid access to these medications to minimize delays associated with treatment of intraprocedural hemorrhagic or thrombotic complications. This delicate balance is well illustrated by the common example of patients undergoing emergency mechanical thrombectomy for acute ischemic stroke with large vessel occlusion. These patients will often receive intravenous alteplase (IV tPA) just before or concurrently with their neuroendovascular procedure. Intravenous tPA prior to mechanical thrombectomy has been shown to increase rates of cerebral reperfusion compared with mechanical thrombectomy alone [62]; however, despite the ultrashort half-life of IV tPA, most hospital policies and practitioners exclude the use of additional antithrombotic medications within 24 h of IV tPA administration due to increased bleeding risk associated with tPA. On occasion, these patients

require emergency stenting for atherosclerotic vascular stenosis and IV antiplatelet options must be considered. These patients must be treated with extreme caution. Revascularization of ischemic brain poses a heightened risk for hemorrhagic transformation despite a frequent, concurrent prothrombotic state which can increase risk of repeat arterial or stent thrombosis. Appropriate management of antithrombotics must consider the individual and real-time risks and benefits of all these factors. These considerations are crucial because, as with all cerebrovascular procedures, the stakes are high.

Conclusion

Anticoagulants and antiplatelets have profoundly impacted management of cardiac and thrombotic conditions. Its uses present a unique perioperative challenge for neurosurgeons and anesthesiologists. Current guidelines for perioperative management of coagulation are not specifically made for neurosurgery. However, optimal perioperative management of anticoagulation and antiplatelet therapy can be drawn from published evidence and experiences. It is essential to understand the anticoagulation and hemostasis physiology and pharmacology of anticoagulants and antiplatelets. For neurosurgical patients on antithrombotic therapy, careful planning and clinical strategy in managing these medications are extremely important in reducing mortality and morbidity.

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Massive Blood Loss in Neurosurgery

Devendra Gupta and Rudrashish Haldar

Abstract

As the spectrum of neurosurgical procedures widen and complicated cases become amenable for surgery, there is a proportionate increase in the incidences of massive intraoperative hemorrhage. Management of massive intraoperative hemorrhage during neurosurgery requires teamwork and coordination between different categories of caregivers amidst what is often a confusing and stressful scenario. Building cohesiveness in the functioning amongst the different caregivers require repeated drills of the institutional Massive Hemorrhage Protocols. This chapter outlines the pathophysiology of massive intraoperative hemorrhage, different therapeutic goals for its management and the various strategies which must be undertaken appropriately and finally, the pharmacotherapeutic agents which need to be administered to manage such a catastrophe.

Keywords

Massive hemorrhage · Massive hemorrhage protocol · Neurosurgery · Blood loss · Massive transfusion

D. Gupta (✉) · R. Haldar
Department of Anesthesiology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India
e-mail: dgupta@sgpgi.ac.in

Introduction

Newer and bolder surgical techniques, effective anesthesia modalities, and holistic postoperative intensive care have facilitated the conduct of variety of complex neurosurgical procedures, which were considered difficult or unadvisable in the past. Thus, patients with large hypervascularized tumors, lesion encasing or in vicinity of major blood vessels, long segment reconstruction spinal surgery or complicated neurovascular procedures are now considered acceptable surgical candidates. However, such invasive surgeries are inevitably accompanied by the inherent risk of significant perioperative blood loss. Thus, despite the considerable improvements in the neurosurgical practices and technological refinements, significant blood loss occurs perioperatively, which often affects the patients' outcome [1].

Effects of blood loss can be reversed as long as the physiological mechanisms can overcome the intravascular volume depletion assisted by timely and adequate fluid resuscitation, and blood transfusion. However, if the rate and volume of blood loss are significantly higher than which can be compensated through physiological mechanisms, a vicious cycle results which worsens bleeding tendencies and affect other systems often causing permanent organ dysfunction, neurological damage or death [2]. Hence, anticipating the likelihood of hemorrhage, and preparing

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for timely fluid resuscitation and transfusion, is the cornerstone of successful management [3]. Inability of neuroanesthesiologists and surgeons to identify and judiciously manage hemorrhage appropriately may lead to significant morbidity and mortality.

Definitions

Massive Blood Loss: The definitions of massive blood loss that may be more helpful in the acute setting include a 50% blood volume loss within 3 h or a rate of loss of 150 ml/min [4].

Massive Transfusion: It is commonly defined as the administration of ≥10 units of packed RBCs (PRBCs) in an individual patient or the transfusion of more than one blood volume. However, during ongoing surgeries blood loss is usually rapid and thus the dynamic definition of blood transfusion is more appropriate in these settings (Box 1).

Box 1 Various Criteria of Massive Transfusion

Standard definition

1. Replacement of one entire blood volume within 24 h [5]
2. Transfusion of ≥10 units of PRBCs in 24 h [6]
3. Transfusion of ≥20 units of PRBCs in 24 h [7]

Dynamic definition

1. Transfusion of ≥4 units of PRBCs in 1 h when the ongoing need is foreseeable [8]
2. Replacement of 50% of total blood volume within 3 h [4]

Effects of Massive Blood Loss

In patients undergoing neurosurgical procedure following trauma, in addition to the surgical measures, perioperative bleeding results from multiple traumas, rupture of major blood vessels and from the other injuries which the patient had sustained. In rest of the neurosurgical procedures intraoperative bleeding is associated with surgical manipulations. Acute hemorrhage initiates a sequence of physiologic responses which involves multiple organ systems (cardiovascular, respiratory, renal, hematologic, and neuroendocrine). However, these responses may be blunted during anesthesia. Irrespective of the cause, bleeding if not adequately controlled or corrected can lead to a combination of hemodilution, hypothermia, clotting factor depletion, and acidosis, which negatively influences the clotting process to further worsen the condition in a vicious bloody circle (Fig. 1).

Hypoperfusion at the cellular level following hemorrhagic shock causes an imbalance between delivery of oxygen (DO2) and the tissue oxygen consumption (VO2) requirements [9]. Blood flow determines oxygen delivery (assessed globally by cardiac output) and oxygen content of arterial blood. At the level of the cell, oxygen delivery is insufficient to meet the tissue oxygen demand after hemorrhagic shock. In multiple organ dysfunction system, the continuous mismatch between DO2 and VO2 of specific tissue or organ beds occurs. As metabolism becomes delivery-dependent, cells shift to anaerobic metabolism leading to lactic acid, inorganic phosphates, and oxygen radicals accumulation. Generation of metabolites like damage-associated molecular patterns (known as DAMPs or alarmins), including mitochondrial DNA and formyl peptides, initiates a systemic inflammatory response [10]. With subsequent ATP depletion, cellular homeostasis gets disturbed, and various events such as membrane rupture, apoptosis, or necroptosis ensue which ultimately cause cellular death.

Initially as hemorrhage begins, activation of carotid and aortic chemoreceptors cause an increase in heart rate and left ventricular stroke volume thereby augmenting CBF. Since blood flow is inversely related to viscosity of blood, passive increase in blood flow occurs when viscosity is reduced. Enhanced production of nitric oxide by perivascular neurons and endothelial cells promotes cerebral vasodilation and increases

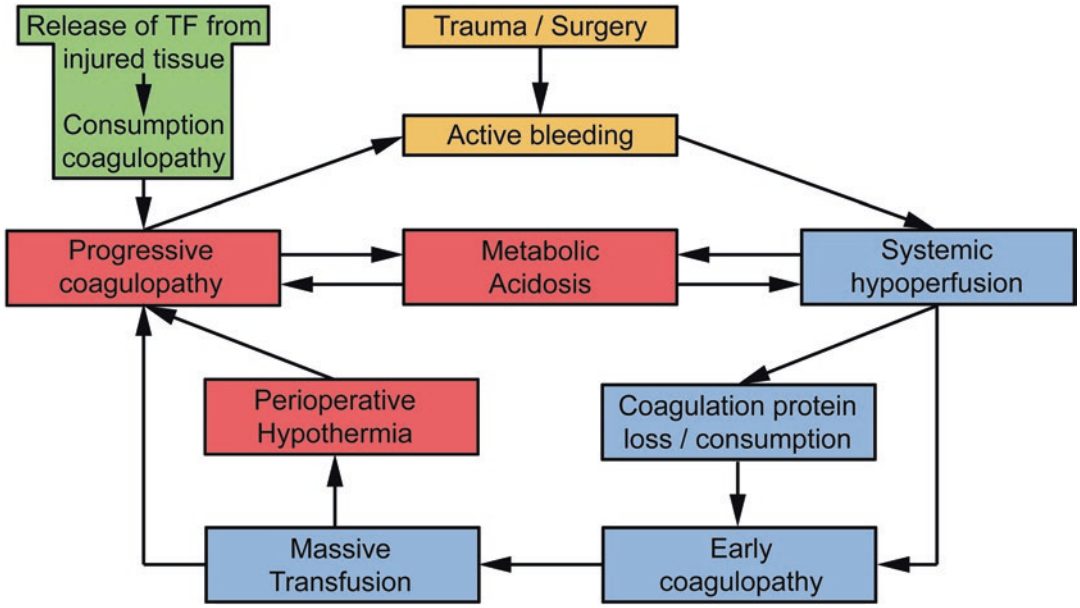

Fig. 1 Key events triggering a vicious cycle following massive hemorrhage in neurosurgical patients; TF: tissue factors, TF released into the circulation following endothelial disruption, tissue damage, or inflammatory or tumor cell expression of procoagulant molecules

CBF to maintain a constant cerebral DO2 [11]. Thus, redirection of this increased output occurs to the brain, relative to other less vital organs such as the kidney and muscles. Blood accentuates vasoconstriction which causes hypoperfusion at cellular level damaging the kidneys, liver, intestines, and skeletal muscle, causing multiorgan failure in survivors. When hemoglobin levels drops below 5–6 g/dl, cerebral vessels are maximally dilated and CBF values reach their maximum [12]. To meet the metabolic tissue requirements, the oxygen extraction ratio then increases. However, if the "cerebrovascular reserve" is compromised due to pre-existing intracranial pathology, at Hb levels around 8–9 g/dl, possibly the maximum CBF will be obtained and any further drop in Hb levels will only lead to reduced cerebral oxygen delivery. In severe hemorrhage with exsanguination, pulselessness causes brain hypoperfusion and ultimately leads to cerebral anoxia [13].

Following hemorrhage, primary hemostasis involving platelets is followed by secondary hemostasis involving coagulation factors. Simultaneously, fibrinolysis increases at remote organs to prevent microvascular thrombosis. Crystalloid fluid resuscitation to preserve intravascular volume and blood pressure precipitate dilutional coagulopathy and further decrease the oxygen-carrying capacity and platelet margination due to anemia [14].

Host's initial response to severe injury and shock is a native systemic inflammatory response syndrome (SIRS), which is usually trailed by relative immunosuppression, termed compensatory anti-inflammatory response syndrome (CARS), and then finally recovery. Any complications during the recovery process may reset cycle of another SIRS followed by CARS [15]. Immediately after injury and shock, activation of proinflammatory and anti-inflammatory innate immunity genes occur while simultaneously, the adaptive immunity genes are downregulated. These responses are reset to baseline levels during the normal recovery phase. Conversely, exaggerated immune responses occur in the patients with complications, which return to baseline more slowly [16].

Epidemiology and Identification

In neurosurgical settings the massive hemorrhage is encountered both in elective as well as emergency procedures. Although often associated with trauma surgery, in pure neurosurgical settings, perioperative massive transfusion is often undertaken to treat severe hemorrhage during long segment spinal surgery, base of skull surgery, vascular neurosurgery, large vascular tumors, craniosynostosis surgery, and cranial vault reconstruction.

Rajagopalan et al. have found a low incidence of massive blood loss (2.4%) in a retrospective analysis of the adult patients who underwent elective brain tumor surgery and identified certain predictors of massive blood loss namely female gender, tumor size >5 cm, high vascularity of tumor assessed based on preoperative imaging as well as intraoperative appearance, colloid transfusion >1 L, and surgery duration >300 min [17].

With regard to spinal surgeries, Anesthesia Closed Claims Project in the United States have reported thoracic or lumbar spine surgery as the second most common procedures (14%) involved in claims associated with massive hemorrhage [18]. In scoliosis surgery the key predictor of intraoperative bleeding is the number of fused vertebrae [19]. Major blood loss is also a serious concern during resection of spinal metastasis. Predictors of large blood loss during metastatic spine tumor surgery are the sacral metastatic tumors, combined surgical approach, number of levels of instrumentation and vertebrectomy, piecemeal resection and revision surgery [20].

In a retrospective cohort study on pediatric population undergoing brain tumor resection reported blood transfusion in 25% of the patients. Certain characteristics such as patients' age (< 4 years), duration of surgery (>270 min), and a preoperative Hb concentration (< 12.2 g dl/L) were found to be independent predictors of allogeneic blood transfusion or indirectly of significant blood loss [21]. Syndromic craniosynostosis, pansynostosis, age < 18 months, and longer duration of procedure are risk factors for large volume blood loss and transfusion in pediatric craniosynostosis surgery [22]. Similarly, a large, multicenter dataset of pediatric complex cranial vault reconstruction identified clinical factors associated with increased allogeneic blood product transfusions as age < 24 months, ASA status ≥ III, preoperative anemia, prolonged surgical duration, lack of intraoperative antifibrinolytic use, lack of intraoperative cell saver use, and the lack of transfusion protocols [23].

Preoperative Strategies

Most often, massive bleeding is usually anticipated. The providers must carefully recognize this risk and consider planning which begins in the preoperative period and consist of identifying high risk patients and initiating appropriate protective and therapeutic procedures in the event of critical bleeding.

Preoperative Evaluation to Anticipate Hemorrhagic Possibilities

1. Size, location, extent and vascularity of the lesion based on relevant radiological investigations (CT, MRI, angiography, etc.)
2. Preoperative physical examination of other organ systems (e.g., pulmonary, cardiac, etc.) and optimization of physiological reserve and risk factors
3. Evaluation of red cell mass and anemia
4. Coagulation status, familial history of bleeding and detailed medication information of the patient
5. Preoperative evaluation of vascular lesion to consider for prophylactic embolization prior to invasive surgery

Managing Anticoagulant and Antiplatelet Therapies

Patients with coronary artery disease, valvular replacement, atrial fibrillation, and stroke are often prescribed antiplatelet agents and anticoagulants. Antiplatelets (for example, aspirin,

clopidogrel) and anticoagulants (such as warfarin, direct oral anticoagulants) therapy prescribed to reduce the risk of major cardiovascular and thrombotic events pose a great risk when massive intraoperative bleeding is anticipated. Numerous recent guidelines exist to assist the perioperative use of antiplatelet and anticoagulant therapy [24]. However, high risk groups like neurosurgical patients are often ignored in the evidence base supporting these guidelines. Individualized risk of discontinuation of these therapies must be considered against the intraprocedural risks of bleeding and necessitate serious preoperative discussions with the patient, neurosurgeon, and neuroanesthesiologist. It is therefore fair to consider discontinuing these agents prior to elective neurosurgery when anticipating massive loss, except in those patients who have a history of percutaneous coronary interventions. In addition, reversal of the antithrombotic or antiplatelet effects prior to emergent surgery, or during the unexpected perioperative major blood loss may be needed. The antiplatelets and anticoagulants and its role in neurosurgery has been discussed in details separately in this book.

To decrease the need for allogenic blood transfusion in certain patient population (e.g., renal insufficiency, anemia of chronic diseases, transfusion refusal), preoperative erythropoietin (with or without iron) administration may be considered [25].

Antifibrinolytics

Antifibrinolytics are synthetic lysine analogues that inhibit plasminogen activation and stabilizes the clot. Significant decrease in blood loss and need of blood transfusion is seen with prophylactic use of tranexamic acid, aprotinin, or recombinant activated factor VII (rFVIIa). Amongst all antifibrinolytics, tranexamic acid is most commonly used during neurosurgical practice. Perioperative blood loss and transfusion requirements; in several major surgical and trauma settings has been significantly reduced with tranexamic acid. The CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage) trial reported lower bleeding progression and mortality in the tranexamic acid treated group compared to those treated with placebo [26]. Tranexamic acid administration significantly reduced blood loss and blood transfusion requirements in patients undergoing meningioma excision, probably by inhibiting local tPA induced by meningioma leading to fibrinolysis [27]. Tranexamic acid can be administered in selected spine surgeries (major complex multilevel surgery, revision surgery, prolonged procedures, and where >20% of the blood volume loss is expected), if no contraindications exist [28]. In adult patients, during preinduction a loading dose of 20 mg/kg may be considered followed by maintenance infusion. Increased postoperative mortality rates have been associated with Aprotinin. Since the efficacy data is less consistent on epsilon- aminocaproic acid (EACA) and desmopressin, they are used very specifically [29].

Many institutions have developed Maximum Surgical Blood Ordering Schedule (MSBOS) algorithm with data analysis and agreement of surgeons, anesthesiologists and blood banks. The purpose of MSBOS is to promote judicious utilization of blood and blood components and reduce their unnecessary wastage. MSBOS offer guidelines on the frequently performed elective surgical procedures and recommends the maximum number of units of blood that need to be cross matched preoperatively. Saringcarinkul et al. developed a MSBOS and found that 82% or more of all patients in their cohort have had sufficient RBC units cross-matched preoperatively if MSBOS had been followed [30]. However, in actual practice, the clinical judgment of the neurosurgeon and neuroanesthesiologists for preoperative ordering of blood and factors specific to the individual patient (age, BMI, surgical factors, preoperative investigation profile) should prevail over MSBOS guidelines.

Organizational Strategies

In any massive hemorrhage scenario, good teamwork and organized approach are essential. Usually, the consultant or the most senior anes-

thesiologist must assume the role of the team leader in the operation room whose role is to liaison and guide the other team members. He must be capable of managing both medical and logistic issues according to Major Hemorrhage Protocol.

Major Hemorrhage Protocol (MHP) has been adapted to specific clinical areas targeted to provide appropriate care of patients suffering from severe hemorrhage. The responsibilities of the medical, nursing, laboratory and support staff should be clearly defined with unambiguous lines of communication so that immediate responses can be initiated. All personnel involved must have sufficient knowledge and understanding of their roles. Regular 'training and drills" should be conducted to increase the efficiency of the e blood transfusion chain. All such cases where MHP were instituted, should be critically analyzed, and to modify the present protocols. Early consultation and early call for help from senior surgical, anesthetic and associate laboratory consultant is warranted. In case of a massive transfusion situation, the hospital transfusion laboratory should be intimated immediately. Radiological embolization or stenting have a proven role in these situations.

Irita et al. analyzed 876 patients in whom life-threatening hemorrhagic events occurred the operating room [31]. Although neurosurgery cases were merely 8.2% in this series, however, it highlighted that the role of human factors in managing the crisis of massive hemorrhage in operation room applied universally. Of these patients, the anesthesiologists had predicted the probability of developing perioperative hemorrhage in 58.0% patients and 66.7% had been counselled about the hazards of massive hemorrhage and consequent complications. Major reasons of surgical hemorrhage were adhesions or invasion of lesion (44.7%) and problems in surgical judgments or techniques (43.7%). Possibly, overenthusiastic adhesiolysis or resection without ready provision of red blood cells might be accountable for life-threatening hemorrhage [31]. Anesthetic management factors responsible for critical events in these patients were deficiency of infusion before hemorrhage, non availability of supportive anesthesiologists, delay in ordering additional blood products, delayed judgment errors in starting blood transfusion, and unavailability of rapid infusion/transfusion apparatus. In 34% of cases inadequate communication amongst surgeons and anesthesiologists existed [31].

Anesthesia Closed Claims Project in the United States had analyzed the closed anesthesia malpractice claims of the previous two decades, (mainly obstetrics and spinal procedures) and reported certain common errors. They were late diagnosis, delayed transfusion, missing warning signs, revision surgeries and timely ordering the blood products, often reflecting poor team communication [18].

Therapeutic Goals

Management of massive blood loss necessitates the taking of account of various physiologic variables such as intravascular volume, oxygenation of tissues, bleeding management, coagulation, and acid-base defects [32].

Box 2 Therapeutic Goals

1. Prompt identification of blood loss
2. Preservation of tissue perfusion and oxygenation by replacing blood volume and hemoglobin
3. Bleeding control surgically or with radiological intervention
4. Cautious use of blood components to treat coagulopathy

Intraoperative Preparations

At least two large gauge peripheral intravenous accesses along with central venous line and invasive arterial line (for monitoring) is recommended to allow the fast infusion of large volumes of intravenous fluids, blood components, electrolytes, factor concentrates and antifibrinolytics along with sources of blood sampling.

Various parameters have been measured aiming at best possible assessment and outcome.

Table 1 Intraoperative monitoring

Blood loss	Periodical visual assessment of the surgical field jointly with the neurosurgeon to assess the presence of surgical or excessive microvascular bleeding
	Quantitative measurement of blood loss including checking suction canisters, surgical sponges, and surgical drains
Perfusion of vital organs	Standard ASA monitors (blood pressure, heart rate, oxygen saturation, electrocardiography)
	Renal monitoring: Urine output
	Cerebral monitoring: Cerebral oximetry and NIRS
	Arterial blood gas analysis
	Mixed venous oxygen saturation
Hemoglobin/ hematocrit	Lab value, estimated blood loss and clinical signs
Coagulation	Viscoelastic assays (e.g., TEG and ROTEM)
	Standard coagulation tests (e.g., INR, aPTT, fibrinogen concentration) if viscoelastic assays are not available
	Platelet count
Adverse events	Checking for hypothermia, hemoglobinuria, microvascular bleeding, hypoxemia, respiratory distress, increased peak airway pressure, urticaria, hypotension, and signs of hypocalcemia before and after every transfusion

Table 1 has described various monitoring modalities and their purposes. Although numerous studies have demonstrated poor association between central venous pressure (CVP) and circulating blood volume, CVP continues to be the commonest parameter to assess volume status, [33]. There is gradual shift of intraoperative use of dynamic parameters such as stroke volume variations (SVV) or Pulse pressure variations (PPV) for prediction of fluid responsiveness in patients who are mechanically ventilated. Recent recommendations do not favor the usage of CVP and pulmonary artery occlusion pressure as the only parameters to determine fluid therapy and preload optimization during severe bleeding. Recommendations support the usage of dynamic assessment of fluid responsiveness and non-invasive measurement of cardiac output [34].

Gravity or electronic rapid infusion devices are advocated if available to administer blood and blood components using a precise infusion rate. Electronic infusion devices have the capacity of transfusing blood product at rate ranging from 6 to 30 liters/hour and they usually include a blood-warming device. External pressure devices (pressure bags) should be used only during emergency situation under certain precautions (i) infusion used in external pressure system should be attached with a large-bore venous access cannula or device at the patient end (ii) driving pressures should not exceed 300 mm of Hg, and (iii) pressure device should exert even pressure throughout the bag.

Volume Resuscitation

Massive bleeding results in reduced delivery of blood to organs and tissues (due to hypovolemia) and decreased oxygen carrying capacity of blood (due to anemia). Effects of prolonged hypoperfusion include acidosis, increased capillary permeability, microvascular consumption coagulopathy and inflammatory mediators release therefore, resulting in coagulopathy and secondary end-organ injury. Severity of tissue damage is determined by the extent and duration of tissue hypoperfusion, and it should be minimized with volume replacement in a timely manner. Stabilization of cardiac preload in an aggressive and timely manner should be accorded priority which should be achieved by rapid infusion of crystalloids and colloids. RBC transfusion should be considered only when the concentration of hemoglobin drops to a level where the overall demands of oxygen requirements cannot be fulfilled.

Properties of crystalloids include being inexpensive, ease of administration, absence of side effects and no effect on coagulation. Crystalloids being able to easily cross semi-permeable membranes, get redistributed all over the extracellular fluid (ECF) compartment, of which 75% consist of the interstitial fluid. The administration of intravenous isotonic saline solution causes the expansion of intravascular space by a

maximum of one third of the volume leaving just 16% in the circulation after 30 min. This suggests that as much as 3–4 times of the volume of crystalloid is needed to correct the blood loss as there is redistribution and rapid elimination from the ECF.

Determination of the properties of these solutions are based on their respective tonicity (osmolality compared to plasma) and their sodium content (which governs their distribution within body compartments). Isotonic or iso-osmolar solutions, having an osmolality ≈300 mOsm/L, like sodium chloride 0.9% (normal saline), Ringer's solution or balanced salt solution (plasmalyte), have no effect on plasma osmolality or raise the water content of the brain [35].

Amongst critically ill adults, balanced crystalloid therapy results in a favorable outcome (in terms of death, necessity of renal-replacement therapy, or continuing renal dysfunction) when compared with normal saline [36]. Multiple studies across various neurosurgical settings also confirmed that saline resuscitation is associated with hyperchloremia, metabolic acidosis, and decreased strong ion difference when compared with balanced crystalloid solutions [37].

Artificial colloid such as hydroxyethyl starch (HES) is recommended when blood loss exceeds more than 20% of one's blood volume. Colloid infusion is often recommended in neurosurgical patients based on the supposition that increase of colloidal osmotic pressure will lower cerebral edema. The volume of HES is usually restricted to 20 ml/kg of body weight because of its potential for inducing platelet inhibition and renal dysfunction. However, currently available low and medium molecular weight HES have relatively less significant interference on coagulation. The use of albumin as a colloid for volume replacement has recently emerged as a debatable subject. In SAFE study, analysis of a subgroup of trauma patients, advantage of using saline over albumin has been observed by the investigators. Exact mechanism of this finding could not be explained and presumably the low hypo osmolarity of albumin might be implicated in increasing the risk of brain edema [38].

Resuscitation commonly involves combining usage of warmed crystalloids and colloids based on the premise that fluid homeostasis will be reestablished with crystalloids and colloids will expand the plasma volume thereby improving the microvascular perfusion. The Guidelines Committee of the European Society of Anaesthesiology in its guideline on the "Management of severe perioperative bleeding" suggested the replacement of extracellular fluid losses with isotonic crystalloids in a timely and protocol-based manner and use of balanced solutions for crystalloids as a basic solute for iso-oncotic preparations [34]. The guidelines also recommends avoiding using crystalloids and colloids beyond the limits of the interstitial space in steady state as consequently hypervolemia may occur when cardiac preload exceeds an optimal level [34].

Vasoactive Agents

The first strategy to restore mean arterial pressure during hemorrhagic shock is fluid resuscitation. However, in face of persisting hypotension, vasopressors may be transiently employed to maintain tissue perfusion during this phase of fluid expansion while hypovolemia is still being corrected. At this vital point arterial pressure is the major determinant of tissue perfusion. Norepinephrine, a sympathomimetic agent is primarily recommended for restoring arterial pressure because of its predominantly vasoconstrictive effects. Norepinephrine, in addition to its arterial vasoconstrictor effect also exerts venoconstriction by α-adrenergic stimulation (especially at the level of splanchnic circulation), which increases the capacitance vessels pressure and actively diverts venous blood into systemic circulation. Additionally, β2-adrenergic stimulation reduces venous resistance and augments venous return. Current evidence supports the transient usage of vasopressors to maintain arterial pressure and tissue perfusion when life threatening hypotension is present. However, speculation exist regarding what constitutes the ideal blood

pressure during hemorrhagic shock resuscitation. The European guideline on the management of major bleeding and coagulopathy following trauma recommended a target systolic blood pressure of 80 to 100 mmHg until arrest of major bleeding during the initial phase after trauma for patients without brain injury [39].

Permissive Hypotension

Permissive hypotension (PH) (also known as controlled or induced hypotension) has been a commonly used strategy to lower intraoperative blood loss in neurosurgical surgeries since years. Over the time, concerns regarding potential adverse effects such as cerebral ischaemia, hemodynamic complications, and kidney injury caused by PH reduced its clinical popularity. According to a recent survey, PH is being commonly used during cerebrovascular surgery, where moderate levels of hypotension (~20% reduction of SBP or MBP) is targeted [40]. Cerebrovascular surgery is known to cause acute and torrential blood loss and intraoperative brain swelling, thereby obscuring the operative field making the surgical control of bleeding difficult. Under these conditions, PH may prove lifesaving and its instant benefits may outscore the known side effects. If used meticulously with appropriate patient selection, extent and duration of arterial hypotension, its safety and efficacy increases and the requirement for blood transfusion decreases. Moreover, the risk of end organ ischemia also reduces.

Blood and Blood Component Therapy

Red Blood Cells

Whenever 30–40% of the circulating blood volume is lost, blood transfusion with packed red cells and other blood components are inevitably needed. Specific requirements of blood and blood components should be assessed individually. Concealed bleeding often leads to underestimation of blood loss in neurosurgical procedures. Although frequent measurement of hemoglobin and hematocrit levels is advocated, in the settings of acute blood loss, hemoglobin level is a poor indicator of blood loss. Transfusion of red blood cells is usually not needed when the hemoglobin concentration is >10 g/dl but almost always indicated when it is <6 g/dl [41]. Transfusion decisions at transitional hemoglobin concentrations should be individualized and taken based on the rate and volume of bleeding, intravascular volume status, indications of organ ischemia, and capability of cardiac reserve [25]. Additionally, whenever possible, red blood cells should be transfused unit by unit with reevaluation at definite intervals [25].

Usage of group-specific red blood cells, or fully cross-matched red blood cell units in routine cases cannot be overemphasized. The degree of clinical urgency dictates whether the patient receives a fully cross-matched red blood cell unit, group-specific red blood cells, or unmatched emergency Type O red blood cells. Transfusion medicine laboratory should be clearly communicated regarding the urgency, and quantity of blood products in terms of availability and timing. In extreme situation, males with no prior history of transfusion with Rh positive blood can be transfused type O Rh-positive red blood cells and females in childbearing age, children or known/suspected alloimmunized to D antigen can be transfused with, type O Rh-negative red blood cells [42]. Hazard of delayed hemolysis due to alloantibody or Rh incompatibility is up to 1% which sometimes is acceptable in ongoing massive bleed in a patient.

Panic caused by massive blood loss carries a significant risk of transfusion error which may worsen the situation and add into morbidity or mortality. It is therefore essential to strictly adhere to the blood and blood components checking and administration protocols before transfusion.

Intraoperative Cell Salvage and Autologous Blood Transfusion

For intracranial surgery and spinal fusion, intraoperative cell salvage may be a safe and cost-effective procedure. It is most commonly used in major spinal surgeries and instrumented spinal fusion, where anticipated blood loss is expected to be high. However, the intraoperative, postoperative, total transfusion rates or the total units transfused have not shown any significant differences [43]. A study suggests that when intraoperative cell salvage is used in tumor resection surgery, meningioma (benign) cells are less likely to be detectable in salvaged blood than glioblastoma (malignant) cells [44]. Unpredictability of blood loss during neurosurgery precludes regular and routine usage of intraoperative cell salvage although whenever hemorrhage occurs, it is rapid and significant. Precisely for the same reason, the practice of preoperative autologous blood donation is limited. Autologous blood donation preoperatively is encouraged in those patients who are undergoing major surgery with anticipated large blood loss and having rare blood types. The details about blood conservation will be discussed elsewhere in this book.

Fresh Frozen Plasma

Fresh Frozen Plasma (FFP) is used to supplement multiple coagulation factors in patients with massive hemorrhage. Prompt and directed treatment of coagulation factor deficiencies in the plasma is recommended [34]. Coagulation factors are sourced from coagulation factor concentrates, high volume plasma or cryoprecipitate and their usage depends upon the clinical condition, nature of bleeding, nature of deficiency and the available resources.

The plasma volume amount needed for transfusion and the ratio of RBCs, fresh frozen plasma and platelets have been debated for years in the scenario of major blood loss. A recent meta-analysis failed to recognize any mortality or morbidity differences when transfusions were administered at a ratio of 1: 1:1 (FFP:PLT:RBC) compared to a transfusion ratio of 1:1:2 (FFP:PLT:RBC) [45]. Viscoelastic coagulation monitoring (with TEG or ROTEM) and goal-directed bleeding management is found to be superior to fixed-ratio transfusion in severe bleeding based on available evidence [46].

The American Society of Anesthesiologists in their guidelines of practice for perioperative blood transfusion recommends the transfusion of FFP in the following scenarios (1) improvement of disproportionate microvascular bleeding (coagulopathy) with concomitant Prothrombin Time (PT) greater than 1.5 times or INR greater than 2.0 or an activated partial thromboplastin time (aPTT) more than two times the normal values, (2) improvement of disproportionate microvascular bleeding due to coagulation factor deficiency in patients transfused who have received more than one blood volume (approximately 70 ml/kg) and in whom timely PT and aPTT cannot be obtained, (3) immediate warfarin therapy reversal when prothrombin complex concentrates are unavailable, (4) treatment of recognized coagulation factor deficiencies for which specific concentrates are unobtainable however, transfusion of plasma is not indicated if PT or INR and aPTT are normal solely for augmentation of plasma volume or albumin concentration.

For practical purposes, an approximate 10% decrease in concentration of clotting protein occurs for each 500 ml of hemorrhage in adults that is replaced. In blood loss which is appropriately supplemented by 8–10 units of packed red blood cells transfusion without any plasma supplementation, the level of individual coagulation factors falls below 25% of the normal.

Practical tips based on various recommendations:

1. Prophylactic administration of plasma along with PRBCs in a 1:1 ratio should be done in any patient with apparent massive hemorrhage, in case the confirmatory test cannot be obtained within a reasonable period with ongoing bleeding.
2. Dose calculation of FFP, when it is indicated should be done to achieve a minimum of 30%

plasma factor concentration (which is generally achieved when 10–15 ml/kg FFP is administered).
3. Whenever depletion of coagulation factors is evident, 800–2000 ml (4–8 FFP packs) for each volume of blood lost in a 70-kg adult should be transfused over a period of 90–120 min. Lower volumes or slower rates of FFP transfusion might not be effective [47].
4. As plasma does not require cross matching and only blood typing is necessary, delay in the plasma availability occurs due to the necessity of thawing the frozen plasma units (average 30 min) prior to their usage. Moreover, pre-thawed plasma unit are asked to be provided from transfusion laboratory for massive bleeding.

Cryoprecipitate

Since 2–5 mg of fibrinogen is present per ml of FFP, therefore 2–5 gm of fibrinogen is expected to be provided from 1 liter of FFP. Therefore, adequate quantities of FFP should be able to correct fibrinogen and most of the coagulation factor deficiencies. However, large volumes may be needed. Pooled cryoprecipitate, on the other hand consist of about 1.8 g per pool (range 1.6–2.0), whereas an adult therapeutic dose (two pools) of cryoprecipitate provides 3.2–4 g fibrinogen in a volume of 150–200 ml. In addition, factor VIII, factor XIII and von Willebrand factor is also present in cryoprecipitate. Major bleeding is accompanied by hypofibrinogenemia. Each prepared unit of cryoprecipitate contains 150 mg of fibrinogen in about 15 ml of plasma.

Indication of fibrinogen replacement include fibrinolysis (as indicated by test of fibrinogen activity) or decrease in fibrinogen concentration to below than 80–100 mg/dl in the presence of excessive bleeding [25]. European guidelines on perioperative bleeding recommends 3–4 gm of fibrinogen supplementation initially which corresponds to 15–20 single-donor units of cryoprecipitate or 3–4 g fibrinogen concentrate. Viscoelastometry and laboratory values of fibrinogen levels should determine the repeat doses.

Patients with von Willebrand disease (Type 1 and 2A) with concomitant bleeding, should receive desmopressin therapy initially followed by specific VWF/FVIII concentrate, if available. In case of no response or unavailability of desmopressin or vWF/FVIII concentrate, cryoprecipitate should be administered. Similarly, patients with von Willebrand disease types 2B, 2M, 2N, and 3 with concomitant bleeding should be treated with specific vWF/FVIII concentrate, if available, else cryoprecipitate should be given [25].

In patients with congenital factor VII deficiency and hemophilia A or B with inhibitors, recombinant factor VII a (rFVIIa) has been approved by FDA only during episodes of severe hemorrhage or perioperative bleeding management. Anecdotal cases indicate the usefulness of factor VII products in patients with massive bleeding [48]. However, the routine usage of rFVIII in patients with massive bleeding was not supported in a review [49].

Platelets

Indication for platelet concentrate include platelet count lower than 50,000 along with bleeding tendencies in normal surgical patients. For patients with ongoing bleeding and/or traumatic brain injury, platelet counts should be maintained $>100 \times 10^9$/L [50].

Bleeding complications in ICH, intracranial surgery and major spine surgery especially when they are occurring together, can be predicted based on low platelet count, low plasma fibrinogen concentration and factor XIII deficiency, although there is no clear recommendation on trigger value of platelet in neurosurgical case [34]. In patients with multiple high-velocity trauma or central nervous system injury, a higher level of 100×10^9/L should be targeted. In all surgical patients, indication of platelet transfusion is when counts drop to less than 50×10^9/L in the presence of excessive bleeding. When counts are greater than 100×10^9/L, transfusion is not indicated [25]. Platelets concentrate if planned to administered, an initial dose of four to eight single platelet units or one aphaeresis pack should

be administered [34]. Serial and frequent measurements of blood cell count is necessary since platelet count changes rapidly in the setting of critical bleeding. Drug therapies (acetylsalicylic acid, glycoprotein IIb/IIIa inhibitors, and others) can cause excessive bleeding with normal platelet counts by causing platelet dysfunction. Identification or strong suggestion of platelet dysfunction should merit platelet concentrate transfusion even with normal platelet counts.

Adverse Effect and Complications of Massive Transfusion

Large amount of inflammatory, immunomodulatory, and potentially infectious fluids administration during massive transfusion into a patient with hemorrhagic shock causing morbidities is well understood. Transfusion reactions may range from mild febrile nonhemolytic reactions (FNHR) and primary urticarial or hypotensive reactions to severe anaphylaxis shock.

Rapid transfusions are fraught with an array of intraoperative complications such as hypothermia, coagulopathy, volume overload, hyperkalemia (may be caused by lysis of stored RBCs and is increased in transfusion of irradiated RBCs), metabolic alkalosis and hypocalcemia (from the citrate additive and may be seen in patients with liver failure, congestive heart failure, or other low-output states). Table 2. shows brief overview of complications of massive transfusion and their management.

Late complications include transfusion-related acute lung injury, infections, graft versus host reaction (GVHR), and transfusion associated circulatory overload (TACO) [51]. Irradiation of the blood products is highly recommended to avoid blood transfusion-related GVHD. Although not entirely understood, TRALI is currently believed to involve pre-transfusion inflammation for

Table 2 Common intraoperative complications

Complications	Cause	Effects	Management
Hypothermia	Lower ambient temperature and use of large amount of cold blood products and fluids	Coagulopathy (10% reduction in coagulation factor activity for each 1° C drop in temperature) Depresses myocardium	1. Efficient blood warming 2. Warm forced-air system and other devices should be used to keep the patient normothermia.
Hypokalemia	Infusion of large amount of stored and irradiated RBC more common in infant and renal impaired patients	Potassium level between 5 to 7 mmol/L lengthen the P-R interval and elevate T-waves. Potassium levels greater than 8 mmol/L impair the myocardial contraction and cause life threatening arrythmias	1. Stopping of all potassium containing solution, 2. Shift extracellular potassium to intracellular by use of glucose insulin infusion and supplementation of calcium gluconate
Hypocalcemia	Rapid transfusion of the citrate containing RBC and FFP	Coagulopathy, prolong QT interval, cardiac depression and rarely circulatory collapse	Slower infusion of citrate-containing plasma Components and supplementation of calcium chloride or calcium gluconate
Metabolic acidosis	Tissue hypoperfusion Excessive use of saline causing hyperchloremic acidosis	Cardiac depression	Restoration of adequate tissue perfusion by fluid resuscitation and vasopressor therapy, sodium bicarbonate
Coagulopathy	Dilutional or hyperfibrinolysis	Increased blood loss, postoperative hematoma formation	Discussed in details in the text

patient-specific reasons, which activates pulmonary endothelial cells to express adhesion molecules and neutrophil activation [52]. A dreaded complication in acutely bleeding patient is disseminated intravascular coagulation (DIC) which has a considerable morbidity and mortality. Factors induces DIC are prolonged hypoxia or hypovolemia, cerebral or extensive muscle damage, and prolonged hypothermia due to administration of cold resuscitation fluids. Frequent laboratory tests should be considered, e.g., platelet count, fibrinogen, PT and APTT, fibrinogen degradation products or D-dimers.

Conclusion

Massive hemorrhage during neurosurgery is a potentially catastrophic scenario which affects the normal physiology and if left uncorrected can cause multisystem involvement. Various agents such as fluids (crystalloids and colloids), blood products (red blood cells, fresh frozen plasma, cryoprecipitate), and different vasopressors need to be used judiciously and in an appropriate manner to avoid setting up an hemorrhagic cascade with deleterious consequences.

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Blood Transfusion in Patients with Acute Traumatic Brain Injury

Elisa Gouvêa Bogossian, Lorenzo Peluso, and Fabio Silvio Taccone

Abstract

Red blood cell (RBC) transfusions are a frequent intervention in critically ill patients, including those with traumatic brain injury. Indeed, anemia is frequent in these patients and is associated with an increased risk of poor outcome; transfusions are often given to try and improve oxygen delivery and tissue oxygenation. The pathophysiology of anemia in patients with traumatic brain injury is multifactorial, including primary blood loss because of bleeding and secondary loss related to minor procedures or phlebotomy, hemodilution secondary to fluid resuscitation, and altered RBC production. The aim of RBC transfusion in patients with traumatic brain injury is essentially to increase cerebral oxygenation, but it is not clear whether RBC transfusion has a beneficial effect on oxygenation in patients with moderate anemia. Moreover, complications of transfusion, including transfusion-associated circulatory overload and transfusion-related acute lung injury, may offset its potential benefits. The optimal hemoglobin level that could be used to trigger RBC transfusion in patients with traumatic brain injury is undefined. In this chapter, we summarize recent data on the effects of anemia and RBC transfusion on cerebral oxygenation and on outcomes in patients with traumatic brain injury and suggest how best to optimize transfusion management in these patients.

Keywords

Red blood cell transfusion · Threshold Anemia · Traumatic brain injury · Brain oxygenation · Brain metabolism

Introduction

Traumatic brain injury (TBI) is a leading cause of death and long-term disability worldwide, especially in children and young adults [1]. In addition to the mechanical damage caused by the trauma itself, secondary brain injury due to reduced oxygen delivery to the brain may further worsen outcome [2]. Since hemoglobin is a major determinant of brain oxygen delivery, anemia can be associated with poor outcome after TBI. Many patients with TBI develop anemia because of acute blood loss, for example from trauma, and/or secondary to phlebotomy, surgical loss, hemodilution secondary to fluid resuscitation, or reduced red blood cell (RBC) production [3–5]. Reduced cerebral oxygenation because of anemia

E. Gouvêa Bogossian · L. Peluso · F. S. Taccone (✉)
Department of Intensive Care, Hôpital Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium
e-mail: ftaccone@ulb.ac.be

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may exacerbate the secondary effects of TBI. In patients with TBI, hemoglobin (Hb) concentration has been shown to be an independent predictor of mortality in patients with TBI [6].

There are relatively few specific data on the incidence of anemia in patients with TBI. In a multicenter European study of 3,534 critically ill patients, the Hb concentration was less than 12 g/dl in 63% on admission to the intensive care unit (ICU) and less than 10 g/dl in 29% [7]; 37% received at least one RBC transfusion during the ICU stay. In an American study of 4892 ICU patients, a Hb concentration less than 9 g/dl was associated with worse outcomes; 44% of the patients had received at least one RBC transfusion during the ICU stay [8]. Importantly, RBC transfusions also carry risks of complications, including acute hemolytic transfusion reactions, transfusion-related acute lung injury (TRALI) [9] and transfusion-related circulatory overload (TACO) [10]. Any potential beneficial effects of RBC transfusion must therefore be carefully weighed against any potential risk in individual patients.

In this chapter, we provided a summary of the recent literature regarding RBC transfusions in patients with TBI.

Effects of Anemia on the Brain

Cerebral oxygen delivery (DO_2) is directly proportional to cerebral blood flow (CBF) and arterial oxygen content (CaO_2) according to the equation:

$$DO_2 = Q \times CaO_2.$$

where Q indicates blood flow. As $CaO_2 = Hb \times SaO_2 \times 1.39$ (SaO_2 indicates arterial oxygen saturation), DO_2 is therefore also directly proportional to the Hb concentration. If the Hb concentration decreases below a critical level, compensatory mechanisms to maintain tissue oxygenation constant will be overwhelmed and brain DO_2 may decrease, leading to cerebral tissue hypoxia [11]. In isovolemic anemia, these compensatory mechanisms include activation of carotid and aortic chemoreceptors, leading to increased sympathetic tone. This effect results in increased heart rate and left ventricular stroke volume, and thus increased cardiac output and CBF [12]. Microcirculatory oxygen extraction is also increased to help maintain tissue oxygenation [13]. In addition, the reduced blood viscosity that accompanies anemia may improve microvascular flow because of decreased endothelial shear stress and reduced systemic vascular resistance [14, 15].

Nitric oxide (NO) plays a key role in maintaining DO_2 during anemia: expression of neuronal NO synthase (nNOS) is increased because of the associated cerebral hypoxia, and microcirculatory disturbances contribute to raise endothelial NOS (eNOS) expression [16]. Increased production of NO by perivascular neurons and endothelial cells leads to cerebral vasodilation [17] and to increased CBF. Moreover, structural changes in the conformation of oxyhemoglobin, on which NO is transported, as oxygen is unloaded to the tissues during hypoxia, promote NO release thus stimulating local vasodilation, particularly in areas where oxygen extraction is high [11]. Expression of hypoxia inducible factor-1α (HIF-1α), an important transcriptional factor, may also be increased because of cerebral hypoxia [17]. HIF-1 comprises two subunits, HIF-1α and HIF-1β, and helps protect brain cells against ischemia [18]. HIF-1 upregulates erythropoietin (EPO) secretion, which inhibits neuronal apoptosis [19], and release of vascular endothelial growth factor (VEGF), which has a crucial role in angiogenesis [20].

Overall, these mechanisms help maintain DO_2 during anemia until a critical Hb concentration is reached below which no they are no longer able to compensate; tissue hypoxia then occurs causing altered brain function (Fig. 1). In healthy volunteers, progressive isovolemic anemia to Hb concentrations of 5 g/dl has been associated with increasing fatigue and cognitive dysfunction (short- and long-term memory loss) decrease; these symptoms were rapidly reversed when the volunteers were transfused with autologous RBCs [15, 21]. However, these data from healthy volunteers may not be representative of the situa-

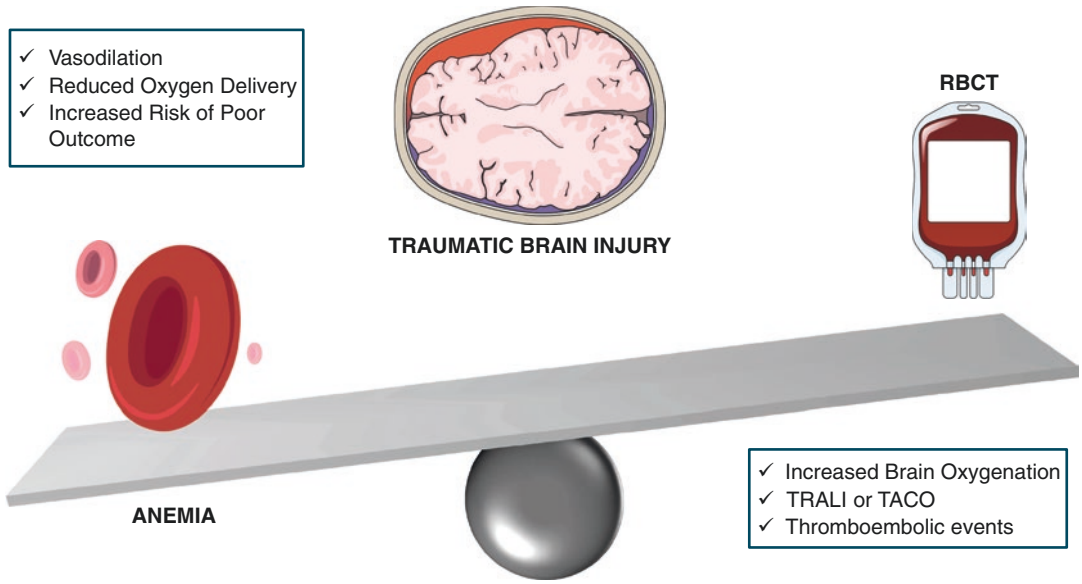

Fig. 1 Schematic effects of anemia and red blood cells transfusions (RBCT) in traumatic brain injury patients. TRALI = transfusion-associated acute lung injury; TACO = transfusion-associated circulatory overload

tion in brain-injured patients for several reasons. First, the studies in healthy volunteers used much lower hemoglobin concentrations than are observed in most critically ill patients with TBI. Second, acute hemodynamic instability or stress-induced heart failure because of TBI may also impair the ability to increase cardiac output to ensure adequate cerebral oxygenation during anemia [22]. Third, the brain lesions observed after TBI may be very heterogeneous in terms of the degree of damage, with normally perfused or mildly ischemic tissue lying in close contact with infarcted areas, such that the global effect of anemia is difficult to predict. Finally, the degree of vasodilation caused by the anemia may be limited by compensatory mechanisms induced by the TBI that are also acting to maintain adequate brain perfusion. Indeed, the ability of cerebral vessels to vasodilate in response to different stimuli (including reduced DO_2 or mean arterial pressure and changes in arterial carbon dioxide tension ($PaCO_2$), which can be called the "cerebrovascular reserve," is reduced in patients with TBI compared to healthy subjects [23]. The critical hemoglobin concentration in patients with TBI is therefore higher than that in healthy volunteers [24], with maximal vasodilation occurring at Hb concentrations of 8–9 g/dL; decreases in Hb concentration below this threshold are thus likely to result in reduced cerebral DO_2. Therefore, for similar Hb concentrations, the CBF will be lower in the injured than in the non-injured brain.

Effects of Anemia on Outcome in Traumatic Brain Injury

Several studies have shown an association between anemia and poor outcome after TBI. In a retrospective study of 1150 patients with TBI, an Hb concentration less than 9 g/dl was significantly associated with increased mortality (adjusted OR: 3.67; 95% CI: 1.13–2.24) [25]. In another retrospective study of 939 patients with TBI, initial and lowest hemoglobin concentrations were significant predictors of poor outcome and for each 1 g/dl increase in hemoglobin value, the likelihood of a good outcome increased by 33% [26]. Sekhon et al. reported that an average Hb concentration of less than 9 g/dl over a seven-day period was independently associated with increased hospital mortality (relative risk [RR]: 3.1; 95% CI: 1.5–6.3; p = 0.03) [27]; several

other studies [28, 29], but not all [6, 30, 31], have reported similar findings.

Changes in cerebral metabolism and oxygenation have been shown to occur with anemia in different forms of acute brain injury [32–34].

RBC Transfusion in Patients with Traumatic Brain Injury

RBC transfusions are used to treat anemia in patients with TBI with the aim of increasing cerebral oxygenation and by so doing improving outcomes.

Effects of Transfusion on Oxygenation and Outcomes in Patients with TBI

There is conflicting evidence regarding whether RBC transfusion increases cerebral oxygenation in patients with TBI. Some studies have reported small increases in brain tissue oxygen ($PbtO_2$) after transfusion [35–39], whereas others have reported no increase [40]. Moreover, when improved, cerebral oxygenation was not always accompanied by marked changes in cerebral metabolism, e.g., reduction in lactate to pyruvate ratio (LPR) [38].

Results from studies that have evaluated the effects of RBC transfusion on outcomes in patients with TBI have been inconsistent. In a large retrospective study of 1150 TBI patients, RBC transfusion in patients with anemia (defined as Hb <9 g/dl) was associated with increased hospital mortality (adjusted OR: 2.19; 95% CI: 1.27–3.75; $p = 0.004$) [25]. In another retrospective study of 139 TBI patients with anemia (hematocrit 21–30%), RBC transfusion was an independent risk factor for poor three- and six-month neurological outcome, but not for mortality [37]. In a meta-analysis of 23 trials in patients with TBI, there was no significant difference in mortality between patients who received an RBC transfusion and those who did not [41]. However, in a retrospective study of 215 patients with moderate or severe TBI, transfused patients ($n = 66$) had a greater risk of neurological complications and of in-hospital death after adjusting for confounders [42]. In a prospective randomized clinical trial, RBC transfusion was associated with poor one-year neurological outcome [43].

Liberal or Restrictive Transfusion Strategy in Patients with Traumatic Brain Injury?

Current recommendations for transfusion in critically ill patients suggest a restrictive approach, with transfusion if Hb concentrations are <7 g/dl, unless there are severe cardiac comorbidities [44]. However, this trigger level is largely based on studies that excluded patients with acute brain injury and may not be optimal in these patients. Indeed, maintaining Hb concentrations at levels greater than 9–10 g/dl may be a more logical therapeutic decision in patients with acute brain injury given the data suggesting worse outcomes in patients with lower concentrations discussed earlier. In an international survey investigating the transfusion practice of 868 ICU physicians involved in treating patients with acute brain injury, 54% indicated that they would give an RBC transfusion after acute brain injury when the Hb concentration was 7–8 g/dl. However, half of these respondents said they would use a higher threshold in certain groups of patients, notably those with traumatic brain injury, subarachnoid hemorrhage, or ischemic stroke [45]. In another survey of 78 intensivists and neurosurgeons from 66 centers, 41% said the transfusion protocol in their center included a threshold Hb concentration of 7–9 g/dl for patients with TBI with the other 59% using a threshold >9 g/dl [46].

There are only a few studies that have compared the effects on outcomes of different transfusion thresholds in populations of patients with TBI. A subgroup analysis of 67 patients with TBI from the multicenter randomized Transfusion Requirements in Critical Care (TRICC) trial, showed that patients who were randomized to receive transfusion using a Hb trigger of 7.0 g/dl (restrictive strategy, $n = 29$) indeed received fewer RBC units than those randomized to be transfused using a Hb trigger of 10.0 g/dl (liberal strategy, $n = 38$); there were no differences in 30-day mortality rates, hospital lengths of stay, or

development of multiple organ dysfunction between the groups [6]. In a retrospective comparison of 1565 TBI patients managed with a restrictive (target Hb > 7 g/dl) or liberal (target Hb > 10 g/dl) transfusion strategy, there were no significant differences in outcomes, but there were lower hospital costs in the restrictive group [47]. Robertson et al. randomized 200 patients with TBI in a factorial design to liberal (10 g/dl) or restrictive (7 g/dl) Hb transfusion triggers and to administration of intravenous erythropoietin (EPO) or saline [48]. There were no significant differences in the proportion of patients with a favorable six-month outcome in the two transfusion groups, although the median Hb concentration was relatively high in both groups throughout the study (9.7–10.8 g/dl in the "restrictive" vs. 11.0–11.5 g/dl in the "liberal" group). Thromboembolic events were significantly more frequent in the liberal than in the restrictive transfusion group (22% vs. 8%; $p = 0.009$). Finally, in a feasibility study of 44 patients with moderate or severe TBI [49], patients randomized to a liberal transfusion strategy (Hb trigger 9 g/dl) had lower hospital mortality (1/21 [4.8%] vs. 7/23 [30.4%]; $p = 0.048$) and there was a tendency for them to have more favorable neurological outcomes at six months ($p = 0.06$). A recent experimental study in TBI found that the exposure to anemia due to a restrictive transfusion threshold, led to a consistent reduction in cerebral microcirculation below ischemic thresholds, independent of the cerebral perfusion pressure [50].

The optimal Hb trigger for RBC transfusion in critically ill patients with TBI is therefore not yet clearly defined. In patients with mild TBI, a restrictive transfusion approach similar to that recommended in other critically ill patients, with a trigger Hb of 7 g/dl, seems reasonable [51]. However, in patients with severe TBI or deteriorating neurological status, a personalized approach to transfusion seems preferable, considering the presence of global/cerebral tissue hypoxia or factors such as ischemic heart disease that suggest poor tolerance to anemia (Fig. 2). Although "trigger"-guided transfusion should be

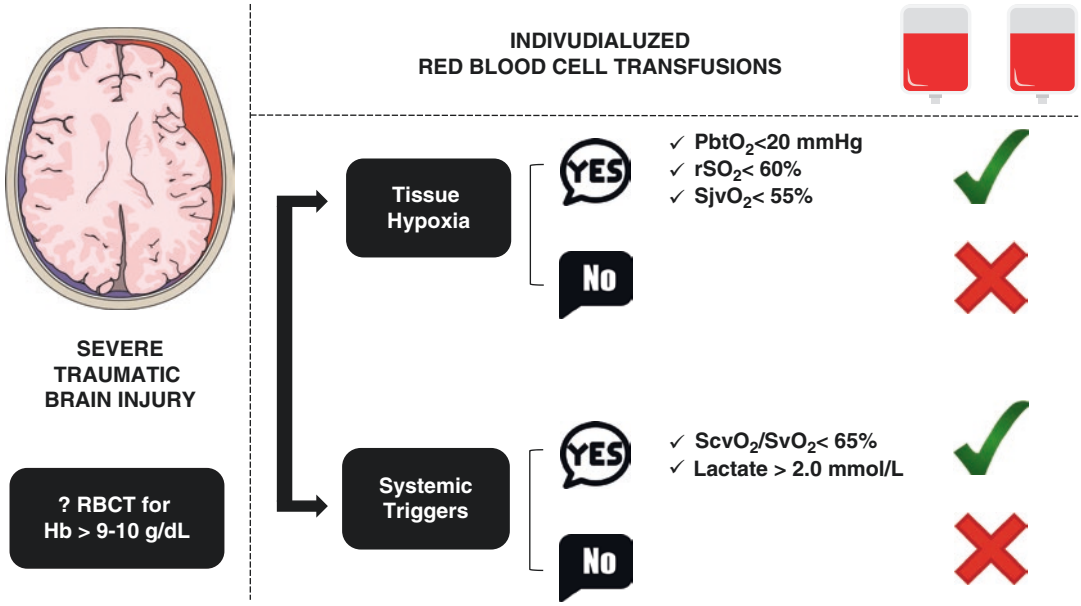

Fig. 2 Individualized administration of red blood cell transfusions (RBCT) in traumatic brain injury patients. RBCT strategy should be rarely considered for hemoglobin (Hb) values above 9 to 10 g/dl. Systemic triggers (i.e., mixed venous, SvO_2, or superior vena cava oxygen saturation, $ScvO_2$ or lactate levels) or potential presence of cerebral tissue hypoxia (jugular vein oxygen saturation, $SvjO_2$ or brain tissue oxygen pressure, $PbtO_2$, or regional saturation, rSO_2) could be used to guide RBCT administration

further evaluated in prospective studies, an individualized strategy could provide a more logical approach to RBC transfusion in this setting.

Alternatives or Adjuncts to Transfusion

Erythropoietin (EPO) has been suggested as a possible therapeutic option in patients with acute brain injury, to increase Hb slowly and minimize the risk of anemia and thus need for RBC transfusion. In experimental models, EPO has been shown to have dose-dependent neuroprotective actions when administered early after injury [52, 53]. In the clinical setting, a small retrospective case-control study suggested that administration of erythropoiesis-stimulating agents was associated with reduced hospital mortality after TBI [54]. However, concerns have been raised regarding an increased risk of thrombotic events or even mortality in patients with stroke or polytrauma receiving EPO [55, 56]. In a randomized trial of 200 patients with severe TBI, there were no significant beneficial effects of EPO compared to placebo on neurological outcome [48]. In 606 patients with moderate to severe TBI randomized to treatment with EPO or placebo, there were no differences between groups in mortality, neurological outcomes, or rate of deep venous thrombosis (DVT) [57]. In a recent meta-analysis of seven randomized controlled trials that included a total of 1180 patients with TBI, administration of EPO reduced the relative risk of mortality (RR 0.68 [95% CI 0.50–0.93]; $p = 0.02$) but had no effect on neurological outcomes or the occurrence of DVT [58]. The results of subgroup analyses indicated that the effects on outcomes may be dose dependent.

Conclusions

Anemia is associated with worse neurological outcomes and increased mortality rates after TBI. However, whether anemia just reflects more severe disease or can directly impact neurological outcomes in such patients remains unclear. The effects of blood transfusion on cerebral oxygenation and outcomes in anemic patients with TBI vary across studies, partly related to the different patient populations included and the different transfusion thresholds used. The decision to transfuse should be individualized based on a patient's likely tolerance to anemia.

Conflict of Interest The authors declare no conflict of interest.

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Transfusion Practice in a Jehovah's Witness

Monica S Tandon, Kiran Kiro, Rajishth Mittal, and Daljit Singh

Abstract

Jehovah's Witnesses are members of a Christian religious sect that strictly forbids the transfusion of whole blood or its primary components. This conviction is based on their interpretation of certain passages from the Bible and is upheld even during life-threatening circumstances. Jehovah's Witnesses who willfully accept a blood transfusion are usually ostracized from the community; and those who receive it against their wishes, even as a lifesaving measure, are known to suffer intense psychosocial trauma. Furthermore, this belief is supported by the ethical and legal frameworks of most countries worldwide.

This transfusion refusal creates significant medical challenges as well as several ethical and legal dilemmas for the neuroanesthetist, especially during neurosurgical interventions that are associated with high blood loss or are performed on an emergency basis. Nevertheless, it is imperative to appreciate that it is a core, non-negotiable religious belief, which must be respected, and alternative blood-free transfusion strategies need to be implemented, for optimal perioperative management of these patients. In this chapter, we provide an overview of the transfusion related beliefs of Jehovah's Witnesses, explore the clinical concerns and ethico-legal challenges faced by neuroanesthetists because of their transfusion refusal; discuss the blood-free transfusion alternatives and suggest a perioperative management strategy for Jehovah's Witnesses undergoing neurosurgical interventions.

Keywords

Jehovah's Witness · Blood transfusion · Erythropoietin · Blood conservation · Blood management

Introduction

Jehovah's Witnesses (JWs) are members of a Christian religious sect that strictly forbids the transfusion of whole blood (allogenic or autologous) or its primary components [1–3]. This conviction is based on their interpretation of certain passages from the Bible, and is upheld even during life-threatening circumstances [4–8]. JWs who willfully accept a blood transfusion (BT) are usually ostracized from the community; and those who receive it against their wishes, even as a lifesaving procedure, are known to suffer from prolonged periods of severe depression and guilt [1, 5, 7]. Furthermore, this belief is supported by

M. S. Tandon (✉) · K. Kiro · R. Mittal · D. Singh
Anesthesiology and Intensive Care, G B Pant Institute of Medical Education and Research, New Delhi, Delhi, India

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the ethical and legal frameworks of most countries worldwide [1, 7].

This BT refusal by JWs creates significant medical challenges as well as several ethical and legal dilemmas for the neuroanesthetist, especially during neurosurgical interventions that are associated with high blood loss or are performed on an emergency basis [8, 9]. Nevertheless, it is imperative to appreciate that it is a core, non-negotiable religious belief, which must be respected, and alternative blood-free transfusion strategies need to be implemented, for optimal perioperative management of these patients.

There is a relative paucity of literature regarding bloodless management of neurosurgical JWs; however, there is sufficient evidence of their successful management in several other major surgical disciplines including cardiac, orthopedic, and liver transplantation surgeries, which has in fact, contributed immensely to the rapid evolution of blood management and blood conservation practices, in the recent decades [10–16]. Results from these studies reveal that a well-informed consent, a multidisciplinary approach, meticulous preoperative preparation, and a multi-pronged blood conservation strategy form the cornerstones of successful management of these patients [10–16].

In this chapter, we provide an overview of the transfusion related beliefs of JWs; discuss the associated clinical concerns and ethico-legal challenges that arise during neurosurgical interventions in these patients; and delineate a comprehensive, blood free transfusion strategy for optimal perioperative management of neurosurgical JWs.

Overview of the BT Related Beliefs of JWs

The JW faith was founded in 1872 (in United States), and presently, has approximately 8.6 million followers in over 240 nations across the world (source—https://www.jw.org/en/library/books/2020-service-year-report/). The Watchtower Society (WTS), their legislative and administrative body, adopts medically relevant doctrines that are in accordance with the teachings of their holy scripture, the "New World Translation of The Bible" [1, 4–6]. The doctrine advising JWs to abstain from transfusion of blood or its primary components, was introduced in 1945, and is based on their interpretation of certain Biblical passages (Genesis 9:3–4; Leviticus 17:10–16; Acts 15:19–29) [1, 4–6]. JWs firmly believe that blood represents "life" and hence, is "sacred". Intake of any blood (enteral or parenteral) apart from that of Christ, is considered to be a sinful act, almost equivalent to cannibalism; it gravely violates their scriptures, and will lead to eternal damnation [1, 5–9, 17, 18]. JWs resolutely follow this religious conviction, and uphold it even if it endangers their lives. Those who voluntarily accept a BT and have no remorse about their action, are subjected to organized shunning by other members of the JW community, and at times, even by their family members and close friends; several former JWs have testified about the intense and prolonged psychological trauma associated with this systematic ostracization [5–8]. The WTS, does however, forgive JWs who have been transfused against their will or in error; a lifesaving BT in children is also condoned.

Initially, the WTS had prohibited the transfusion of whole blood (including preoperatively stored autologous blood, because it has been removed from the body) and primary blood components [PBC; red blood cells(RBC), white blood cells (WBC), platelets, unfractionated plasma], though it had no objections to use of blood-free volume expanders, and synthetic hemostatic/hemopoietic pharmacological agents (Table 1). In 2000, this policy was moderated, and subsequently, JWs are allowed to make a personal decision regarding acceptance of minor blood fractions (MBF; blood fractions derived by further processing of PBCs) and intraoperative autotransfusion techniques, based on their individual conscience and after careful introspection (Table 1) [1, 5, 6, 17, 19–22]. Furthermore, the expulsion of non-compliant JWs is no longer initiated by the WTS's judicial committee ("disfellowship"); rather it is revoked automatically, only if there is a self-disclosure or sufficient incriminating evidence regarding acceptance of a prohibited blood product by a JW (disassocia-

Table 1 Position of Jehovah's Witnesses regarding acceptance of various transfusion related products and therapies

NOT ACCEPTED
• Whole blood
• Major blood components: Packed red blood cells, platelets, fresh frozen plasma (FFP), white blood cells
• Preoperative autologous donation
• Use of any sample of their blood for cross-matching.
ACCEPTED
• Crystalloids: Normal saline, lactated Ringer's
• Synthetic colloid fluids: Dextran, hydroxyethyl starches (Tetrastarch, Hetastarch)
• Synthetic hemostatic agents:
– Antifibrinolytics (Tranexamic acid (TXA), aminocaproic acid, aprotinin)
– Desmopressin
– Vitamin K
– Recombinant Factor VII ([a]NovoSeven)
– Recombinant Factor VIII ([a]Xyntha, [a]Advate)
– Recombinant Factor IX ([a]BeneFIX)
– Recombinant FXIII-A2 (rFXIII-A2)
• Topical hemostatic agents: Topical thrombin ([a]Recothrom), absorbable collagen hemostat ([a]Avitene), [a]Fibrillar
• Supplements: Iron, vitamin B12, folate
• Artificial blood substitutes: Perfluorocarbon emulsions
• Erythropoietin stimulating agents: Recombinant human erythropoietin (albumin-free formulations [a]Epoetin beta, [a]Darbepoetin alfa).
VARIABLE ACCEPTABILITY (PERSONAL DECISION)
• Red cell fraction (minor fraction): Hemoglobin based oxygen carriers ([a]Hemopure)
• White cell fraction (minor fraction) : Interferons, interleukins
• Platelet fractions: platelet factor 4
• Plasma-derived hemostatic agents (minor fraction/plasma-derived minor fractions):
– Prothrombin complex concentrates (PCC) ([a]Kcentra, Octaplex, Beriplex—4-factor PCC; [a]Bebulin, Preconativ, ProplexT, Profilnine SD—3-factor PCC; [a]FEIBA—factors 2, 7, 9, 10 & Factor 8 inhibitor bypassing activity) octaplex does not contain albumin and may be more acceptable to JWs
– Cryoprecipitate
– Fibrinogen concentrate ([a]Riastap)
• Factor VIII concentrate ([a]Hemophil, [a]Koate DVI); Factor VIII + VW Factor concentrate ([a]Humate P); Recombinant Factor VIII ([a]Helixate, [a]Kogenate)
• Factor IX concentrate ([a]Mononine)
• Albumin
• Erythropoietin stimulating agents: Epoetin alfa ([a]Epogen/Procrit; human erythropoietin produced with recombinant DNA technology and contains human albumin)
• Topical hemostatic agents: Thrombin sealants
• Fibrin glue/sealant ([a]Tisseel)
• Gelatin-based sponge (Gelfoam® Pfizer, New York, NY)
• Flowable hemostatic matrix (Surgiflo®, Ethicon, Somerville, NJ)
• Oxidized regenerated cellulose (Surgicel® Ethicon, Somerville, NJ)
• Autologous platelet gel
• Autotransfusion
– Acute normovolemic hemodilution, acute hypervolemic hemodilution, cell salvage with autologous transfusion, plasmapheresis, plasmapheresis (precondition—closed circuit)
– Extracorporeal membrane oxygenation
– Renal dialysis/Renal replacement therapy with hemodialysis or hemofiltration
– Epidural blood patch.

[a]Trade names

tion) [5, 6]. Though both these sanctions result in excommunication, nevertheless JWs can choose to remain silent about their decision and avoid religious punishment; however, the "guilt pangs" that arise due this decision, are generally difficult to erase.

The WTS also recognizes the medical complexities that are associated with their sect's religious practices and has established an extensive support network of dedicated Hospital Liaison Committees [(HLC) >1700 worldwide)] whose work is coordinated by The "Hospital Information

Services" [(HIS); at the International Office of Jehovah's Witnesses (+1718-560-4700 or his@jw.org)]. The HLC members (community based ministers) provide valuable pastoral and liaison support round the clock; they counsel the JWs about the various bloodless treatment options, facilitate their communication with the treating team, and help them to take appropriate transfusion related decisions (to contact a local HLC representative-www.jw.org/en/medical-library and click "contact Local Representative") [1]. The HIS provides authoritative information regarding the transfusion related beliefs of JWs, disseminates pertinent clinical information from peer reviewed medical journals, and maintains an international database of clinicians with experience in "blood less surgery." On request, it can organize a referral for these doctors and can also arrange a communication if the patient's treating team wishes to seek their experience and practical advice in challenging situations [10].

Ethical and Legal Concerns

In most countries, all adult JWs with capacity (mentally competent) have absolute legal and ethical rights to refuse a BT, despite being fully aware of the potential clinical implications of their decision (right to autonomy and self-determination) (Table 2) [1, 2, 4, 23, 24]. Several of them even carry portable "Advanced Directives" (AD) cards to ensure that their religious convictions are respected in case they become incapacitated; these legally binding documents explicitly state their preference and the specific settings in which they are applicable, including their decision to decline a transfusion even in lifesaving situations (Table 2) [1, 3, 10]. They may also anticipatively authorize a "patient's representative" to execute these directives on their behalf, when they are incapacitated (Table 2) [1, 3, 23, 25].

Neuroanesthetists are legally and ethically bound to honor these religious convictions, even though they are in conflict with the patients' best interests, their personal values (desire to preserve life), the basic principles of bioethics (principles of non-maleficence and beneficence), and even restrict their therapeutic freedom that is vital for providing optimal perioperative care (Table 2) [4, 7, 9, 23]. Management during emer-

Table 2 Glossary of legal terms

CAPACITY:
- Patient's ability to understand the treatment and alternatives, to make a medical decision.
- Fundamental precondition for a patient's "right to autonomy" (e.g., right to decline a blood transfusion) and signing an "informed consent."
- Pathological conditions that influence a patient's capacity: alteration of consciousness, loss of concentration, alteration of memory. In case of doubt about a patient's capacity, protection of the patient's well-being (thus transfusion) can take priority over autonomy.

BENEFICENCE:
- Provider's obligation to maximize possible benefits and minimize potential risks to the patient.

NON-MALEFICENCE ("do no harm" principle):
- Avoid causing harm disproportionate to the benefit of treatment.
- Autonomy prevails over beneficence.

INFORMED CONSENT:
- A legally binding written document that states an individual's decision or agreement to allow a medical intervention.
- Is considered valid only if it is given voluntarily (free from duress), by a person with the "capacity," after receiving the appropriate information (e.g., knowledge of the diagnosis, risks, and benefits of the intervention, etc.)

ADVANCE DIRECTIVE (AD) "Advance medical directive cards" (aka, Durable Power of Attorney, Health Care Proxy, Power of Attorney for Health Care, Health Care Advance Directive/Living Will/no blood card):
- A legally binding written document that outlines the treatments an individual would not consent to in the future, should they lack capacity
- Is considered valid only if:

(i) The individual has the decision-making capacity at the time of signing the AD
(ii) Has been signed in presence of a witness
(iii) Clearly documents what medical treatments are acceptable or not; must also specify if the decision to refuse the specific treatment applies even if the individual's life is at risk.

PATIENT'S REPRESENTATIVE:
- A person who is authorized by a Jehovah's Witness to execute the decision of the AD
- This representation is only valid if confirmed by a specific written document, dated, and signed by both parties.

gent high blood loss neurosurgeries is particularly challenging, as a detailed discussion with the JW patient may not always be possible, due to the time constraints. Both, compliance as well as non-compliance can have serious ethico-legal repercussions. A non-consensual BT is a serious offence, liable to a criminal prosecution even if it ultimately ensures a patient's survival; but at the same time, a deterioration in the patient's clinical condition due to withholding an essential transfusion, also potentially increases the liability for criminal charges of negligence, and if the patient dies, of culpable homicide [1, 2, 7, 8, 19].

Ethico-legal considerations for children of JWs are even more complex. The legal age for decisional autonomy in most countries, is 18 years; but in several countries—adolescents between 16 and 18 years, and in some countries—children less than 16 years, can also give a legally valid consent without parental permission, if they are mentally competent to take such decisions ("mature minor" or "emancipated minor" or "Gillicks competent") [1–4]. However, the law also recognizes that JW children, besides having a limited experience outside of their religion, may also be naive about the potential consequences of refusing a necessary BT; hence, their parents/guardians are authorized to take "proxy" decisions on their behalf, based on the assumption that they would safeguard the interests of their children [1–4]. But this decisional authority is not "absolute," and the law can override a transfusion refusal by the children or the parents, especially during life-threatening circumstances. The parents/guardians of these children usually want an assurance that their religious sentiments will be respected; but the treating team's medical, legal, and ethical responsibility is to ensure the well-being of these children, and takes priority over the former.

Clinical Concerns and Considerations

The perioperative strategy during low blood loss, elective neurosurgical interventions in JWs is relatively straightforward; however, the management of acute anemia and the associated hemodynamic and hemostatic perturbations during high blood loss and/or emergency neurosurgeries can be fairly challenging; the complexity increases further in the presence of a concomitant anemia, coagulopathy, or a cardiovascular morbidity [8, 11, 26, 27]. Results of several observational studies in post-surgical JWs reveal a sharp increase in the mortality when the hemoglobin (Hb) levels fall below 5 g/dl, and the odds of death increase by almost two and a half times for each gram reduction in Hb [27–32]. The mortality is approximately 33% with Hb levels below 6 g/dl and reaches almost 100% when these values fall below 3 g/dl, respectively [27–32].

Furthermore, anemia per se is very detrimental in patients with acute brain injury, given their limited cerebrovascular reserves, the brain's appreciably high oxygen (O_2)consumption (20% of total body O_2 consumption at rest), and its exquisite vulnerability to hypoxemia. Anemic neurosurgical patients are reported to have a three times higher incidence of postoperative complications and twice the mortality as compared to non-anemic patients undergoing intracranial or spinal surgeries [33, 34]. Result of multiple studies show that Hb concentrations less than 9 g/dl are associated with a higher incidence of tissue hypoxia, metabolic crises, and poor outcomes in patients with traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), and acute ischemic stroke (AIS) [35–44]. A concomitant perioperative hemostatic dysfunction not only exacerbates the perioperative blood loss but can also result in severe neurological impairment (due to hemorrhagic or thromboembolic complications) and even death in neurosurgical patients [45].

Conventionally, the acute perioperative anemia and hemostatic disturbances can be effectively managed with transfusion of blood or appropriate blood components, but these options are not available for JWs. Moreover, there are no evidence-based guidelines regarding the optimal blood-free transfusion strategy for these patients. The available literature comprises largely of case reports or case series and very few retrospective studies of clinically stable JWs undergoing elective neurosurgical interventions; data about transfusion practices during emergency neurosurgery in JWs is

Table 3 Summary of literature regarding blood management and blood conservation strategies used in neurosurgical Jehovah's Witness patients

Author/year/ Type of study	Pathology/procedure performed No. of cases	Pertinent blood management techniques
Ki Seong Eom (2021) *Case Report* [a]*47*	Craniotomy and excision of a posterior fossa meningioma	*Intraoperative:* Moderate Deliberate Hypotension (DH) Systolic blood pressure—80–90 mmHg; Mean arterial pressure—55–65 mmHg
Kisilevsky A.E (2016) *Retrospective case series* [a]*48*	Complex spine surgery for spine tumor *4 cases*	*Preoperative*: iron therapy ± erythropoietin stimulating agent (ESA) Tumor embolization (1 patient) *Intraoperative*: antifibrinolytics [aprotinin/tranexamic acid (TXA) Cell salvage (CS); Albumin Average Hb nadir—12.4 g/dl
Reddy SK et al. (2016) *Case Report* [a]*49*	Craniosynostosis correction surgery *2 cases*	*Preoperative*: iron therapy ± ESA *Intraoperative*: antifibrinolytics (EACA/ TXA); Acute normovolemic hemodilution (ANH)
Hardesty DA et al. (2016) *Observational Study* [a]*11*	Intracranial surgery—craniotomy for arteriovenous malformation (AVM)-2, aneurysm-1, tumor-12 Spinal surgery—lumbar laminectomy without fusion-19, lumbar or cervical posterior decompression with instrumentation and fusion-13, anterior cervical discectomy and fusion-16, thoracic lipoma resection-1, deep brain stimulation-2, ventriculoperitoneal shunt-1, and suboccipital craniectomy-1 *68 patients*	*Preoperative*: iron therapy ± ESA *Intraoperative*: CS; Albumin; meticulous hemostasis
Andrews W et al. (2009) *Retrospective case series* [a]*24*	Spine fusion for spondylosis; Tumor Craniotomy for tumor excision; Stereotactic Brain Biopsy *19 patients; 21 procedures*	Subtotal meningioma resection (2 patients)
Joseph et al. (2008) *Retrospective case series* [a]*9*	Spinal deformity surgery *19 patients*	ANH, CS, DH (all patients); ESA+ iron (15 pts); Aprotinin (3 pts) Avg. Hb. drop-3.1 g/dl 1 case abandoned due to excessive blood loss
Koziarski A et al. (2003) *Case Report* [a]50	Craniotomy for multiple intracranial meningiomas	Preoperative endovascular embolization
Boadu M.A et al. (2002) *Case report* [a]*51*	Craniotomy for tumor resection Craniectomy for traumatic brain injury *2 cases*	ANH
Seuss et al. (2001) *Case series with control Group* [a]*12*	Spinal surgery for intervertebral disk herniation, spondylolisthesis, fracture, tumor, facet syndrome, spinal dysraphism Intracranial surgery for resection of tumors (meningioma, glioma, metastasis, acoustic neuroma, pituitary tumor), AVM, aneurysm clipping, hematoma evacuation *103 patients*	C.S

Table 3 (continued)

Author/year/ Type of study	Pathology/procedure performed No. of cases	Pertinent blood management techniques
Safwat et al. (1997) *Case series* [a]*52*	Scoliosis correction surgery *4 cases*	*Intraoperative*: CS, plateletpheresis, plasmapheresis. Moderate DH Desmopressin (1 patient) *Postoperative*: Iron therapy ± ESA
Barczewska M (1997) *Case series* [a]*53*	Cerebrovascular surgery (Resection of arteriovenous angioma-1; Aneurysm clipping-2, endovascular coiling-1) *4 cases*	ESA + iron therapy Endovascular embolization-1 patient
Chaney MA et al. (1996) *Case Report* [a]*54*	Resection of a midline skull base chondrosarcoma	Extensive surgery; Initial postoperative Hb: 2.3 g/dL. *Postoperatively:* ESA+ iron therapy; Sedation, paralysis, moderate hypothermia (30 degrees); Inotrope (dobutamine); FiO2-1.0—continued for 28 days. Hb on 28th day: 9.1 g/dl
Kantrowitz AB et al. (1994) *Case report* [a]*55*	Craniotomy and resection of a petrous apex meningioma *1 case*	Tumor embolization; ANH; Staged surgery ESA (preoperative and postoperative period)
Schiff et al. (1993) *Case report* [a]*75*	Hemispherectomy for epilepsy *1 case*	ESA; Staged surgery—two stages
Brodsky JW et al. (1991) *Case series* [a]*56*	Scoliosis correction surgery *12 cases*	DH

[a]*Reference number*

even more sparse (Table 3) [8, 9, 11, 12, 47–56]. Moreover, evidence regarding the lowest acceptable Hb values, optimal transfusion triggers, and use of non-transfusional alternatives in neurosurgical patients per se, is very limited [34, 41]. Corresponding data regarding management of JWs in other surgical disciplines may not be entirely applicable in a neurosurgical setting. In these circumstances, an effective blood-free transfusion strategy largely hinges on the collective expertise of a multidisciplinary team (MDT) and formulation of a comprehensive plan, which is individualized in accordance with the religious convictions of the JW. The success of this strategy has been demonstrated by a reasonable body of evidence (from neurosurgery as well as several other high-risk surgical disciplines, especially cardiac and liver transplant procedures) which reveals similar clinical outcomes in JWs when compared with conventional management, in both elective and urgent circumstances [10, 11, 13, 15, 16].

The MDT usually comprises an experienced neuroanesthetist and neurosurgeon, hematologist, intensivist, blood-banking specialist, a Hospital Ethics Committee member, personnel involved in the patient's perioperative care, and if indicated, other specialists such as cardiologist, nephrologist, gastroenterologist; additionally, the support of a HLC member is invaluable. Communication between the MDT, the JW, and the HLC member should be established early so that the patient's wishes regarding transfusions can be timely incorporated into management plan.

The perioperative plan per se relies heavily on the basic physiological principle of "acute anemia tolerance," and utilizes a preemptive as well

as proactive, multimodal approach, throughout the preoperative, intraoperative, and postoperative phases, to optimize the patient's RBC mass, reduce the perioperative blood loss, ensure an optimal cerebral oxygen delivery, and promptly manage acute blood loss and the associated hemodynamic and hemostatic instability. In the following sections, the principle of acute anemia tolerance, and each of the components of the strategy (preoperative, intraoperative, and postoperative) are discussed in further detail.

Tolerance to Acute Anemia

The oxygen delivery to the brain (DO_2) is determined by the cerebral blood flow (CBF) and cerebral oxygen content (CaO_2), which in turn, are dynamically regulated by several cardiovascular and cerebrovascular factors, which strive to maintain a normal DO_2 in the event of an acute physiological instability.

$$\mathrm{DO}_2 = CBF \times CaO_2$$

$$CaO_2 = Hb \times SaO_2 \times 1.39 \ \left(SaO_2 : \text{arterial oxygen saturation}\right)$$

$$CBF = \frac{\pi \Delta P r^4}{8 \mu l} \left[\begin{array}{c} \Delta \mathrm{P} : \text{pressure gradient or Cerebral Perfusion Pressure}\left(CPP\right).\mathrm{r} : \text{radius of blood vessel;} \\ \mu : \text{dynamic viscosity of blood;l : length of the blood vessel} \end{array}\right].$$

$$CPP = \mathrm{MAP} - ICP \ \left(\mathrm{MAP} = \text{Mean arterial pressure;} ICP = \text{intracranial pressure}\right)$$

$$\mathrm{MAP} = CO \times HR \ \left(CO : \text{cardiac output;} HR : \text{heart rate;}\right)$$

$$\text{Determinants of } CO : \text{cardiac contractility, preload, afterload}$$

During acute intraoperative bleeding, an increase in CO and its preferential distribution to the cerebral circulation; a rise in CBF (due to autoregulatory cerebral vasodilatation) and an enhanced cerebral oxygen extraction, maintain a normal DO_2 despite the acute fall in Hb values [34, 41]. Additionally, the lower blood viscosity due to the anemia (in normovolemic patients) further augments the CO by improving the venous return and lowering the systemic vascular resistance; and the improved rheology and the reduced endothelial shear stress enhance the cerebral microvascular perfusion. These adaptive mechanisms increase the patient's "anemia tolerance" and in fact, form the core strategy of perioperative blood-free management of JWs [4].

However, these compensatory mechanisms can alleviate the effects of a low hematocrit only to a certain extent, and when their limits are overwhelmed, the brain tissue oxygen levels start decreasing in proportion to the falling Hb values. Signs of cognitive impairment reportedly become evident when Hb falls below 7 g/dL, and the morbidity and mortality increase sharply as it decrease below 5 g/dL [34, 41]. The lowest acceptable hemoglobin value during acute brain injury is not yet defined due to lack of evidence-based guidelines, but is expected to be higher, in view of the limited "cerebrovascular reserve" in these circumstances [34, 41, 46]. Coexisting cardiovascular or respiratory dysfunction further reduces the anemia tolerance. Hence, despite the recent shift toward a restrictive transfusion policy (Hb target 7–9 g/dl), a more liberal target is advocated in patients with acute brain injury (Hb target: 8–10 g/dl) [34, 46], especially in those with a coexisting cardiovascular morbidity (e.g., Hb ≥9 g/dl) [34, 41, 46]. This understanding provides a good reference point for the intraoperative Hb target level in neurosurgical JW patients.

Furthermore, though the World Health Organization's defines anemia as a cutoff hemoglobin value of 13 g/dL and 12 g/dL for males and females, respectively, recent advocates argue

that these values may not accurately address the risk of preoperative anemia in the setting of high intraoperative blood loss [57–61]. This disagreement is based on the premise that since women have a lower circulating blood volume, they lose a greater proportion of RBC mass than men, for a similar volume of blood loss. Hence, the recent guidelines propose a uniform preoperative hemoglobin target of 13 g/dL for both genders [1, 57].

Preoperative Phase: Preoperative Planning and Optimization

During the preoperative preparation phase, the MDT clearly establishes the transfusional choices of the JWs; performs a comprehensive evaluation; optimizes their RBC mass, coagulation status, and significant comorbidities; formulates a meticulous intraoperative plan; and finally, obtains a written informed consent. The extent of evaluation and optimization, however, varies for elective and emergency procedures; while the management in the elective setting can be more considered, however, given the limited time available during emergency situations, a more aggressive, comprehensive, and preferably, a predefined approach is desirable.

Preoperative Discussion

JWs are usually well informed of their rights to refuse BT, consequences of this refusal, as well as the availability of alternate means of transfusion and hemostasis. However, their information may be incomplete or inaccurate and moreover, the transfusion choices can vary among individuals. A detailed discussion regarding these aspects enables the JW to make an informed decision, as well as the treating team to clearly establish the preference of each patient; moreover, this collaborative decision-making fosters an environment of confidence and communication that can help to prevent and resolve several of the legal and ethical dilemmas that may arise during the management of JWs.

During the discussion, the neuroanesthetist should understand the transfusion related beliefs of the JWs; reassure them that the views would be respected; apprise them about the hemorrhagic risks of the proposed procedure, the potential consequences of withholding a BT; and give them a detailed explanation about the benefits and risks of all the alternative options, especially drugs/procedures that have a variable acceptability. ADs, if available, should also be noted. If major blood is anticipated, the feasibility of a "rescue transfusion indication" (transfusion of blood/PBC is refused in elective situations, but is acceptable as a lifesaving measure), as well any other contingency measure, such as the possibility of aborting the procedure, should also be discussed.

If the proposed neurosurgical intervention poses a significantly increased bleeding risk due to the BT related constraints, alternative options that cause lesser or no blood loss should also be discussed, such as a staged surgery, minimally invasive endoscopic approach, an endovascular neuro-intervention [for aneurysm, arteriovenous malformation (AVM)], radiofrequency ablation for trigeminal neuralgia, or gamma knife surgery for resection of tumors; based on this information, they may opt for an alternative procedure or an alternative center, or may even consider conservative treatment if the morbidity due to refusal of a BT/PBC is extremely high. In surgeries with a very low likelihood of BT, they should be reassured that their views will be respected, but should also be forewarned about the possibility of BT/PBC in the event of life-threatening hemorrhage.

The options accepted by the JWs on basis of this discussion, largely determine the perioperative bloodless transfusion strategy. Hence, the importance of appropriate elucidation, especially of modalities such as autologous blood management, and hemostatic agents such as PCCs, cryoprecipitate, and fibrinogen, which have a vital role during management of acute excessive intraoperative bleeding, but a variable acceptability among JWs cannot be over-emphasized. A recent retrospective analysis of surgical JW patients

over a period of 11 years reveals that the acceptability of several therapies increased markedly after appropriate elucidation, and in particular, of those therapies that had been previously declined by these patients (e.g., coagulation factor concentrates, autologous blood conservation strategies); this enabled a more effective management of serious bleeding complications [32].

At the end of the interaction, the specific preferences/refusal of the patient should be explicitly documented in the medical records. Some hospitals have a specific "blood component consent form" for this purpose; alternatively, the form created by the American Society of Anesthesiologists Committee on Patient Blood Management (available on the American Society of Anesthesiologist website) may be adapted for use [1, 3, 13]. This record serves as an important legal document, hence it is also prudent to document all the pertinent aspects of the discussion (explanation of risks of transfusion refusal, benefits/risks of the alternative interventions, rescue indications, contingency plans, etc.) to ensure protection from any potential future liabilities. A copy of the AD card should also be placed in the patient record. While JWs often solicit the advice of their relatives, friends, community elders, and/or local HLC members, however the final decision regarding these options has to be made by the patient, and maintaining strict confidentiality is of paramount importance [6, 19].

Incapacitated Pts

The preferences of an incapacitated JW who has a "AD" must be honored, unless there is doubt about its validity or presence of reasonable evidence that the patient was mentally incompetent when the AD was made, or that the patient has changed his/her mind since signing it (Table 2) [1, 2, 16]. Likewise, the decision of the "patient's legal representative" is acceptable only after proper validation (Table 2). In absence of an "AD" the law can authorize a "surrogate" to take decisions on behalf of the incapacitated patient. The hierarchy varies across legal frameworks, but usual order of priority of surrogates is as follows: patient's legal representative—spouse, partner, or legal cohabitant–adult children–parents–adult brothers and sisters–and finally close relatives; alternatively, the law may designate a legal administrator to take decisions for the patient [2, 4, 8, 16, 23].

Children

Parents and children (if they are old enough to understand) should be reassured that all measures will be taken to avoid a transfusion; but they should also be forewarned, that a lifesaving BT would not be withheld [1, 16].

If a competent child declines a consent for transfusion, the parents/guardians can override this decision, if the transfusion is deemed to be medically necessary for a minor patient; however, it may be prudent to take a prior referral from the court [1, 23]. If the child as well as the parents/guardians decline to give BT consent, and the MDT opines that it may be unsafe to perform the neurosurgical intervention without the freedom to transfuse, then legal permission for transfusion should be sought for non-emergency surgeries; in most circumstances, it is granted, without removing all parental authority [1, 16, 25]. However, if there is not enough time for such an application, especially in life-threatening situations, MDT is legally empowered to act in the "best interest" of the patient, and transfuse blood, without the need for a consent [4, 23]. In fact, failure to give a lifesaving transfusion to a child can result in a criminal prosecution [1–3, 23].

Informed Consent

A JW (with capacity) must also sign a written, informed consent stating his/her decision to decline the transfusion of blood or PBC. This important legal document protects the treating team from any liability should an untoward event occur related to the refusal of transfusion [1–3, 16, 23, 25]. It is taken confidentially, after the patient's clinical condition has been thoroughly assessed, all alternative options explored, and the perioperative plan has been shared with and approved by the patient. Prior to taking the consent, the team should ensure that the patient's decision is firm, has been taken voluntarily with-

out any external duress and with full cognizance of the potential consequences of transfusion refusal.

Emergency Situations

Though there is a time constraint during urgent or emergent neurosurgical interventions, nevertheless, a written and "free" informed consent from a "mentally competent" JW is still mandatory, as per the legal framework in most countries. The beliefs of an incapacitated JW should also be honored if it is known that the patient would have declined a transfusion of blood/PBC, even if a valid AD card/"patient's representative" is not available [1, 2, 8]. In case of any ambiguity (e.g., lack of consensus among family members), it may be prudent to seek guidance from the hospital's ethics committee and legal advisors regarding the best course of action [8, 13].

Serious, life-threatening neurosurgical emergencies, however, are an exception. In these circumstances, the inordinate delay due to the time taken to evaluate the patient's capacity or obtain a "free" and informed consent, may result in catastrophic patient's outcome; hence, the neuroanesthetist is legally empowered to transfuse blood immediately as a lifesaving measure, without taking a formal informed consent [2, 8]. For incapacitated JWs also, the law of most countries permits administration of a lifesaving transfusion, if the patient's preferences are unknown (no documented AD) or unclear (insufficient time to assess validity of AD is valid), irrespective of the opinion of relatives or associates (standard of presumed consent). The legal framework, though, may require that the clinical necessity of the transfusion is re-confirmed by another colleague [1, 2, 25]. Importantly, the circumstances leading to the transfusion, the clinical and biological data motivating the transfusion and the opinion of the second doctor, should also be documented in the medical records; and patients (with capacity) should be informed about the use of the specific blood derivatives, after the surgery.

Neuroanesthetists have the right to refuse perioperative care to a JW in an elective situation, if they do not wish to work under the constraints imposed on them due to the BT refusal [1, 2, 7]. In this case they must refer the patient to a suitably skilled neuroanesthetist who is prepared to take care of the JW patient; the refusal, its justification, and the referral should also be documented in the patient's records [2].

In situations of ambiguity or a conflict, a second opinion with another doctor, and/or if required, consultation with the hospital ethics committee or hospital administration should be considered [1, 8, 25].

Preoperative Evaluation

Besides the standard perioperative concerns, the preoperative assessment (history, examination, investigations, medical chart review; Table 4) should specifically focus on the evaluation of:

a. Surgery related hemorrhagic risk factors: nature of surgery (elective, urgent, or emergent); type of pathology and the proposed surgical intervention; risk of significant perioperative blood loss, hemodynamic instability, and coagulopathy (acute blood loss >500 ml in adults irrespective of preoperative Hb levels, is usually considered as "significant").
b. Patient related risk factors, e.g. anemia, coagulopathy, coexisting comorbidities (e.g., cardiovascular, hepatic, renal, poor nutritional status), that can reduce the tolerance to anemia or enhance the perioperative blood loss.

Interventions associated with a high likelihood of significant blood loss, with a conventionally high incidence of perioperative BT, and common emergency neurosurgical procedures are listed in Tables 5 and 6, respectively. The likelihood of BT is reported to especially high during resection of inherently vascular tumors and AVMs, ICH evacuation, craniosynostosis correction, and complex multilevel spine surgeries (e.g., especially scoliosis correction, anterior thoracic vertebral reconstruction surgeries) [11, 62–64]. In contrast, simpler procedures, e.g., lumbar discectomy, single level spine procedures, ventriculoperitoneal (VP) shunts, low

Table 4 Preoperative evaluation of neurosurgical JW

Medical History
- History of anemia
- History of abnormal bleeding (personal and family history)
  - Congenital bleeding disorders (known from birth; frequent, spontaneous, or easy bruising that does not heal readily, e.g. nosebleeds, gum bleeds; prolonged and severe bleeding after dental or surgical procedures; menorrhagia; any previously unexplained post-traumatic or post-surgical bleeding; abnormal result from a laboratory test on blood clotting; unexplained anemia)
  - Severity of the bleeding (spontaneous versus requiring surgery)
  - Type of bleeding (petechial rash, small bruises suggest a platelet-type bleeding disorder; large soft tissue hematomas, visceral bleeding, and hemarthrosis suggest a coagulation-type bleeding disorder)
- Coexisting disease that predispose to bleeding (renal, hepatic, cardiac, pulmonary, hematological, amyloidosis, sepsis, and neoplastic conditions)
- History of thrombotic events (e.g., deep vein thrombosis, pulmonary embolism)
- Risk factors for organ ischemia (e.g., cardiorespiratory disease)
- Past medical or surgical history that may increase the risk of blood loss (e.g., repeat surgery at proposed operative site, known or suspected significant adhesions, radiation therapy)
- Current medications that may adversely affect hemostasis:
  - Antiplatelet drugs (aspirin, clopidogrel, prasugrel, ticagrelor)
  - Vitamin K-dependent oral anticoagulants (Warfarin)
  - NOACS (dabigatran, rivaroxaban)
  - Platelet aggregation inhibitors (e.g., abciximab, ticlopidine)
  - Heparin
  - Thrombolytic drugs
  - Non-steroidal anti-inflammatory drugs
  - Antibiotics (e.g., beta-lactams such as penicillin, ticarcillin)
  - Antiepileptic drugs (thrombocytopenia, thrombocytopathy, von Willebrand syndrome, decreased coagulation factor XIII activity—mainly associated with valproic acid (VPA)
  - Dietary or herbal supplements: herbal supplements (Garlic, Ginkgo biloba, ginseng); blueberries, bromelain, flaxseed oil, ginger, grape seed extract.

Physical Examination
- Systemic, Cardiovascular, Respiratory, Neurological examination
- Potential features of hemostatic dysfunction (hepatomegaly, splenomegaly, petechiae, purpura, ecchymoses, hemarthrosis, evidence of collagen-vascular defects, telangiectases, etc.)

Laboratory Assessment
- Diagnosis of anemia:
  - Complete blood count (CBC)
  - Serum ferritin, transferrin saturation, reticulocyte count, serum creatinine
  - Vitamin B12, folate
  - Reticulocyte hemoglobin content if available (a functional measure of iron status).
- Coagulation profile:
  - Platelet count
  - Prothrombin time (PT*-extrinsic and common coagulation cascades;)
  - Activated partial thromboplastin time (APTT*-intrinsic and common coagulation cascades)
- Arterial blood gas determinations.
- Renal function tests
- Liver function tests (LFTs), Bone profile

***PT assay** [detects deficiencies of Factors II, V, VII, X, fibrinogen; monitors warfarin effect (international normalized ratio (INR)]

***APTT assay** (detects deficiencies of Factors VIII, IX, XI; to a lesser extent II, V, X, fibrinogen; monitors intravenous unfractionated heparin therapy)

Judicious additional tests (if indicated by medical history, abnormal clinical data, current medications, and degree of hemostatic challenge)
- Platelet function, adhesion, aggregation tests
- Fibrinogen concentration
- Fibrin degradation products (FDP)/D-Dimer
- Specific coagulation factor assays
- Viscoelastic hemostatic assays: ROTEM.

Table 5 Surgeries associated with likelihood of significant blood loss

Cerebrovascular Surgeries:
• Arteriovenous malformation resection
• Intraoperative aneurysmal rupture
• Intracranial aneurysm clipping
Intracranial Tumor Surgeries:
• Large tumors
• Highly vascular tumors, e.g., meningioma, glomus jugulare tumor, choroid plexus papilloma, metastatic tumor (hypernephroma), hemangioblastoma, hemangioma, glioblastoma multiforme, aneurysmal bone cyst; (low-moderate vascularity—neurofibroma, ependymoma, oligodendroglioma, medulloblastoma, pituitary adenoma)
Multilevel Spine Surgeries:
Complex multilevel spine instrumentation surgeries for tumor, trauma, deformity (e.g., scoliosis), infection; anterior thoracic vertebral reconstruction surgeries.
Trauma Surgeries:
• Intracranial hematoma evacuation
• Decompressive craniectomy, especially in patients with acute traumatic coagulopathy.
Re-Do Surgeries
Skull Base Surgeries
Surgeries associated with a likelihood of iatrogenic vascular injury due to proximity of pathology to blood vessels, sinuses.

Table 6 Common neurosurgical emergencies

Acute Increase In Intracranial Pressure
• Head trauma: Skull fractures, intracranial hematomas, diffuse axonal injury
• Anticoagulant-associated intracranial hematoma
• Diffuse cerebral edema: due to severe hypoxia, trauma, severe hypoglycemia, or any acute intracranial insult
• Intracranial hemorrhage and intracranial vascular lesions: cerebral aneurysm rupture, arteriovenous malformations (AVM) bleed
• Intracranial thrombosis: e.g. Superior sagittal sinus thrombosis
• Intracranial tumors, meningitis, or other intracranial infections
• Obstructive hydrocephalus
• Hypertensive emergencies, reperfusion injuries.
Intracranial Vascular Emergencies
• Ischemic or hemorrhagic stroke
• Ruptured intracranial aneurysms.
SPINAL CORD EMERGENCIES
• Unstable cervical spine
• Trauma
• Epidural or subdural hematomas
• Abscesses
• Tumors causing pressure symptoms.

grade gliomas, transsphenoidal microscopic resection of pituitary tumors, astrocytomas have a very low risk of BT(<1%) [62].

The maximum surgical blood order, if available, is also a useful tool, to assess the likelihood of significant intraoperative blood loss; it classifies surgeries on basis of "no sample needed," "type and screen," and "type and crossmatch" categories into low, medium, and high blood loss procedures, respectively [10, 65].

The screening of these patients should ideally be initiated 4–8 weeks prior to the scheduled surgery, to allow sufficient time for further evaluation and optimization (minimum of 4 weeks required for improvement in Hb levels) [3, 19, 25].

Iron deficiency is the most common cause of anemia (reduced total body iron stores); other common etiologies include chronic renal insufficiency and anemia of chronic disease (also called anemia of inflammation; secondary to autoimmune mechanisms, infection, or malignancy; impaired iron mobilization despite normal or elevated iron stores); quite often these conditions coexist [3, 25, 59–61, 66]. Several algorithms are available in the literature to help differentiate between these conditions; a simplified version is suggested in Fig. 1 [57, 60]. Pertinently, serum ferritin <30ng/ml is highly predictive of an absolute iron deficiency; and levels >100 ng/mL reliable exclude its possibility in the absence of any inflammatory process [10, 25, 57].

Preoperative coagulopathy can be due to medications [e.g., antiplatelet and anticoagulant drugs, non-steroidal anti-inflammatory drugs (NSAIDs), herbal supplements), liver disorders, and inherited coagulopathies; antiplatelet drugs are reported to be the most common cause of postoperative hemorrhagic complications in neurosurgical patients [45]. Additionally, the primary brain pathology, and the associated intracranial hypertension and/or brain ischemia, together with the abundance of tissue factor (TF) in the normal brain parenchyma (primary trigger of coagulation cascade), can contribute to coagulopathy in neurosurgical patients [45, 68]. Elevated TF levels have also been documented in

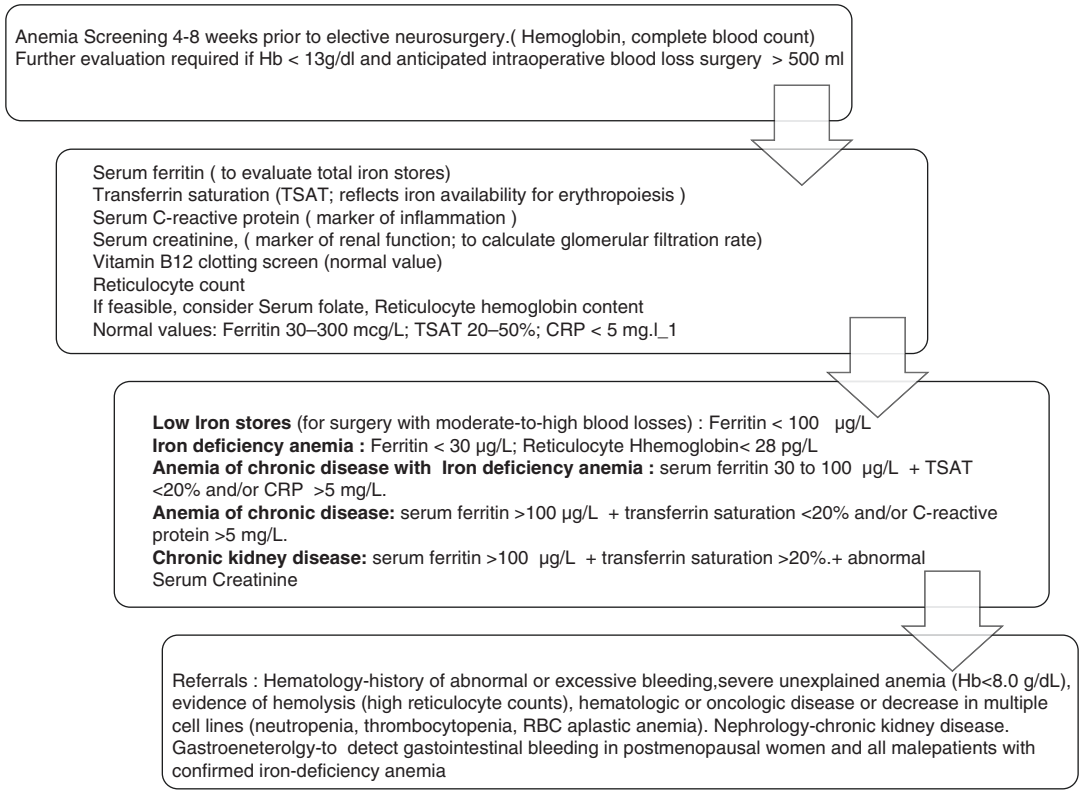

Fig. 1 Differential diagnosis of anemia

certain astrocytoma's and in severe TBI [45, 69]. Glioblastomas and intracerebral metastasis are associated with high tissue plasminogen activator (t-PA) levels; t-PA-induced hyperfibrinolysis can worsen a perioperative consumption and/or dilutional coagulopathy [45, 67, 68, 70]. Acute traumatic coagulopathy (ATC) is observed in approximately one-third of TBI patients, and can enhance the progression of traumatic hemorrhagic injuries [69, 71].

Coexisting morbidities also contribute to a poor outcome in JWs. Two scoring systems, the Auckland Anemia Mortality Risk Score (Auckland AMRS) and The Hamilton AMRS, have attempted to stratify the effect of patient factors besides anemia, on the mortality risk in JW patients. The risk factors in the Auckland AMRS are: age greater than 45 years, weight greater than 90 kg, hypertension, cardiac arrhythmia, angina, previous myocardial infarction (MI), valvular heart disease, heart failure, hemodialysis, emergency admission, and Hb level of not more than 8 g/dL; a composite score of these risk factors stratifies mortality rates from 4% to 83% (AMRS 0–3, 4% mortality; AMRS 4–5, 32% mortality; AMRS 6–7, 50% mortality; AMRS ≥8, 83% mortality) [72]. The Hamilton AMRS also includes treatment related mortality risk factors [shock, acute gastrointestinal bleeding, pneumonia, nadir Hb ≤7 g/dL, sepsis, congestive heart failure, neurologic complications (stroke and hypoxic encephalopathy)]. Hamilton AMRS scores of 0–2, 3–4, 5, and ≥6 are associated with a mortality of 4%, 29%, 40%, and 67%, respectively [73].

Anemic JW patients (Hb < 13 g/dl) who are likely to lose more than 500 ml. blood during the surgery; those with a known or a likely coagulopathy, or those with comorbidities, require extended evaluation and if required, specialist consultation, e.g. a hematologist, gastrointestinal, or urology specialists as indicated.

Preoperative Optimization

Optimization of RBC Mass and Correction of Anemia

Transfusion of blood or PRBCs is not an option in JWs, but the detrimental effects of intraoperative bleeding and hemodilution can be mitigated by preoperative correction of the anemia and optimization of the RBC mass. A supranormal Hb (> 13 g/dl) is recommended by current guidelines, as it greatly improves the tolerance to the acute intraoperative blood loss [1, 3, 12, 57, 58]. This is usually achieved by administration of iron, sometimes in combination with erythropoiesis-stimulating agents (ESAs), Vitamin B12 and folate (for correction of nutritional deficiencies), and if required, optimization of associated cardiorespiratory disorders, renal insufficiency, gastrointestinal loss, and other inflammatory conditions (Table 7) [1, 14].

Intravenous (i.v) iron therapy is usually preferred; most of the presently available formulations are relatively safe, well tolerated (risk of infusion reaction-1–3%), and effective (iron stores increase in 1 week; hemoglobin levels start rising in 1–2 weeks; optimal effect observed within 3–4 weeks of I.V iron infusion) [57, 60, 61, 74]. Preparations such as low-molecular-weight iron dextran, ferric carboxymaltose1000 (FCM), iron isomaltoside 1000, or ferumoxytol offer the convenience of short duration (one–two doses), rapid, and high dose iron therapy (≥1000 mg), administered over 15–60 min) [16, 59, 61]. Patients with severe iron deficiency anemia should be re-evaluated after 2 weeks (blood counts, serum ferritin) to monitor the response and determine the need for another dose of iron [61]. Deferral of elective neurosurgical procedures may be considered (if feasible), to allow sufficient time for optimization of the preoperative RBC mass; for nonelective procedures, any available time should be used to initiate treatment, which ultimately can be started or continued in the postoperative period [60, 61].

Oral iron can be considered if more than 6 weeks are available for anemia correction (re-evaluate after 4 weeks); however, a poor compliance due to gastrointestinal side effects (abdominal pain, constipation, diarrhea), and moreover, an inadequate response in patients with functional iron deficiency make it a less suitable option [57–59]. Vitamin B12 and folate are administered if a preoperative deficiency is identified or alternatively, can also be given empirically, if diagnostic testing is not possible; the potential benefits of these relatively innocuous agents are likely to outweigh any potential risk of administration.

Current guidelines advise the preoperative use of erythropoietin stimulating agents (ESAs), e.g., Recombinant erythropoietin (r-HuEPO), in conjunction with IV iron (minimizes ESA-induced iron deficiency), to raise the Hb levels (up to 15 g/dl) in anemic JWs (Hb <13 g/dl) who have to undergo extensive surgeries that entail substantial perioperative blood loss; and also to facilitate intraoperative autologous transfusion [1, 3]. ESA therapy rapidly raises the hematocrit levels; RBC production is reported to increases by up to seven times, and an equivalent of one and five units of blood are produced in 7 and 28 days, respectively [2]. It is also used postoperatively, to accelerate erythropoietic recovery in severely anemic JWs (hematocrit <25%) [23]. Interestingly, it may also provide cerebral protection during ischemia (e.g., vasospasm) via its effect on the innate stress response [34]. ESA has been efficaciously used in anemic neurosurgical JW patients undergoing high blood loss intracranial surgeries including hemispherectomy, resection of meningioma and AVM, aneurysmal clipping, and complex multilevel spine deformity surgeries [9, 11, 48, 55, 75, 53]. During a staged resection of a hyper-vascular petrous apex meningioma in a JW, Kantrowitz et.al used it preoperatively—to raise the hematocrit to supraphysiological levels in anticipation of the extensive intraoperative blood loss and hemodilution; after the first surgery—to shorten the time interval between the two stages; and also postoperatively—to normalize the Hb values after the second surgery [55]. In another JW

Table 7 Pharmacological therapy for correction of anemia: dosages and pertinent considerations

INTRAVENOUS IRON THERPAY

Dose:

- Low-molecular-weight iron dextran, 1000 mg× 1
- Ferric carboxymaltose, 750 mg × 2
- Ferumoxytol, 1020 mg × 1 or 510 mg × 2

Given by slow i.v infusion over less than 1 h, in one sitting or in two divided doses, depending on the preparation used.

Side effects (relatively rare):

- Minor infusion reactions (pressure in the chest or back, or flushing; resolve without intervention)
- Severe anaphylactic reactions (≈1 in 250,000 administrations).

ORAL IRON

40–60 mg elemental iron daily or 80–100 mg on alternate-days (better absorption and improved tolerability).

ERYTHROPOIETIN STIMUALTING AGENTS

Dosage

- **Preoperative regimens:**
  - If preoperative period is at least 3 weeks: 600 U/kg subcutaneously every week, total of 4 doses (last dose is at the day of surgery)
  - If preoperative period <3 weeks: 300 U/kg once daily, total of 15 doses
  - If Hb < 7 g/dL: 40,000 units ESA administered daily until Hb > than 7 g/dL; reduce ESA dosing thereafter
  - Iron sucrose 100 mg IV is administered concurrent with ESA therapy daily
  - Stop ESA therapy if a sufficient response is seen after the second or third dose (Hb > 15 gm/dl)
  - "Ultra–short-term" protocol: Slow infusion of 20 mg/kg ferric carboxymaltose, 40,000 U; Subcutaneous (s.c) erythropoietin, 1 mg s.c vitamin B12, 5 mg oral folic acid, 1 day prior to the surgery
  - Patients with severe inflammation may not respond to ESAs (due to marrow suppression); daily dose of up to 40,000 U may be required.
- **Postoperative regimens:**
  - 600 μg kg^{-1} daily for 7 days; or 600 μg kg^{-1} every alternate day; or 600 μg kg^{-1} at 24 and 48 h after surgery, followed by three doses of 300 μg kg^{-1} on days 3, 4, and 5, respectively.

Contraindications:

- Baseline Hb >13 g/dL (increased risk of postoperative thrombotic events, e.g., deep vein thrombosis (DVT) or pulmonary embolism (PE))
- Uncontrolled hypertension
- Arterial diseases, recent MI or CVA (within the past month), unstable angina
- History of thrombosis.

Precautions:

- Age > 70 years
- Pregnant or lactating patients
- History of chronic liver failure, hypertension, thrombocytosis, epilepsy, or malignancy
- Provide adequate pharmacological thromboembolic prophylaxis.

Complications:

- Hypertension
- Hypertensive encephalopathy with seizures
- Rarely hyperviscosity leading to thrombosis. (mostly observed in patients with renal failure; relatively rare in the surgical setting.)

NUTRITIONAL SUPPLEMENTATION

- Vitamin B12 deficiency: 1–2 mg vitamin B12 orally
- Folate deficiency: Oral folic acid 1 mg/day through the time of surgery.

patient undergoing a two-staged hemispherectomy for refractory epilepsy, administration of ESA throughout the perioperative period helped to maintain safe hemoglobin levels during both the procedures [75].

The use of ESA has been tempered by potential concerns regarding thromboembolic events (stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE)) and tumor progression. These complications, however, have mostly been

reported with use of higher doses (>80,000 IU) that are administered for chemotherapy or chronic kidney disease related anemia, and may not be applicable to surgical patients who receive a short duration of low dose ESA therapy [19, 48, 76]. Nevertheless, it is prudent to take an informed and individualized decision on basis of the potential thromboembolic risk, and also consider use of perioperative DVT prophylaxis. Most JWs accept the trace amounts of human albumin present in erythropoietin alpha (used as a preservative, akin to the protein in vaccines), nevertheless this information should be disclosed during the discussion; epoetin beta and darbepoetin alfa do not contain albumin and may be used preferentially in these patients [3, 4, 12, 19].

Alternatively, an ultra-short-term combination treatment (ferric carboxymaltose, erythropoietin, vitamin B12, folic acid, 1 day prior to the surgery) can be considered for rapid anemia correction in urgent or semi-urgent situations; a recent study by Spahn et.al documented its efficacy in reducing the intraoperative BT requirement in anemic patients undergoing elective cardiac surgery [77].

In JW patients with life-threatening anemia (Hb <5 g/dL) and associated symptoms of hypoperfusion, a Hb-based oxygen carrier (HBOCs), e.g., Hemopure, can temporarily supplement the oxygen-carrying capacity till ESA and/or iron therapy restores the endogenous Hb levels [16, 19, 31]. However, logistic, and regulatory challenges; a short half-life (19 h), vasoactive side effects (e.g., hypertension, coronary artery vasoconstriction, MI), and an increased mortality are pertinent concerns related to its use [16, 19, 31].

Correction of Coagulation Defects and Promotion of Hemostasis

Prior to elective surgeries, drugs and supplements associated with increased bleeding complications should be temporarily discontinued or substituted with shorter acting agents, in consultation with the cardiologist, hematologist, or neurologist, and based on the perioperative bleeding versus thrombosis risk (Table 8) [1–3, 16, 78]. Non-urgent surgeries should be postponed, till the effect of the drug wears off. Patients with a known congenital/acquired coagulopathy may need extended laboratory workup and appropriate clotting factor replacement therapy, in consultation with a hematologist. Thrombopoietin agonists (avatrombopag, lusutrombopag, eltrombopag) may be considered for raising the platelet counts to safe levels in thrombocytopenic JWs undergoing elective neurosurgical interventions. They are started at least 2 weeks prior to the surgery and should be continued for 2 weeks following the procedure to ensure hemostasis. (dose: avatrombopag—20 mg daily, lusutrombopag—3 mg daily, eltrombopag—50 mg daily.) [19].

However, rapid correction of the coagulopathy is a priority in emergency situations, such as, ICH [subdural hematoma (SDH), epidural hematoma (EDH), subarachnoid hemorrhage (SAH), and intra parenchymal bleed] or TBI related ATC, especially if the patient needs an emergent neurosurgical intervention (Table 6). Hence, all measures are directed to achieve a normal hemostatic function, in order to avoid secondary brain damage due to hematoma expansion and/or rebleeding after the neurosurgical interventions; besides discontinuation of the drug, these may include reversal of drug effect, and administration of a specific antidote for the drug (Table 8) [71].

JWs decline the use of FFP and platelets for correction of the coagulopathy, but prothrombin complex concentrates (PCC), Vitamin K, desmopressin, and most synthetic recombinant coagulation factors (Factors VII, VIII, IX, XII) are accepted by these patients. Recombinant coagulation factors are primarily approved for use in congenital and inherited bleeding disorders, but they are also widely used off label for promoting hemostasis (by targeted factor repletion) during acquired coagulopathy in neurosurgical patients [79]. The acceptability of cryoprecipitate, fibrinogen concentrate (both derived from human plasma), and some Factor VIII concentrates (Kogenate, Helixate; synthesized in culture media containing human plasma protein solution) varies among JWs, and consent should be taken prior to their administration [79]. Besides reversing the drug related hemostatic dysfunc-

Table 8 Anticoagulant, antiplatelet and thrombolytic agents: pertinent management considerations in Jehovah's Witnesses

Duration of preoperative drug discontinuation prior to elective/non-urgent surgeries	Antidote/reversal agent (for emergency reversal of drug effect)
ANTICOAGULANT DRUGS	
Vitamin K Antagonists • Warfarin: 5 days (target INR <1.5) • Consider substitution with shorter acting agent—UFH or LMWH in coordination with a cardiologist/ neurologist	Prothrombin complex concentrate (PCC)
Direct factor Xa inhibitors • Rivaroxaban: 3 days • Apixaban: 3–5 days	• PCC (if intracranial hemorrhage (ICH) develops/neurosurgery required within 3–5 terminal half-lives of drug exposure; in liver failure). • Antidote: Andexanet alfa
Direct thrombin inhibitors (DTI) • Dabigatran: 5–7 days • Argatroban: 8–10 h	• Dabigatran antidote: Idarucizumab (5 g IV in two divided doses) • For other DTIs/if idarucizumab not available for dabigatran: PCC In patients with normal renal function, reversal agents administered only if ICH occurred/neurosurgery required within 3–5 terminal half-lives of drug exposure
UFH, LMWHs, heparinoids Heparin • Subcutaneous ultra-fractionated heparin (UFH)—no need to discontinue • Intravenous UFH-6 hours • Low-molecular-weight heparin (LMWH)-12 hours • Enoxaparin: 24 hours	• IV protamine sulfate (for all LMWHs except danaparoid) • Recombinant Factor VIIa (rFVIIa): For danaparoid; all other LMWHs if protamine contraindicated Protamine dose **UFH** • IV heparin: Protamine sulfate 1 mg i.v (over 10 min) for every 100 units of i.v heparin given in previous 2–3 h; Repeat if (0.5 mg 100 units of UFH), if aPTT still elevated • Subcutaneous heparin: Reverse if aPTT is significantly prolonged; prophylactic administration not recommended. **LMWH** • Enoxaparin (therapeutic doses) Last dose within 8 h: Protamine 1 mg IV per 1 mg of enoxaparin (maximum single dose: 50 mg). Last dose within 8–12 h: 0.5 mg protamine IV per 1 mg of enoxaparin Protamine not required if reversal >12 h. From dosing • Dalteparin, nadroparin, tinzaparin (therapeutic doses): Last dose within 3–5 half-lives: 1 mg protamine IV per 100 anti-Xa units of LMWH Consider redosing (0.5 mg per 100 anti-Xa units or per 1 mg of enoxaparin) if life-threatening bleeding persists, or if renal insufficiency. • Prophylactic LMWH: Reversal not recommended in ICH. Maximum single dose of protamine sulfate: 50 mg.
THROMBOLYTICS (SELECTIVE PLASMINOGEN ACTIVATORS)	
• Alteplase-10 days • Reteplase-10 days • Tenecteplase-10 days	Cryoprecipitate Alternatively, antifibrinolytic (if cryoprecipitate not acceptable/ contraindicated or not available in a timely manner)
ANTIPLATELET DRUGS	
• Aspirin, 3–5 days • Prasugrel-7–10 days • Clopidogrel, Ticagrelor-5–7 days	Desmopressin

Table 8 (continued)

Duration of preoperative drug discontinuation prior to elective/non-urgent surgeries	Antidote/reversal agent (for emergency reversal of drug effect)
Glycoprotein IIB/IIIA antagonist: • Abciximab-2–5 days • Eptifibatide-8–24 h • Tirofiban-8–24 h • Vorapaxar reversible protease-activated receptor-1 (PAR-1) thrombin receptor antagonist (effectively irreversible due to long half-life)	
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) • Aspirin-7 days • Ibuprofen, flurbiprofen, ketorolac-2 days, • Naproxen-4–5 days • Diclofenac, ketoprofen, meclofenamate-1 day • Ketorolac-2 days • Diflunisal, Etodolac, tolmetin-3 days • Piroxicam-10–11 days	
HERBAL SUPPLEMENTS	
• Garlic (antiplatelet properties; potentiates warfarin effect) • Ginseng (antiplatelet effect)-7 days • Ginkgo biloba (antiplatelet effect)-36 h	

tion, these agents are also useful for correction of excessive perioperative bleeding or TBI related coagulopathy.

Standard coagulation tests [SCT, prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), Platelet count] are useful for preoperative evaluation of hemostasis during elective neurosurgeries but have a limited utility during these emergency situations [long turnaround time (> 60 min), relative inability to differentiate between different pathological mechanisms of bleeding].

In contrast, point-of-care (POC) viscoelastic hemostatic assays (VHA) such as rotational thromboelastometry (ROTEM) or thrombelastography (TEG) can quickly analyze (10–30 min) and identify the specific hemostatic defect (hyperfibrinolysis, hypofibrinogenemia, fibrin polymerization defect, coagulation factor deficiencies, heparin effects, thrombocytopenia, platelet dysfunction, etc.) and hence enable a fast and targeted correction of the coagulopathy. VHA based algorithms are increasingly being used in the neurosurgical setting—to monitor the coagulation state and guide hemostatic therapy during surgeries associated with a high likelihood of critical bleeding and coagulopathy (spine surgeries, craniosynostosis) to assess hypercoagulability and risk postoperative VTE; for management of TBI related coagulopathy; to predict hematoma expansion in ICH, and the outcome in SAH patients [45, 68, 71, 80]. Current guidelines also recommend the use of standardized VHA-guided algorithms with predefined intervention triggers over SCTs, to guide hemostatic therapy during emergency situations [1, 75, 81].

Additional Optimization Measures

There are several case reports of use of preoperative embolization in JWs, to decrease flow through pathological vessels and decrease the intraoperative blood loss during resection of highly vascular pathologies, especially meningi-

omas [48, 50, 53, 55]. It can also be considered during resection of other vascular tumors such as hemangioblastoma, glomus jugulare and other paragangliomas, juvenile nasopharyngeal angiofibroma, hemangiopericytoma.

Additionally, avoidance of unnecessary blood tests, limiting the blood sampling, use of pediatric collection tubes/blood sampling bottles can further aid in minimizing the blood loss in these patients [1, 2].

Formulation of the Intraoperative Plan

Prior to the surgery, the MDT should formulate an individualized intraoperative plan, on basis of the complexity and expected blood loss of the proposed neurosurgical procedure, the patient's ability to tolerate acute anemia (Hb level, coagulation profile, comorbidities), and the acceptable transfusion alternatives. This plan should clearly specify the various intraoperative blood management and blood conservation modalities; the strategy for prompt detection and management of acute significant bleeding; any contingency plan; and postoperative optimization measures that will be implemented for the patient. This overall strategy should be discussed in detail with the patient (prior to taking the informed consent) and, with the perioperative team (prior to the surgery).

Intraoperative Management

Intraoperatively, the neuroanesthetist uses several strategies to limit the intraoperative blood loss and prevent coagulopathy; enhance the patient's tolerance to anemia (optimize circulation, ventilation, oxygenation to improve oxygen delivery; minimize oxygen consumption); and maintain a vigilant monitoring of the blood loss, coagulopathy, and tissue perfusion indices, to initiate prompt corrective action if acute significant blood loss is detected.

The cardiac output is optimized by maintaining normovolemia (adequate preload) with isotonic crystalloids, and if required, use of inotropes such as dobutamine (5 to 15 mcg/kg/min i.v); hypervolemia/fluid overload should be avoided. The inspiratory oxygen fraction (FiO_2) is titrated to prevent arterial hypoxemia ($PaO_2 < 60$ mmHg) while avoiding excessive hyperoxia ($PaO_2 > 200$ mmHg). Furthermore, use of mechanical ventilation, sedation, neuromuscular blockade, and normocapnia (end-expiratory carbon dioxide pressure—38–42 mmHg) help to decrease the metabolic rate and reduce the oxygen consumption [23, 54, 66, 74]. Hypothermia and acidosis can impair oxygen delivery (by increasing affinity of Hb for oxygen) and also predispose to coagulopathy by delaying clot formation; hence, forced air warmers and warmed intravenous/irrigation fluids are used to maintain normothermia, and acidosis is promptly corrected [23, 68, 74]. Pneumatic compression boots should be used after anesthesia induction to prevent DVT. Elevating the head 20–30 degrees above the heart during intracranial interventions; keeping the abdomen free of any pressure during prone spine surgeries (increased intra-abdominal pressure promotes bleeding due to epidural venous plexus congestion) and use of appropriate prone positioning tables (e.g., Jackson table, Wilson frame with wide interpad spacing) which allow free suspension of the abdomen, can further help in decreasing the blood loss [4, 10, 25, 54, 66].

Monitoring Blood Loss and Coagulation Status

Besides monitoring the patient's cardiorespiratory parameters (heart rate, blood pressure, central venous pressure, oxygen saturation, $etCO_2$), temperature, fluid status, urine output, Hb, arte-

rial blood gases, and adequacy of tissue perfusion (serum lactate, base deficit, mixed venous oxygen saturation), a periodic visual assessment of blood loss (by checking the surgical field, suction canisters, surgical sponges) is extremely important.

If severe intraoperative bleeding is anticipated, dynamic indices of fluid responsiveness [e.g., stroke volume variation (SVV), pulse pressure variation (PPV)] and non-invasive cardiac output monitoring should be used in addition to static measures [central venous pressure (CVP)], to guide the fluid therapy and optimize the preload [74]. Additionally, the use of cerebral oximetry (to detect cerebral ischemia and provide an alternative trigger when to re-administer salvaged blood) and continuous Hb can also be considered, in this situation [74, 83].

Several autologous blood management techniques and pharmacological agents are available to the neuroanesthetist, to optimally manage the intraoperative blood loss and coagulation disturbances; this section gives a brief overview of this "toolkit" (Table 9). Importantly, these modalities should be used in combination, for an optimal synergistic effect.

Table 9 Perioperative blood conservation and blood management strategies for Jehovah's Witnesses—dosages and pertinent considerations

ACUTE NORMOVOLEMIC HEMODILUTION
Calculation of volume of blood to be withdrawn
V = EBV × (HI–HT/Hav)
where V = volume of blood collected,
EBV = Patient's estimated blood volume (body weight (kg) × 75 ml (male) or 70 ml (female))
HI = patients initial hematocrit; HT = desired target hematocrit; Hav = average of initial and target/final hematocrit.
Withdraw blood from a suitable peripheral or central venous access, or arterial line, after anesthetic induction and prior to the commencement of surgery, and transfer to an in-line reinfusion bag, containing an anticoagulant.
Simultaneously, administer crystalloid (3:1) or colloid (1:1) infusion, to maintain normovolemia. Measure physiologic parameters and hematocrit after removal of half of the blood volume target; then remove additional blood up to the target volume if these parameters are within normal limits.
Closely monitor the patient's hematocrit, intravascular volume status, and adequacy of tissue perfusion (base deficit/serum lactate/mixed venous oxygen saturation).
Reinfusion begins with the last bag; the first bag (highest concentration of blood cells and clotting factors) is the last to be reinfused.
Relative contraindications and precautions:
Significant cardiac (ischemic vascular disease, ventricular dysfunction), respiratory, hepatic, or renal disease
H/o stroke, anemia, coagulopathy, sepsis, fever (increased oxygen requirements)
ANH not recommended in combination with controlled hypotension.
PROTHROMBIN COMPLEX CONCENTRATE (PCCs)
Dosage:
Warfarin reversal: 25–50 U/kg i.v co-administered with vitamin K (5 to 10 mg by slow intravenous infusion)
If INR 2–4: 25 U/kg (not to exceed 2500 U)
If INR 4–6: 35 U/kg (not to exceed 3500 U)
If INR >6: 50 U/kg (not to exceed 5000 U)
Direct thrombin inhibitors: 50 U/kg; consider PCCs (plus tranexamic acid) if idarucizumab is not available, and DTI was administered within 3–5 half-lives (and no evidence of renal failure) or there is renal insufficiency leading to continued drug exposure beyond the normal 3–5 half-lives.
Perioperative coagulopathy: 50 U/kg
Traumatic brain injury (TBI) related coagulopathy: Administer PCC to normalize the EXTEM clotting time, if the EXTEM clotting time remains prolonged, despite a fibrinogen level > 1.5 g/L.
Special considerations
*Repeat INR testing after 15–60 min and serially every 6–8 h for the next 24–48 h.
Avoid overcorrection of warfarin reversal or overuse of PCC (risk of thromboembolic complications, DIC)
Use with caution in high-risk patients (e.g., thromboembolic events in previous 3 months; or other coagulopathic states)

Table 9 (continued)

DESMOPRESSIN
Dosage
Intracranial hematoma (ICH): 0.4 mcg/kg i.v
Perioperative Bleeding: **0.3 µg/kg iv**, diluted in normal saline (children—15–30 ml; adults—50–100 ml) and infused over 15–30 min (to avoid hemodynamic changes)
Repeat dose: Every 12–24 h depending on the type and severity of bleeding.
Special considerations
Peak effect: 30–60 min after iv infusion; duration of effect: 6 to 8 h (this timing should be considered if desmopressin is used prophylactically before the surgery)
Relatively safe drug with low rates of serious adverse events
Most common side effects: Tachycardia, facial flushing, headache; rarely: Thromboembolic complications, hyponatremia, seizures
Use with caution in elderly patients with atherosclerotic disease
Monitor serum sodium levels and osmolality especially if >one dose given over a 24-h period
Contraindication: Patients with thrombocytopenic purpura.
CRYOPRECIPITATE, FIBRINOGEN CONCENTRATE
Transfusion Trigger: S. Fibrinogen levels <200 mg/dL or viscoelastic guided monitoring: A5Fib <9 mm and AfEx<30 mm (target A5Fib > = 12 mm)
Cryoprecipitate doses: Initial dose: 1–2 units per 10 kg body weight (usually increase fibrinogen concentrations by 1 g/L); given additional doses if fibrinogen levels <150 mg/dl
Fibrinogen concentrate: Initial dose of 25–50 mg kg
(70 mg/kg raises fibrinogen level by 120 mg/dL; desired rise in fibrinogen level)/1.7 × body weight
RECOMBINANT FACTOR VIIA
Dosage:
Optimal dose is not well established; **Range: 10–90 ug/kg**; common regimen: 40–65 µg/kg, repeated after 15–30 min if no improvement.
Lower doses (10–20 µg/kg) are being increasingly preferred (thrombotic risk with higher doses).
Dose in danaparoid, dalteparin, nadroparin, tinzaparin use related ICH**:** 90 mcg/kg IV
Preconditions for use: pH > 7.2, normothermia, normal levels of other coagulation factors & platelets, exclusion of heparin effects and hyperfibrinolysis as the underlying cause of bleeding

Autologous Blood Management Techniques

JWs do not accept preoperative autologous blood donation, but most of them give consent for intraoperative autologous blood (whole or component) collection and re-transfusion techniques such as acute normovolemic hemodilution (ANH), acute hypervolemic hemodilution (AHH), cell saver (CS) blood salvage, and component sequestration (plateletpheresis, plasmapheresis). Usually, this consent is accompanied with a precondition that the collected blood/blood components should remain in continuity with their own circulation; hence, maintenance of a closed loop circuit (patient, collection system, processing unit, and blood bag are continuously connected) is sacrosanct [1–4, 10].

These techniques are an immensely useful option for JWs, as they are the only ones, which can immediately provide fresh whole blood (or its components) for correction of anemia (and/or coagulopathy), in the event of a sudden, severe, blood loss. Several studies have reported their efficacy during high blood loss neurosurgical procedures in JWs, such as resection of meningiomas and other tumors, AVMs resection, aneurysmal clipping, craniosynostosis correction, craniectomy for trauma, and complex, instrumented spinal fusions for scoliosis, degenerative and traumatic spine pathologies(Table 3) [9, 11, 12, 48, 51, 52, 55, 75].

ANH, AHH

ANH involves an isovolemic exchange of whole blood with a crystalloid (3:1 exchange) or a colloid (1:1 exchange), prior to the start of the surgery; the harvested fresh whole blood, replete with functioning platelets and coagulation factors, can subsequently be re-transfused, during

(preferably after blood loss has subsided) or after the surgery (Table 9) [84–87]. The hemodilution not only decreases the surgical blood loss (lost blood has a lower hematocrit), but also lowers the blood viscosity and systemic vascular resistance, and hence increases the CO; the consequent improvement in the microcirculatory flow, tissue perfusion, and oxygen supply is especially beneficial for patients undergoing intracranial surgeries. Studies in neurosurgical patients demonstrate that hemodynamic, coagulation, and cerebral oxygenation parameters are well maintained; and better clinical outcomes have been observed after aneurysm clipping in patients with good initial clinical grades [84–88].

The quantity of blood removed usually varies from 1 to 3 U and is determined by the patient's preoperative blood volume, preoperative hematocrit, and the target hematocrit. Though a wide range of target hematocrit (21–32%) has been mentioned in the literature, most of the reported studies in neurosurgical patients use moderate hemodilution, with target hematocrit of 27 to 30% [84–88]. Both, crystalloids as well as colloids have been used for inducing hemodilution. Colloids have a longer intravascular half-life, but a risk of clinically significant coagulopathy when large volumes are administered; given their antiplatelet effects and the risk of hypersensitivity reaction, use of crystalloids might be preferable in neurosurgical patients [34, 54, 85].

AHH, a simpler and cheaper alternative to ANH, involves a rapid infusion of a plasma expander without simultaneous withdrawal of autologous blood, and may be considered in JW who do not accept ANH [23, 89–91]. Typically, HES is infused (15–24 ml/kg, over 15–45 mins), in conjunction with a vasodilator to prevent the hemodynamic effect of a volume overload; however, despite use of a vasodilator, the existing hypervolemia (approximate surplus of 20% of the circulating volume) can still exert detrimental effects. In a small randomized controlled trial in patients undergoing elective craniotomies, Qiao et al. observed a significantly higher CVP and cerebrospinal fluid pressure in the AHH than the control group; cerebral oxygenation-supply parameters and cardiac index though, were well maintained [92]. The excessive volume loading can also cause pulmonary congestion and edema, hence caution is advised in elderly patients, and in those with a raised ICP, or compromised myocardial or renal function [89, 91]. Furthermore, ANH as well as AHH has a definite albeit small, dilutional effect on the platelet count and coagulation parameters, which may not be detected with routine coagulation tests, but can be discerned with VHA monitoring [91].

CS

In intraoperative and postoperative CS, the blood which would otherwise be lost from the operative field or wound drains, respectively, is collected, processed, and filtered to obtain an "upcycled" re-transfusable, red cells RBC-enriched unit (50%–80% hematocrit) [3, 4, 10, 93–95].

Its use in non-JW neurosurgical patients has been rather limited, possibly due to concerns about the requirement of minimum prerequisite amount of blood loss to produce a transfusable unit, cost efficacy, need for special equipment and trained personnel, fear of tumor dissemination during malignant or metastatic tumor resection neurosurgeries, and risk of a dilutional coagulopathy (due to reinfusion of a solution free of platelets and coagulation factors). Nevertheless, it is a relatively safe and very useful technique for neurosurgical JWs; its use has been documented in several case reports/cases series, and is also recommended by several current guidelines [9, 11, 12, 48, 55, 96]. The Italian Society of Transfusion Medicine and Immunohematology guidelines, specifically endorse its use during clipping of giant basilar artery aneurysms [96]. Current guidelines also recommend a concomitant administration of TXA, if the intraoperative blood is expected to exceed 500 ml. (consent is required for use of CS) [1, 74, 93].

The risk of tumor dissemination is unvalidated, and coagulopathy is a concern only with reinfusion of large volumes (greater than 3 L) of salvaged blood [25, 93–95]. In case of uncertainty about the amount of anticipated blood loss, a "collect only" (set up only the suction and anticoagulation tubing and reservoir of the CS device) can be set up initially; the "processing

set" can be loaded later, if a sufficient volume of blood has been collected for processing [93]. Furthermore, concurrent use of leucocyte depletion filter and avoidance of blood aspiration close to the tumor site are also recommended, during resection of intracranial or spine malignancies [1, 74, 93].

Plateletpheresis, Plasmapheresis

Plateletpheresis and plasmapheresis enable conservation of the patients' platelets and clotting factors, respectively; and can be considered in addition to CS and ANH, when dilutional coagulopathy is anticipated, e.g. during massive blood loss or consequent to transfusion of large amounts of colloids or salvaged RBC units [52, 97–99]. It involves the introduction of another separation unit that separates blood cells from the platelets and plasma; these units also must remain connected to the CS unit until completion of transfusion. Phlebotomizing 5 to 7 L of blood at a flow rate of 60 mL/min and processing through the plateletpheresis unit are estimated to provide one pheresis product of 250 to 300 mL with a platelet count of 3×10^9/L to 8×10^9/L [98]. Occurrence of hypotension due to volume loss can be effectively managed by volume replacement and if required, use of inotropes. Though this technique is more widely used during cardiac and liver transplant surgeries in JWs, Safwat et al. have documented its successful use in four patients with anticipated massive blood loss during an instrumented spine fusion for scoliosis surgery [52].

Deliberate Hypotension

DH is an effective technique for reducing the intraoperative blood loss, if used judiciously and with appropriate precautions [23, 100]. While its use has relatively declined in recent years due to potential ischemic concerns, nevertheless neuroanesthetists still use it selectively and with minimal early postoperative complications, during aneurysmal clipping, AVM resections, and occasionally pituitary resection and spine surgeries [100]. In JWs, its use has largely been documented during scoliosis correction and large post fossa meningioma resection surgeries [47, 52, 56].

Several pharmacological agents are available for inducing DH and are often used in combination in order to minimize their adverse effects. These include anesthetic agents (propofol, sevoflurane, isoflurane, opioids), beta adrenergic antagonists (e.g., esmolol, labetalol), α2 adrenoceptor adrenergic agonists (e.g., dexmedetomidine, clonidine), direct vasodilators (e.g., sodium nitroprusside, nitroglycerin), calcium channel antagonists (e.g., clevidipine, nicardipine), or angiotensin converting enzyme (ACE) inhibitors.

The detrimental effects of DH largely correlate with its extent and duration; and can be effectively prevented by taking adequate precautions. These include use of moderate hypotension (systolic BP 90–100 mmHg and mean arterial pressure (MAP) not less than 60–65 mmHg; or reduction of MAP by just 20–30% of baseline values); ensuring normovolemia and maintaining an adequate hematocrit; limiting the duration of DH to the period of maximal anticipated bleeding risk; and meticulous intraoperative neurophysiological monitoring [electroencephalography (EEG; raw recordings or processed), evoked potentials (EP), and/or cerebral oximetry] to detect cerebral ischemia [100]. DH should preferably be avoided in patients with significant cardiovascular, cerebrovascular, renal, hepatic disease, and in those at risk of neurologic injury from poor perfusion; it has, however, been safely used in patients with chronic arterial hypertension [3, 82, 100].

Systemic Hemostatic Agents

Antifibrinolytics

Synthetic lysine analogs such as Tranexamic acid (TXA), aminocaproic acid (EACA), and aprotinin competitively block the conversion of plasminogen (colocalized to fibrin) to plasmin, to inhibit (plasmin-mediated) fibrinolysis and degradation of the fibrin linked clot; TXA is preferred as it is 10 times more effective than EACA [10, 14, 19, 25, 66, 101, 102]. These relatively

safe and inexpensive hemostatic drugs are extensively used and recommended in JWs as well as nonJWs, for prophylaxis as well as management of excessive perioperative blood loss [1, 9, 14, 48, 49, 65, 66, 74, 79, 102, 103]. Current guidelines also recommend them for reducing the risk of rebleeding in aSAH, and as an alternative to cryoprecipitate for management of thrombolytic agent related ICH; TXA administration has been reported for limiting the hematoma expansion in a JW patient who developed symptomatic ICH following administration of alteplase for AIS [1, 104–106]. Furthermore, results of the CRASH 3 trial demonstrate its efficacy in reducing the early mortality, when administered early in non-moribund TBI patients [107]. Concerns regarding the occurrence of vaso-occlusive events and seizures are largely unfounded, as results from several large clinical trials and metanalysis do not demonstrate an increased incidence of PE, myocardial infarction or ischemia, and cerebral infarction or ischemia or death, with use of these drugs; furthermore, seizures have not been observed with use of routine clinical dosages [3, 14, 19, 81, 108].

Agents which Augment the Clotting Factor Activity

PCCs

PCCs contain variable amounts of vitamin K-dependent procoagulant factors (Factors II, VII, IX, and X), small amounts of anticoagulant proteins C, S, and Z, and sometimes, minimal amounts of unfractionated heparin and antithrombin 3. Multiple types of PCC preparations are commercially available; Four-factor PCCs are usually preferred because of their appreciably higher Factor VII content than Factor3 PCCs (Octaplex® does not contain human albumin and therefore may be more acceptable for JWs) [10, 19, 79, 104].

PCCs have been used for management of severe perioperative bleeding in JWs who are on vitamin K-dependent anticoagulants (VKA; e.g., Warfarin), and are recommended (in conjunction with Vitamin K), as the first line agents for emergency reversal of these drugs in the setting of ICH, TBI and prior to an urgent surgery [74, 81, 104, 109, 110]. They can also be considered for urgent reversal of directly acting oral anticoagulant effect, and for rapid correction of INR during massive, refractory intraoperative bleeding not related to VKA use [19, 65, 104, 109].

PCCs provide a rapid and predictable correction of coagulopathy; however, their pharmacologic effects start waning after approximately 12–24 h; repeated doses or overuse (overcorrection when INR is in the normal range) can lead to thrombotic complications (DVT, PE, MI, cerebrovascular accident) and also a risk of DIC [74, 81, 104]. Hence, their administration, especially of multiple doses, should preferably be guided by VHA monitoring, and thromboprophylaxis should be initiated as early as possible after the bleeding has been controlled [74, 81, 104].

Desmopressin

Desmopressin promotes hemostasis by stabilizing platelet function and stimulating the endothelial release of Von Willebrand factor and Factor VIII; platelet adhesion to the sub-endothelium is enhanced and blood level of FVIII and vWF is reported to increase by 2–6-fold after its administration [104, 111–113]. There is no literature pertaining to its use in neurosurgical JWs; nevertheless, several clinical studies in other major surgeries in JW and in non-JW neurosurgical patients have documented its efficacy in patients with as well as independent of antiplatelet drug-induced platelet dysfunction,—to reduce the risk of rebleeding in SAH; to reverse platelet dysfunction in TBI, and to limit hematoma expansion in ICH [112–117]. Current guidelines largely recommend its use in the setting of antiplatelet drug related platelet dysfunction—during excessive perioperative bleeding [mitigates pathological microvascular bleeding and the antiplatelet effect of colloid infusions(if administered)]; to limit hemorrhagic progression in antiplatelet medication-related ICH (especially prior to a neurosurgical intervention), and to decrease coagulopathic TBI related bleeding [65, 74, 81, 104].

Cryoprecipitate, Fibrinogen Concentrate, Factor XIII Concentrate

Fibrinogen is the first coagulation factor to reach critically low levels during excessive perioperative bleeding (dilutional or consumption coagulopathy) or TBI-induced coagulopathy, and in combination with Factor XIII ("fibrin stabilizing factor") is an important modulator of clot firmness. Low levels of these coagulation factors, especially in presence of a low platelet count, are highly predictive of increased bleeding complications in ICH, TBI, and during neurosurgical interventions [45, 74, 81, 118]. Early correction, especially of hypofibrinogenemia by administration of cryoprecipitate or fibrinogen concentrates, is critical for restoring the hemostasis in these situations. The conventional trigger for fibrinogen replacement is 150 mg/dL; however, some guidelines recommend a higher and probably a more prudent threshold (200 mg/dL) in acquired coagulopathy, given the heightened risk of hemorrhagic morbidity and mortality in neurosurgical patients [74, 79, 81, 101]. FXIII concentrate (30 IU/kg) should be considered in patients with excessive perioperative bleeding and a FXIII level less than 30% [75]. Cryoprecipitate is also recommended as the first line agent in Thrombolytics (plasminogen activators, e.g. rTPA) related symptomatic ICH (if thrombolytic has been administered within the previous 24 h). Besides a high fibrinogen concentration (200–250 mg/unit), cryoprecipitate also provides Factor VIII (100 U/unit), and some fibronectin, Factor XIII, and von Willebrand factor (each U _ 15 ml) [4, 74, 81, 101, 104, 119]. Notably, use of these agents, particularly repeat dosages, should be guided by VHA monitoring or a plasma Clauss fibrinogen level ≤ 1.5 g/L) [45].

Recombinant Factor VIIA (RFVIIA)

RF VIIa enhances thrombin generation after a vascular injury; it binds to the surface of activated platelets and augments the activation of FIX and FX, to generate a "thrombin burst" which, consequently, accelerates the coagulation cascade at the injury site [79].

Numerous case reports and small case series have reported its efficacy in controlling diffuse refractory bleeding during intracranial surgeries; and in limiting hematoma expansion in coagulopathic and non-coagulopathic ICH [45, 120–123]. It has also been used in JWs for management of intractable bleeding in a wide variety of clinical scenarios, such as major surgeries (cardiac, pancreatic, orthopedic, liver transplantation), postpartum hemorrhage and gastrointestinal bleeding [4, 10, 19]. However, it is an expensive drug and its use is associated with a relatively high rate of thromboembolic complications, myocardial injury, and even mortality (12.8–24%), likely due to the procoagulant state and thrombin burst associated with higher doses [45, 123–127]. Nevertheless, it is a useful option, especially in JW who do not accept PCC or cryoprecipitate. Current guidelines oppose its use as a prophylactic or first line agent, but do suggest it as a "last resort" to control diffuse, intractable perioperative bleeding or traumatic coagulopathy related ICH (after all conventional hemostatic therapies have been exhausted); it can also be considered for reversal of drug effect in patients with low-molecular-weight heparin and heparinoid use related ICH [74, 81, 104].

Vitamin K

Vitamin K normalizes the INR by providing the necessary substrate to synthesize vitamin K-dependent coagulation factors; since it has a slow (onset of action—2 hours), but sustained effect (reduction of INR <1.4 may take up to 24 h), it is primarily used in conjunction with other therapies to reverse the anticoagulant effect of vitamin K-dependent oral anticoagulants (warfarin), and may also be considered for prophylactic preoperative use to increase levels of vitamin K-dependent coagulation factors during high blood loss surgeries; (10 mg, slow i.v infusion of over 20–60 min; can be repeated after 12 h if required [104].

Operative Technique

Besides the above-mentioned strategies, use of a meticulous surgical technique by the neurosurgeon is crucial for reducing the perioperative

blood loss. It entails use of local skin infiltration with low dose epinephrine/with local vasoconstrictors to minimize blood oozing from the skin edge, bone wax to stop bone bleeding, atraumatic tissue dissection with meticulous handling of neural tissues (e.g., opening the dura without damaging a superficial parenchymal vessel), prompt recognition and coagulation of bleeding vessels (e.g., small scalp arteries), and use of hemostatic devices such as electrocautery, ultrasonic scalpels, bipolar sealer device [2, 4, 8, 16]. Furthermore, topical hemostatic agents can rapidly and effectively control small sources of bleeding and aid hemostasis within 10 min in most patients, by mechanical occlusion of bleeding vessels (bone wax, gelatin sponge), enhancing platelet aggregation (passive agents-collagen-based, cellulose-based, or gelatin-based products, e.g. microfibrillar collagen and cellulose pads) and/or by directly participating at the end of the coagulation cascade to generate a fibrin clot at the bleeding site (active agents, e.g. flowable matrix, fibrin glues and sealants, thrombin) [66, 82]. Since these agents bypass the initial enzymatic steps and are directly involved in the final physiological events of the coagulation cascade, their hemostatic effect is less susceptible to clotting factor deficiencies or platelet dysfunction-induced coagulopathies.

Management of Acute Blood Loss and Coagulopathy

Unfortunately, acute and significant bleeding may still occur despite use of multiple blood management strategies. The initial management of acute blood loss involves maintenance of an adequate circulatory volume, while the neurosurgeon attempts to identify and treat the underlying source of bleeding. Moderate blood loss (up to 20% of total blood volume) can be managed with infusion of isotonic crystalloids (Normal saline, Ringer's Lactate) and colloids (e.g., hydroxyethyl starch preferably tetrastarch). Though isooncotic colloids cause less tissue edema than crystalloids, however, they can a aggravate dilutional coagulopathy during severe bleeding by inhibiting fibrin polymerization and platelet aggregation [68]. The volume replacement should be prompt, but hypervolemia should be avoided as it predisposes to an iatrogenic or dilutional coagulopathy.

Because of transfusion limitations, the treatment of hemorrhagic shock in JWs can be particularly challenging, and often requires use of vasopressors to maintain pressures. Transfusion of the salvaged autologous blood (if available) may be necessary if the blood loss is severe (>40% of total blood volume) or the Hb drops to critical levels (<5 g/dl; recommended minimum Hb target—7–8 g/dl) [3, 4, 10, 12, 21]. If the blood loss exceeds 50% of the total blood volume, then transfusion of salvaged plasma and plateletpheresis units (if available) may be necessary to prevent complex coagulation disorders [12].

Assessment of ongoing coagulopathy requires the concerted efforts of both the neurosurgeon and the neuro-anesthetist. It should be suspected if there is excessive diffuse bleeding at the surgical site, occurrence of bleeding simultaneously at multiple sites, slow oozing from a non-identifiable source, or a delayed bleeding after an initial adequate hemostasis.

Fibrinogen is usually the first factor to fall to critically low levels during massive blood loss, and its aggressive replacement not only results in a faster and stronger clot formation, but also partially compensates for the thrombocytopenia [1, 45, 101]. Therefore, cryoprecipitate or fibrinogen concentrate is the first line option, followed by PCCs; however, if none of these are acceptable to the JW, then individual recombinant factor concentrates (VIII, IX, XIII) should be administered [4, 101]. TXA can be used as supplemental measure; desmopressin is useful if there is evidence of platelet dysfunction due to recent platelet drug use, and also to reverse some of the coagulation effects of colloids. RF VIIa may be considered if the bleeding is unresponsive to all other measures of restoring hemostasis.

The management of coagulopathy should be guided laboratory parameters, preferably POC-VHA [ROTEM: two or more of the following parameters: EXTEM CT > 80 s, EXTEM

CFT > 159 s, EXTEM MCF < 50 mm, INTEM CT > 240 s, INTEM CFT > 110 s, INTEM MCF < 50 mm, and FIBTEM MCF < 9 mm; Standard coagulation tests: INR > 1.3, aPTT >35 s, fibrinogen <1.5 g/L, and platelet count <100,000/mcL] [18–21].

A close communication between the neurosurgeon, neuroanesthetist, and perioperative team; anticipatory measures by the neuroanesthetist and expedient decisions by the neurosurgeon, such as a change in the surgical strategy, are of paramount importance, at this time; limiting the extent of surgical resection has occasionally been used as a lifesaving measure during neurosurgery in JWs [9].

Postoperative Management

The postoperative management is a continuum of the intraoperative care and focuses on maintenance of an optimal circulation, oxygenation, ventilation, normothermia, correction of postoperative anemia and coagulation defects. A comprehensive verbal and written handover of the patient should be provided to the recovery/ICU staff; they should be apprised of the transfusion related wishes of the patient, and the occurrence of any significant adverse intraoperative events. A high level of vigilance should be maintained for occurrence of an ICH; postoperative hematomas can occur in the immediate postoperative period or may be delayed, but usually are most common within 6 h after surgery [71]. NSAIDs are preferably avoided for postoperative analgesia, because of their propensity to cause platelet dysfunction. H2 blockers may be considered for prophylaxis of upper gastrointestinal hemorrhage. Intermittent pneumatic compression devices should be used for prevention of VTE; prophylactic administration of ultra-fractionated heparin/low-molecular-weight heparin should be initiated within 24 h after an elective craniotomy or aneurysmal clipping procedure, and within 48 hours of evacuation of ICH, in stable patients who have no ongoing coagulopathy [71].

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Transfusion Practice in Patients with Hereditary and Acquired Coagulation Disorders

Archana Hinduja, Sherraine Della-Moretta, and Payal Desai

Abstract

Both inherited and acquired bleeding disorders are commonly encountered in inpatient and outpatient settings. Clinical presentation varies from mild bruising to life-threatening hemorrhage. The location, frequency, severity, family history, and provocation of bleeding provide insight into the etiology of bleeding disorders. Various laboratory parameters further aid in elucidating its diagnosis. Optimal management is based on the diagnosis and severity of the bleeding. These products should be used judiciously to avoid various infectious and noninfectious complications. This chapter discusses the transfusion practice in various inherited and acquired coagulation disorders.

Keywords

Inherited · Hereditary · Acquired
Coagulation disorders · Bleeding disorders
Transfusion

A. Hinduja (✉)
Department of Neurology, The Ohio State University, Wexner Medical Center, Columbus, OH, USA
e-mail: archana.hinduja@osumc.edu

S. Della-Moretta · P. Desai
Department of Hematology, The Ohio State University, Wexner Medical Center, Columbus, OH, USA

Introduction

Hemostasis involves a complex interaction of blood vessel wall, platelets, coagulation factors, coagulation factor inhibitors, and fibrinolytic enzymes leading to clot formation and clot resolution. In normal conditions, a constant balance exists between, procoagulant and anticoagulant activities and any disruption leads to bleeding or clotting disorders.

Thrombin generation is key to successful hemostasis. Historically, the coagulation "cascade" model described the activation of intrinsic and extrinsic pathways that led to conversion of fibrinogen to fibrin [1, 2]. This was inadequate in explaining several scenarios. The "cell-based model" with three phases—initiation, amplification, and propagation provides an explanation of complex network. Initiation of coagulation occurs when exposure of tissue factor (TF) bearing cells leads to generation of activated factor VII (FVIIa) and formation of TF–VIIa complex activates factors IX (FIXa), and X (FXa) with trace amount of thrombin generation. Concurrently, Von Willebrand Factor (VWF) is bound and released from endothelial cells leading to further platelet activation. During amplification and propagation, small amounts of thrombin generated activate factors V, VIII, and XI. This causes formation of the "tenase" complex (FIXa/FVIIIa) to generate FXa and "prothrombinase" complex (FXa/FVa), which leads

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to large amounts of thrombin generation, activation of fibrin and factor XIII, and production of cross-linked stable clot.

To prevent excessive thrombosis, there are mechanisms that control the procoagulant pathways. These include tissue factor pathway inhibitor (TFPI) that inactivates TF–VIIa complex; antithrombin that complexes and inactivates FIXa, FXa, FXIa, and thrombin; protein C and S pathways that inactivate FVa and FVIIIa; and thrombomodulin that binds to thrombin and alters its substrate specificity for factors V, VIII, and fibrinogen. Fibrinolysis, a normal hemostatic response is carried out by plasminogen that breaks down cross-linked fibrin to form D-dimers and fibrinogen degradation products (FDP) (Figs. 1 and 2).

Investigation of Abnormal Hemostasis

A detailed history of the bleeding type, provocative factors, transfusion needs, and surgical intervention is important. These may be mild or life threatening and congenital or acquired. Initial laboratory investigation includes complete blood count including platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and peripheral blood smear. Viscoelastic testing like thromboelastogram (TEG) and rotational thromboelastogram (ROTEG) are point-of-care tests for evaluation of global hemostasis and treatment.

The congenital and acquired hemostatic disorders that will be discussed in this chapter are:

Inherited hemostatic defects

- Hemophilia A
- Hemophilia B
- Von Willebrand disease
- Glanzmann's thrombasthenia
- Bernard-Souliers syndrome
- Other factor deficiencies—Factors II, V, VII, X, XI, XIII
- Other Inherited disorders
- Sickle cell disease

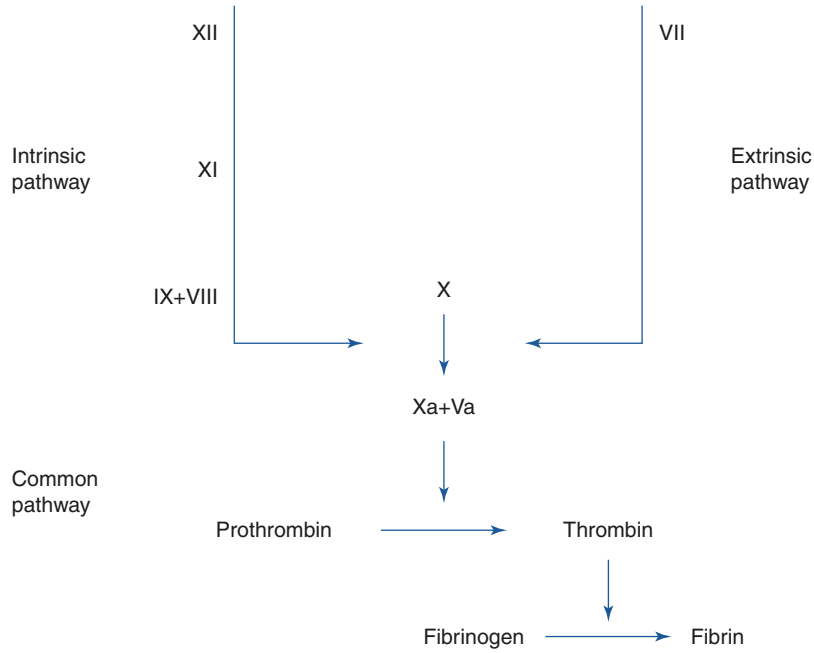

Fig. 1 Classical coagulation cascade

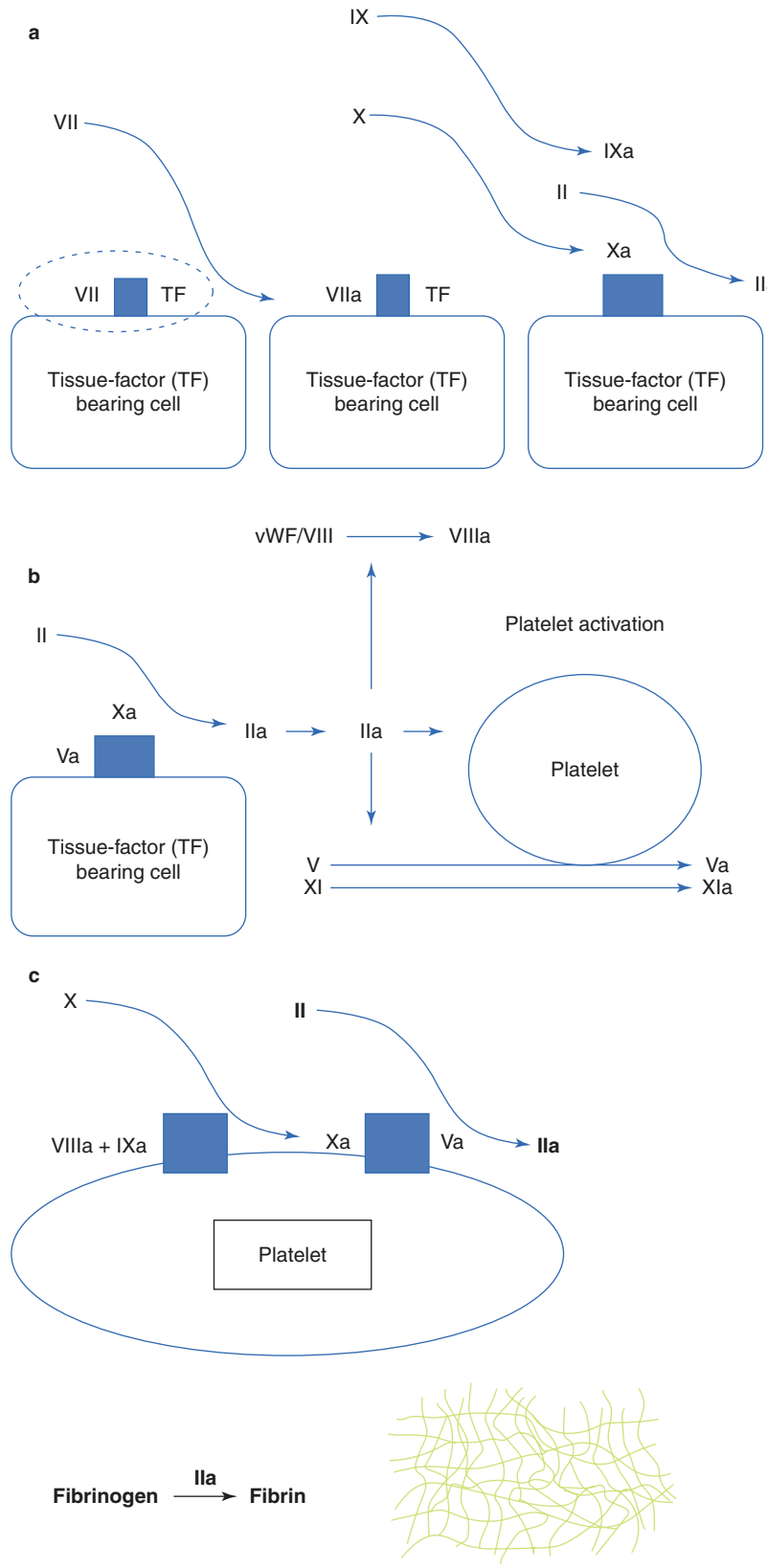

Fig. 2 Cell-based model **a**: initiation, **b**: amplification, **c**: propagation

Acquired hemostatic defects

- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Idiopathic thrombocytopenic purpura
- Trauma
- Liver disease
- Uremia
- Reversal of anticoagulants and thrombolytic drugs
- Miscellaneous: Vitamin K deficiency

Inherited Hemostatic Defects

Hemophilia A and B

Hemophilia A and B are deficiencies of factors VIII and IX, respectively, which can be inherited or acquired. Inherited hemophilia A and B are X-linked recessive disorders of varying severity based on the concentration of FVIII or FIX with severe being <1 IU/dl, moderate being 1–5 IU/dl, and mild being 5–40 IU/dl. Treatment of severe hemophilia consists of plasma-derived or recombinant factor. In severe bleeding, it is important to maintain factor levels of at least 50%. In Hemophilia A, the initial dose is FVIII 50 units/kg and Hemophilia B, the initial dose is 100–120 units/kg to target levels of 100% in both. Subsequent doses are determined by peak and trough levels. For hemarthrosis with the exception of hip, iliopsoas, or target joint bleeding, goal factor levels are 40–50%. This requires ~25 units/kg of FVIII or 50–60 units/kg of FIX. The same dosing is used for intramuscular bleeding. With mild hemophilia A, desmopressin raises FVIII level for a short duration and used for mild bleeding. For minor bleeding, like cutaneous bleeding or epistaxis, topical antifibrinolytics are used, but if prolonged or profound, factor replacement is necessary.

For major surgery such as coronary artery bypass grafting factor replacement is used preoperatively [3, 4]. The goal level in hemophilia A is 80–100% and hemophilia B is 60–80%. Postoperatively, replacement is tapered to achieve level of ~50% for 10–14 days.

Unfortunately, with frequent factor replacement use inhibitors develop. Low titer inhibitors are overcome by increasing the dose of factor given, however, this increases the risk of low titer inhibitor progressing to a high titer inhibitor, defined as >5 Bethesda Units with 1 Bethesda Unit being equal to the amount of inhibitor needed to inactivate 50% of the FVIII or FIX present in pooled normal plasma. Patients with high titer antibodies cannot be treated with factor concentrates due to no response. Instead, bypass agents like recombinant activated FVII (rFVIIa) or activated prothrombin complex concentrates (aPCC) are used although not always efficacious for bleeding or prophylaxis [5]. Newer agents like emicizumab that binds FIXa to FX, leading to FX activation and mimics FVIII activity. Some patients who receive emicizumab require FVIII bypassing agents to control bleeding. There are rare reports of microangiopathy or venous thromboembolism from co-administration of aPCC with emicizumab [5].

Overcoming inhibitor is important as neutralizing antibodies occur in ~30% of hemophilia A and 2–4% of hemophilia B patients. This is achieved by immune tolerance induction (ITI). In patients with low titer levels, high-dose factor is administered to overcome antibodies. Plasmapheresis is used temporarily in patients with high titer to lower these levels. It is important to monitor infusion reaction in patients with antibodies. Dosing of high-dose factor is not fully established. In patients with inhibitors, even with ITI, repeat exposure to factors can cause repeat inhibitors. Therefore in patients with prior ITI, selection of replacement product should be done in conjunction with a hematologist.

Von Willebrand Disease

Von Willebrand disease (VWD), the most common inherited bleeding disorder has 3 types with types 1 and 2 inherited in an autosomal dominant pattern and type 3 as autosomal recessive. Type 1 is the most common type from quantitative reduction in VWF. Type 2 is the next most common from a qualitative defect in VWF, which causes more severe bleeding than type 1. Type 3 is the rarest and most severe from absence of

VWF. Despite having normal FVIII synthesis, there is increased proteolysis of FVIII from reduced binding to VWF leading to decreased FVIII levels. When treating with VWF/FVIII, factor VIII levels increase transiently from decreased proteolysis, which increases the thrombotic risk.

Treatment is dependent on the type and severity of VWD [6, 7]. Desmopressin is used in mild cases of Types 1 and 2, which increases endogenous production of FVIII and VWF. This would not be an option in Type 3. Test doses of desmopressin are recommended to determine if there is a response. If there is no response to this trial or contraindication to desmopressin, or with type 3, plasma-derived VWF and FVIII are used [8]. The dose of plasma-derived VWF and FVIII is based on VWD units/kg. Infusion of 1 IU/kg VWF will raise VWF to approximately 1.5 IU/dl whereas 1 IU/kg of FVIII will raise the FVIII levels to about 2 IU/dl. For mild-to-moderate bleeding, the goal peak is >50–80 IU/dl on day 1 and trough is >30 IU/dl thereafter for up to 3 days. For severe bleeding, the goal peak is >100 IU/dl and trough is >50 IU/dl for 3–10 days.

For supportive treatment, antifibrinolytics are utilized. Tranexamic acid (TXA) is recommended in mucocutaneous bleeding. Other options include oral contraceptives containing progesterone and estrogens in menorrhagia and platelet transfusions. Donor platelets contain functional VWF, however, there is lack of evidence that guides platelets transfusion.

For pregnant women, the type of VWD is important for management. In the third trimester, VWF and FVIII levels can be 2–3 times higher than baseline levels. In mild type 1, the levels can normalize. The VWF and FVIII levels should be measured at least once during the third trimester. If VWF and FVIII levels are >50 IU/dl during the third trimester, no treatment is necessary. Desmopressin can be considered after umbilical cord clamping with type 1 if they have previously shown good response. After delivery, FVIII and VWF levels can fall precipitously and return to baseline levels within 3 weeks postpartum but sometimes drop to 50% within 24–48 h. Close monitoring and treatment are needed postpartum even with normal levels in the third trimester. In type 2, despite increase in factor levels, hemostasis may not normalize. In type 3, VWF remains undetectable resulting in continued low levels of FVIII. In types 2 and 3 disease with levels <50 IU/dl, VWF/FVIII concentrates are recommended with goal levels of 150–200 IU/dl to decrease risk of postpartum hemorrhage. It is also important to avoid an epidural unless VWF and FVIII levels are normalized. After delivery, they should continue to receive VWF/FVIII concentrates for 3–7 days and TXA for 7–14 days.

For gastrointestinal bleeding, VWF/FVIII concentrates are required while awaiting endoscopic management to evaluate for bleeding source as angiodysplasia is described in VWD. Drugs like statins, lenalidomide with antiangiogenic properties are used in patients with gastrointestinal bleeding, but larger studies are required.

In patients that undergo surgery, prevention of bleeding is the key by increasing factor levels from administration of VWF/FVIII concentrates administration to goal levels of 100 IU/dl on day 1. Dosing for major surgery for VWF:RCo (Ristocetin cofactor) is 50–60 IU/kg loading dose followed by half the dose every 8–24 h for maintenance. For minor surgery, the loading dose is same, but maintenance dose is administered every 12–48 h to goal FVIII and VWF levels of 50–80 IU/dl on day 1. Antifibrinolytics may be used to prevent rebleeding.

Finally, alloantibodies to VWF from plasma-derived factor concentrates develop. Options include a continuous high-dose FVIII concentrate infusion, however, anaphylactic reactions can occur with high titer alloantibodies. High-dose VWF/FVIII concentrates are given successfully in those without high-titer antibodies [8]. Agents like rFVIIa or FVIII inhibitor bypassing activity have limited evidence in patients with alloantibodies.

Glanzmann Thrombasthenia

Glanzmann thrombasthenia (GT) is a rare inherited autosomal recessive disorder of platelet function from a quantitative or qualitative defect of platelet membrane glycoprotein IIb/IIIa.

GPIIb/IIIa is a fibrinogen receptor that is required for platelet aggregation. It is diagnosed by flow cytometry or monoclonal antibodies. Type 1 GT is the most common (75%) from absent or trace expression of GPIIb/IIIa. Type 2 GT (~15%) has substantially reduced (5–20%) expression of GPIIb/IIIa. The last type, variant type GT represents ~10% has abnormal GPIIb/IIIa which is unable to bind fibrinogen with >20% expression. Each type has mild-to-severe bleeding risk from inability to form a stable hemostatic plug.

The treatment of bleeding and pre-surgical prophylaxis is platelet transfusion [9, 10]. The development of platelet antibodies remains an issue from multiple transfusions that leads to potential delays in treatment. Development of platelet antibodies can lead to refractoriness if transfused with unmatched platelets. Alternatively, rFVIIa 90 mcg/kg/dose every 2–6 h is administered, which activates FX to FXa that generates increased thrombin. Increased thrombin generation bind to activated platelets, which improves fibrin clot structure and formation of primary hemostatic plug. While there is an increased risk of arterial thromboembolism from high concentrations of rFVIIa, this is not observed in patients with coagulopathy [11, 12].

Bernard-Soulier Syndrome

Bernard-Soulier syndrome is a rare inherited autosomal recessive disorder from mutations in glycoprotein Ib-IX-V, which is an important platelet adhesion signaling complex. For bleeding events and prophylaxis prior to high-risk procedures platelets are transfused [9]. Antifibrinolytics like TXA, are used in less severe bleeding.

Other Factor Deficiencies—Factors II, V, VII, X, XI, XIII

Deficiencies of other coagulation factors like factors II, V, VII, X, XI, XIII, combined factors V and VIII account for 2–5% of inherited rare coagulation disorders (RCD) [13]. These are heterogeneous, mild, or severe and may be spontaneous mucosal bleeding, excessive bleeding following trauma or invasive procedures, heavy menstrual or postpartum bleeding, muscle, and joint bleeding. Abnormalities in clotting time, PTT, APTT, and thrombin time are observed depending on the type of factor deficiency. After exclusion of inhibitors by mixing studies, specific deficiency is diagnosed by a reduction in specific factor levels. Management of bleeding depends on the severity, specific factor that is deficient and the available treatments. Nonreplacement therapies include antifibrinolytic drugs like TXA and epsilon-aminocaproic acid, combined oral contraceptives, progesterone, and levonorgestrel-releasing intrauterine device and vitamin K. Replacement therapies include FFP, cryoprecipitate, PCC, single factor plasma-derived concentrates, and recombinant coagulation proteins.

Other Inherited Disorders

Storage Pool Disease

It is a heterogeneous group of inherited or acquired disorders from defects in the platelet granules. The content inside platelet granules is required for primary hemostasis and platelet plug formation. Its diagnosis is made by electron microscopy and abnormal platelet aggregation. Treatments include antifibrinolytic drugs, DDAVP, and platelet transfusions.

Hereditary Hemorrhagic Telangiectasia

Hereditary Hemorrhagic Telangiectasia (HHT) or Osler-Weber-Rendu Syndrome is an autosomal recessive condition. The mutation leads to abnormal vessel formation leading to arteriovenous malformations (AVMs). Patients develop telangiectasias that are visible on multiple mucosal surfaces like tip of the nose, ears, lips, tongue, and fingertips. They may present with their first bleed as intracerebral hemorrhage and family members show significant phenotypic variability in the pattern of bleeding. While mutations in the *ENG*, *ACVRL1*, or *SMAD4* genes are common, multiple genes have been identified. Treatment includes direct interventions, cautery, embolization, topical estrogen, fibrinolytics, and systemic therapy like antiangiogenic drugs such as bevacizumab. Concurrent treatment for iron deficiency is frequently needed.

Hermansky-Pudlak Syndrome, Chediak-Higashi Syndrome, and Griscelli Syndrome

These are all rare autosomal recessive conditions associated with oculocutaneous albinism and moderate-to-severe coagulopathies. Most have mucocutaneous bleeding treated with antifibrinolytics.

Sickle Cell Disease

Sickle cell disease is an autosomal recessive disorder in which a point mutation causes glutamic acid to be replaced by valine in the beta-globin chain of hemoglobin leading to a propensity for hemoglobin polymerization resulting in sickling of red blood cells. Due to the fragility of these sickled cells, there is marked hemolysis causing low baseline hemoglobin levels. The transfusion parameters are different from the general population. Unneeded transfusions can lead to complications including the development of antibodies and iron overload. Transfusion to a hemoglobin >10 g/dl, can lead to hyperviscosity [14]. To combat hyperviscosity and iron overload, transfusion options other than simple transfusion, which is transfusing donor blood are preferred [15]. To prevent hyperviscosity, patients are transfused to target hemoglobin of <10 g/dl. In milder subtypes like Hemoglobin SC disease or SB^+, the baseline hemoglobin must be taken into account to set the goal hemoglobin level. Other options include manual exchange transfusion that alternates isovolumetric phlebotomy and blood transfusion. Alternatively, automated red cell exchange utilizes an apheresis machine to decrease hemoglobin S percentage by replacing blood with donor red cells. The rate of iron overload is greatest in patients who receive simple transfusion and least from automated red cell exchange. Alloimmunization remains an issue and is dependent on the number of total units. Since exposure to the total number of units is higher in automated red cell exchange, this complication is worse following exchange transfusions.

Emergency indications for transfusion include acute anemia, acute ischemic stroke, acute chest syndrome, acute priapism, and multiorgan failure including acute sickle hepatopathy. In acute anemia, defined as a decrease in hemoglobin of >2 g/dl below the patient's baseline, a simple transfusion is performed. In acute ischemic stroke, exchange transfusion with goal hemoglobin (Hb) of 10 g/dl and HbS <30% is recommended. For acute chest syndrome, transfusion to Hb of 10 g/dl is considered in those with increased oxygen requirements. In patients with acute syndrome with worsening hypoxia, increased respiratory rate, decreasing Hb, multilobar disease on chest radiograph, neurologic complication, or those with clinical deterioration despite simple transfusion, exchange transfusion should be considered. In acute priapism, simple or exchange transfusion is considered when refractory to treatment with irrigation or alpha-adrenergic agents. Finally, in an acutely ill patient, exchange transfusion with goal Hb >10 g/dl and HbS <30% is recommended.

Chronic transfusion is beneficial in patients with a history of stroke or elevated risk of stroke. The SIT trial examined children with silent cerebral infarcts. They were randomized to prophylactic transfusion or to observation to determine the effects on stroke, new infarct, or progression of prior silent cerebral infarct [16]. A 58% relative risk reduction in incidence was observed in the chronic transfusion group [16]. The SWiTCH trial randomized patients with prior stroke to either transfusions and iron chelation or hydroxyurea and phlebotomy to determine if hydroxyurea and phlebotomy were non-inferior for recurrent stroke and decreasing iron overload [17]. There was no recurrent stroke in those who received transfusions versus 10% recurrent stroke in those randomized to hydroxyurea and phlebotomy. While those results were consistent with non-inferiority, the study was terminated due to no difference in liver iron levels. As such, transfusion and iron chelation are recommended. The TWiTCH study compared chronic transfusion to hydroxyurea in primary stroke prevention in high-risk children based on elevated transcranial doppler flow velocity (TCD) [18]. It showed that hydroxyurea could be used instead of chronic transfusion after 4 years of transfusion in those without severe vasculopathy on imaging. Other indications for chronic transfusion that have not yet been studied include recurrent pain, leg

ulcers, sickle hepatopathy, renal dysfunction, recurrent acute chest syndrome, priapism, and pulmonary hypertension. Transfusion can be considered if there is no response to disease modifying treatments.

Prophylactic periodic transfusion is considered for severe SCD-related complications, recurrent acute chest syndrome, repeated pain episodes, other SCD-related comorbidities, high-risk pregnancy, twin pregnancy, or SCD-related complications while pregnant.

For patients undergoing surgical procedures, preoperative transfusion in those requiring general anesthesia and lasting more than 1 h with goal hemoglobin >9 g/dl before surgery is recommended [19]. In patients with a baseline of 9–10 g/dl, exchange transfusion is used. Patients with severe genotypes (HbSS and $HbSB^0$) showed increased rate of postoperative complications with acute chest syndrome being the most common.

Screening for iron overload with annual ferritin levels and in chronic transfusions, MRI to determine liver iron content every 1–2 years is suggested. In patients that have elevated ferritin an iron overload, chelation therapy is recommended.

Acquired Hemostatic Defects

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a type of consumption microangiopathic coagulopathy. This defibrination syndrome results from an inappropriate hemostatic response that manifests as thrombotic and hemorrhagic complications. It is an acquired syndrome from systemic activation of blood coagulation, which generates intravascular fibrin, leading to thrombosis of small and medium-sized vessels, and organ dysfunction [20]. It presents as an acute life-threatening emergency (uncompensated) with decreased levels of hemostatic components or as chronic (compensated) subclinical process with more normal coagulation parameters. In normal hemostasis, following endothelial vascular injury a clot is formed at the site of vessel injury followed by clot resolution by the fibrinolytic mechanism. In DIC, this is dysregulated causing massive thrombin generation that is disseminated to sites remote from endothelial injury. Common causes include sepsis, malignancy, end-stage liver disease, obstetric disorders, and trauma. The main triggering mechanism is exposure of blood to tissue factor source that initiates coagulation leading to thrombin generation and fibrin formation. Subsequently, secondary activation of fibrinolytic pathway occurs leading to excessive fibrin degradation products that inhibit the action of thrombin and platelets leading to bleeding diathesis. The liver is unable to compensate for the ongoing consumption of clotting factors leading to factor deficiency that worsens the bleeding tendency. Although the coagulation system plays a crucial role, this syndrome can develop from damaged endothelium, damaged erythrocytes and leucocytes, plasma proteins, and activation of immune system.

The laboratory abnormalities observed [21]:

- Thrombocytopenia
- Increased fibrin degradation products: Raised D-dimers, increased fibrin monomers
- Prolonged PT and APTT
- Reduce fibrinogen levels
- Anemia, schistocytes, elevated reticulocyte count

There is no single gold standard test for its diagnosis. The International Society of Thrombosis and Haemostasis (ISTH) has proposed a diagnostic scoring system to diagnose overt DIC [22].

Scoring System for Overt DIC

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

If yes: Proceed

If no: Do not use this algorithm

Order global coagulation tests (PT, platelet count, fibrinogen, fibrin related marker)

Score the Test Results

- Platelet count: >100 × 10^9/l = 0, <100 × 10^9/l = 1, <50 × 10^9/l = 2
- Elevated fibrin marker (e.g., D-dimer, fibrin degradation products): no increase = 0, moderate increase = 2, string increase = 3
- Prolonged PT: <3 s = 0, >3 but <6 s = 1, >6 s = 2
- Fibrinogen level: >1 g/l = 0, <1 g/l = 1

Calculate Score

≥5 compatible with overt DIC: Repeat score daily

<5 suggestive for nonovert DIC: Repeat next 1–2 days

Treatment of DIC

- Treatment of the underlying disease is the cornerstone.
- Prevention and treatment of bleeding [21, 23]. Prophylactic administration of platelets and coagulation factors is not recommended in patients who are not actively bleeding or have a high risk of bleeding as long as the platelets is ≥10,000/microL
  1. Platelet transfusion is recommended with active bleeding and platelet count <50,000/microL or at high risk of bleeding and a platelet count <20,000/microL.
  2. Patients with platelet count <10,000/microL should be transfused due to risk of spontaneous bleeding.
  3. FFP is transfused with active bleeding and prolonged PT/APTT (>1.5 times normal) or decreased fibrinogen (<150 mg/dl).
  4. Fibrinogen concentrate or cryoprecipitate is recommended in active bleeding with persistent severe hypofibrinogenemia (<150 gm/dl) despite FFP transfusion.
  5. PCC is used where transfusion with FFP is not possible.
  6. Antifibrinolytic agents like TXA and epsilon aminocaproic acid are used in severe bleeding from hyperfibrinolytic state.
- Anticoagulants [21, 23]. Prophylaxis with prophylactic doses of UFH or LMWH is recommended in critically ill, nonbleeding patients with DIC. Therapeutic doses of heparin are recommended where thrombosis predominates to target a PTT of 1.5–2.5 times the normal. In general, LMWH is preferred over UFH but in patients with high bleeding risk UFH is preferred.

Mortality is dependent on the underlying mechanism and degree of coagulation impairment. Marked reduction in antithrombin levels and protein C are associated with a persistent procoagulant state and a predictor of mortality [24].

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening thrombotic microangiopathy (TMA) from deficiency or inhibition of ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) predominantly affects young women. The incidence of acquired TTP is 2–5 cases /100,000/year and the median age for diagnosis is 41 years (9–78 years). It may be congenital from mutations of ADAMTS13 gene or acquired from autoantibodies targeting ADAMTS13. In normal circumstances, ADAMTS13 degrades the ultralarge VWF multimers, but in TTP, VWF is not cleaved from deficiency or immune-mediated mechanism. The VWF multimers, platelets, and red blood cells bind together causing widespread microvascular thrombosis and hemolysis. Common triggers are autoimmune diseases, infections, and medications. The classic pentad of TTP includes fever, thrombocytopenia, hemolytic anemia, renal dysfunction, and neurological dysfunction. Its diagnosis is made from the clinical features and severe ADAMTS13 deficiency (<10%) [25]. Severe thrombocytopenia (10–50 × 10^9/l), hemoglobin concentration 8–9 g/dl, schistocytes, elevated lactate dehydrogenase, low haptoglobulin, negative direct Coomb's test. The differential diagnosis includes DIC, atypical hemolytic uremic syndrome, immune-mediated thrombocytopenia, and mechanical destruction. The PLASMIC score is used to determine the severity of ADAMTS13 deficiency. If untreated the mortality is 90%, which decreases to 10–20% with appropriate management. TTP requires

rapid diagnosis and management. Plasma exchange, the mainstay treatment should be started emergently [26]. High-dose steroids with plasma exchange have improved remission and reduced the number of plasma exchange treatments [27]. High-dose methylprednisolone (10 mg/kg/day for 3 days followed by 2.5 mg/kg/day) is more efficacious than standard doses (1 mg/kg/day) as adjunctive therapy [25]. Despite low platelet counts, they do not require platelet transfusion including for a procedure, unless actively bleeding. If plasma exchange is readily unavailable, FFP should be transfused as a temporary measure [28]. Although platelet transfusions are contraindicated in general, evidence has not demonstrated morbidity and mortality from their use and may be used in severe hemorrhagic manifestations [28]. Several days are required to observe improvement in plasma exchange. Treatment response is defined as normal platelet count (>150 × 10^9/l) for two consecutive days, normalization of LDH, and clinical improvement. Durable response is considered with normal parameters for more than 30 days after completion of plasma exchange. Despite plasma exchange and corticosteroids the relapse rate is 36%. With suboptimal response or refractory or relapsing TTP therapies like rituximab, vincristine, splenectomy, bortezomib, N-acetylcysteine, anfibatide, caplacizumab, and recombinant ADAMTS13 are first-line agents [29]. Older age, high LDL levels, and increased troponin are associated with increased mortality and refractory form [30]. Prevention of thromboembolic events using mechanical methods and pharmacological methods (once platelets reach 50,000/l) are initiated. In cardiac involvement oral aspirin once the platelet count reaches 50,000/l is recommended. Long-term follow up is required to manage relapses, other autoimmune disorders, depression, cognitive impairment, and post-traumatic stress disorder.

Congenital TTP (Upshaw-Schulman Syndrome)

It arises from homozygous or compound heterozygous mutations in ADAMTS13. They are managed with plasma and recombinant ADAMTS13 infusions. Yearly assessment of their systemic organs is required.

Immune Thrombocytopenia

Immune thrombocytopenia (ITP) has replaced the term idiopathic thrombocytopenic purpura is an acquired autoimmune disorder. Primary ITP (platelet count <100 × 10^9/l) is caused by autoantibodies against platelet in the absence of other causes or disorders associated with thrombocytopenia [31]. Secondary ITP is immune thrombocytopenia from systemic causes like systemic lupus erythematosus, antiphospholipid syndrome, lymphoproliferative disorders, *Helicobacter pylori*, and chronic viral infections.

Primary ITP a rare autoimmune disease affects 1.6–3.2/1000,000 adults of all age groups. Bleeding is the most common manifestation and is associated with morbidity in the elderly. It is separated into newly diagnosed (<3 months from diagnosis), persistent (3–12 months from diagnosis), and chronic (>12 months from diagnosis). Bleeding manifestations occur in two-thirds as petechiae, purpura, epistaxis, severe hemorrhage, e.g., intracranial hemorrhage, gastrointestinal, and genitourinary bleeding. Diagnosis is based on the presence of thrombocytopenia (platelet count <100 × 10^9/l) and exclusion of secondary causes. A complete blood count, peripheral smear, testing of viral, and serological tests are required to exclude secondary causes [32]. Testing for antiplatelet antibodies is not recommended due to low sensitivity.

The major goal of treatment is to provide a safe platelet goal that prevents major bleeding rather than correcting the platelet count to normal. Treatment depends on the bleeding tendency, platelet count, disease state, and side effects. In adults with newly diagnosed ITP without or with mild bleeding and platelet count <30,000 × 10^9/l, a short course of ≤6 weeks corticosteroids (prednisolone 1 mg/kg/day orally with a 4–6 week taper after obtaining response or methylprednisolone 30 g/kg/IV with rapid taper every third day to 1 mg/kg/day or dexamethasone 40 mg/day orally or intravenously × 4 days with

multiple rounds and taper) is recommended [33]. Either IVIG or anti-D and platelet concentrates are used if corticosteroids are contraindicated or in conjunction for life-threatening bleeding. Anti-D binds to rhesus positive erythrocytes and is phagocytosed by the spleen. These inhibit degradation of the antibody-loaded platelets by saturating the macrophage and clearing the red cells thus increasing the platelet count with a slight drop in hemoglobin. Anti-D is effective only in Rh-positive patients with an intact spleen. If there is no response, in severe bleeding thrombopoietin receptor antagonist (TRO-RA), antifibrinolytic agents, and splenectomy are alternatives. Rituximab is a second-line therapy, especially in secondary ITP. In adults with ITP≥3 months who are steroid dependent or have no response to corticosteroids, treatment with either splenectomy, TPO-RA, rituximab, or fostamatinib is recommended. Third-line agents include danazol, dapsone, immunomodulators—azathioprine, cyclophosphamide, mycophenolate, vinblastine, vincristine, and cyclosporine A [34]. In secondary ITP, treatment of the underlying condition improves platelet count.

Trauma

Bleeding is a leading preventable cause of death observed in 30–40% of trauma patients. Factors for trauma-related coagulopathy include consumption of clotting factors, platelet hyperactivity, dilution of clotting factors from fluid resuscitation, acidosis, and hypothermia leading to clotting factor dysfunction, endothelial dysfunction, and release of microparticles and hyperfibrinolysis [35]. Various coagulation abnormalities occur. In massive hemorrhage, empiric and goal-directed resuscitation strategies have been utilized. A Cochrane review suggested insufficient evidence to recommend that TEG-based transfusion was superior to traditional transfusion practice [36, 37]. However, several single center studies have demonstrated superiority in terms of reversal and survival from TEG and ROTEM. In massive transfusion protocol, balance transfusion ratio of PRBCs: FFP: platelets as 1:1:1 to mirror whole blood are used to limit the crystalloid use. The PROMMTT trial, demonstrated that transfusion with high FFP: RBC ratio early regardless of INR was associated with decreased mortality [38]. The PROPPR trial demonstrated a significant difference in hemostasis but no significant difference in mortality when plasma:platelets:PRBC were used as 1:1:1 compared to those that received 1:1:2 [39]. The target hemoglobin is >7–9 g/dl and platelets $>50 \times 10^9$/l but with ongoing bleeding and TBI $>100 \times 10^9$/l. FFP is transfused if INR >1.5 and fibrinogen levels <1.5 g/l. Further resuscitation should be supported by point-of-care tests. Antifibrinolytics are used in hyperfibrinolytic conditions. The CRASH-2 trial showed a small mortality benefit from TXA compared to placebo if administered within 3 h with no significant increase in thromboembolic complications [40]. The MATTERs trial demonstrated decreased mortality from TXA in patients with massive transfusion [41]. Other empiric agents include rVIIa, PCC, fibrinogen concentrate, and desmopressin.

Liver Disease

It decreases procoagulation and anticoagulation factors leading to complex but balanced coagulopathy. Despite exhibiting features of coagulopathy, thrombotic complications develop [42]. The liver is responsible for synthesis of all coagulation factors (except Factor VIII and VWF). The decrease in anticoagulants and procoagulants is proportionate leading to a "balanced hemostasis" [43]. There is an elevation in factor VIII and VWF from increased production by the endothelial system and decreased plasma clearance. There is failure of enzymatic removal of sialic acid from fibrinogen resulting in dysfibrinogenemia (high fibrinogen level and decreased function). Both hyperfibrinolysis and hypofibrinolysis occur. Hyperfibrinolysis results from upregulation of tissue plasminogen activator (tPA), low thrombin activatable fibrinolysis inhibitor (TAFI), and low antiplasmin level. Thrombocytopenia occurs from impaired production, decreased hepatic synthesis of thrombopoietin, bone marrow suppression, and splenic sequestration.

Factors that promote clotting:

- Elevated VWF, low ADAMTS13
- Elevated Factor VIII
- Reduced antithrombin, protein C, protein S
- Reduced plasminogen

Factors that promote bleeding:

- Thrombocytopenia/abnormal platelet function
- Reduced factors—fibrinogen, II, V, VII, IX, X, XI, XIIIa
- Dysfibrinogenemia
- Reduced TAFI and antiplasmin levels
- Elevated tPA levels

Elevation in PT, APTT, and INR is not reflective of bleeding risk. FFP transfusion prior to procedures to correct INR is not routinely recommended, as INR is not a reliable marker of coagulation status. Besides, the additional volume may increase the pressure in the portal system thereby increasing the risk of variceal bleeding. Correction of coagulopathy and preparation of invasive procedures are common indications of transfusion. Below is a brief summary of management of coagulopathy in liver disease [44].

- Hemorrhagic shock, anemia—Transfuse PRBC to target hemoglobin 7 g/dl
- Asymptomatic thrombocytopenia—Observation.
- Surgery or invasive procedures with platelets >50 × 10^9/l—Measure fibrinogen level. Consider cryoprecipitate if low fibrinogen level (120–150 mg/dl).
- Surgery or invasive procedures with platelets <50 × 10^9/l—Measure fibrinogen level. Consider platelet transfusion based on the bleeding risk rather than a specific target as these may not be achievable from splenic sequestration. Transfuse cryoprecipitate if low fibrinogen level (120–150 mg/dl).
- Active life-threatening bleeding—PCC. Consider cryoprecipitate if low fibrinogen level (120–150 mg/dl). TXA or epsilon aminocaproic acid may be given in hyperfibrinolysis state. In individual cases, rVIIa may be considered.

Empiric vitamin K is administered with suspected deficiency or unsure status. Other interventions that increase platelet counts like TPO-RAs and other agents are used in elective procedures to avoid althrombopag [45]. In severe thrombocytopenia (<50 × 10^9/l) mechanical thromboprophylaxis is recommended over pharmacological prophylaxis.

In patients with thrombosis, safety of anticoagulation will need to be individualized. LMWH is preferred over vitamin K antagonists from deranged INR. There is a high bleeding risk with thrombocytopenia (<50 × 10^9/l).

Kidney Disease

They present as ecchymosis, purpura, epistaxis, bleeding from puncture sites from impaired platelet function. The pathophysiology for platelet dysfunction is complex and includes dysfunctional VWF, decreased thromboxane production, increased cyclic AMP and GMP levels, uremic toxins, anemia of renal disease, and altered platelet granules that are essential for platelet plug formation [43]. There is a loss of laminar flow from anemia leading to prolonged bleeding time and treatment of anemia corrects this. Treatment is indicated in patients with active bleeding or prior to surgical procedures. Desmopressin is the initial line therapy that increases the release of VWF from endothelial cells. Other interventions include correction of anemia, dialysis, cryoprecipitate, estrogen, and TXA [43].

Reversal of Anticoagulants and Thrombolytic Drugs

Reversal depends on the bleeding severity, anticoagulation status, and indication of anticoagulation. Oral charcoal is used to remove unabsorbed drugs within a few hours of administration [43, 46].

Vitamin K antagonists (warfarin).

- No active bleeding—Hold warfarin, oral vitamin K based on INR and bleeding risk.

- Severe bleeding—Vitamin K subcutaneously or intravenously, PCC. If PPC is unavailable, FFP is administered.

Direct oral anticoagulants

- Minor bleeding—conservative management
- Major bleeding with Factor Xa inhibitors: Apixiban, rivaroxaban, endoxaban—Andaxanet alfa or PCC
- Major bleeding with direct thrombin inhibitors: Dabigatran—Idaruzimab or PCC, hemodialysis

Thrombolytic agents

- Life-threatening bleeding—Cryoprecipitate or FFP or TXA or epsilon aminocaproic acid

Antithrombotics

- Life-threatening bleeding—Platelet transfusion or desmopressin

Heparin, low molecular weight heparin

- Life-threatening bleeding—Stop heparin, protamine

Vitamin K Deficiency

It is common in newborns but occurs in adults from malabsorption, nutritional deficiency, especially in critically ill patients. It causes bleeding from cutaneous and mucosal surfaces, gastrointestinal tract, and intracranial hemorrhage. Treatment involves administration of vitamin K subcutaneously and for life-threatening bleed with intravenous vitamin K, PCC, or FFP.

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Blood Transfusion Practices in Sepsis

Subhal Dixit and Khalid Ismail Khatib

Abstract

For years, blood transfusion followed the 10/30 approach without major deliberations on the adverse effects, if any. From the early 1980s, studies started emerging in various clinical settings, describing the impact of transfusion of blood and blood products on patient outcomes. RCTs (TRICC, EGDT, TRISS, and TRICOP) and observational/epidemiological studies (CRIT, ABC) were almost unanimous about the need to reduce RBC transfusion in patients. The deleterious effects of blood transfusion on patient outcomes came as a surprise for what was till that time thought to be a harmless/beneficial intervention with positive physiological effects on oxygen delivery. Thresholds for triggering RBC transfusion were studied and defined in different clinical patient populations. A restrictive RBC transfusion policy (Hb trigger < 7 gm/dl) was adopted almost universally in critically ill patients with very few exceptions (associated with ischemic heart disease and maybe seriously ill cancer patients). Septic patients were studied with respect to their outcomes in patients receiving RBC transfusions from varying angles. RBC transfusions received within first 24 h of hospitalization or receiving transfusion during entire hospital stay or 28 days before or after developing sepsis have been taken into account. Different outcome measures have been considered. The restrictive transfusion strategy has passed the test on all accounts. Patient blood management programs based on reducing the use of blood and blood products have been advocated to improve patient care. Also incorporating prudent clinical judgement and individualizing according to patient characteristics, the decision to transfuse blood will help in improving the quality of patient care.

Keywords

Anemia in ICU · Red blood cell transfusion · Transfusion threshold · Transfusion trigger · Sepsis · Septic shock

Introduction

A major cause of morbidity and mortality in patients of all age groups (from neonates to geriatric population), Sepsis causes almost 50 million cases and 11 million deaths worldwide [1]. Sepsis is complicated by organ dysfunction

S. Dixit
Critical Care, Sanjeevan & MJM Hospital, Pune, Maharashtra, India

K. I. Khatib (✉)
Department of Medicine, SKN Medical College, Pune, Maharashtra, India

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and organ system failure. Hematological abnormalities are common in patients with sepsis. These include anemia, leukocytosis, thrombocytopenia, and activation of the coagulation cascade.

Anemia in critically ill patients is multifactorial and widely prevalent in intensive care unit (ICU) patients. An editorial reported almost 95% of patients admitted to ICU had hemoglobin (Hb) levels below the normal range within 72 h of hospitalization [2]. When we consider all patients admitted to ICU for more than one week, more than 2/3rd of patients had at least one blood transfusion [3, 4]. The various causes of anemia in critically ill patients admitted to ICU are sepsis, chronic kidney disease, bleeding (posttraumatic, postoperative, Gastrointestinal bleed, blood loss due to frequent investigations), and abnormal erythropoietin production, iron metabolism, and nutritional deficiency. These often lead to what is called acute anemia of chronic disease [5–7]. One important but entirely preventable cause of anemia developing in critically ill patients after ICU admission is due to repeated phlebotomies and repeated aspiration of blood for various investigations and due to invasive hemodynamic catheters. This is somewhat euphemistically known as "anemia of chronic investigation" [8]. Frequent, ill-advised, non-coordinated investigations at varying times of the day can lead to blood loss of almost 50 ml/day [9]. In some ICUs, this is the cause of anemia in 1/3rd of the patients [8].

Anemia in critically ill patients is usually treated with transfusion of blood and blood products. Around 15% of medical ICU patients and almost 1/3rd of surgical patients receive some form of blood transfusion in a 24-h cycle [10]. Though there is a widespread use of blood and blood products in the ICU, there is still some confusion regarding the optimal management of anemia in critically ill patients. Let us take a look at the various aspects of this issue. Some evidence is reviewed in general critically ill patients while other evidence when available is presented in specifically septic patients.

Whether Anemia in Critically Ill Patients Is Associated with Increased Morbidity and Mortality?

The presence of anemia leads to reduced Oxygen delivery (DO2) and a mismatch between DO2 and oxygen consumption (VO2). This mismatch may lead to increased complications, morbidity, and mortality. A large (almost 6000 patients) retrospective study in patients admitted to surgical ICU found reduced hemoglobin levels to be associated with increased severity of illness, higher ICU mortality, and length of stay (LOS) and higher in-hospital mortality and LOS [11]. Another study in patients with chronic obstructive pulmonary disease demonstrated positive effects of correction of anemia on successful liberation from ventilation due to reduction in the work of breathing [12]. The CRIT study showed that a decreasing Hb (<9 gm%) during ICU stay in critically ill patients was associated with greater mortality and LOS [4].

There are several studies with similar findings in postsurgical patients with severe anemia due to various reasons (including non-transfusion of blood or blood products for religious reasons). There was an increased likelihood of death as the Hb levels fell below 7 gm%, or occurrence of increased complications or adverse events in patients with anemia [13–16].

Whether RBC Transfusion to Correct Anemia Is Beneficial in ICU Patients?

This is a debatable topic with evidence overwhelmingly in favor of eliminating/reducing RBC transfusion or giving it until absolutely necessary. Though all the evidence is from observational studies, they direct us toward an unfailing trend that RBC transfusion in critically ill patients (with or without sepsis) is associated consistently with worse outcome measures. One needs to keep in mind the inherent bias that may creep into these observational studies and their results.

Patients who receive RBC transfusion have worse APACHE and SOFA scores (therefore are more seriously ill) and these patient cohorts usually have worse outcomes [17].

RBC Transfusion in General Critically Ill Patients

The CRIT study is a large (4892 patients) prospective multicentric observational study of clinical practices regarding anemia and blood transfusions in ICU patients in the United States. The study observed RBC transfusions to be associated with longer ICU and hospital LOS, more complications and greater mortality [4]. The ABC study was another large (almost 3500 patients), multicentric, prospective, observational European study which looked at the association between blood transfusion and outcomes. It showed an association of transfusion with increased ICU LOS and increased ICU, hospital, and 28 days mortality, even after matching for the severity of organ dysfunction [9]. Patients who received blood transfusion had increased risk of dying [odds ratio 95% confidence interval (OR 95% CI)-1.37 (1.02–1.84)]. A meta-analysis of 45 studies with a total of 272,596 patients was performed to assess the effect of RBC transfusion on outcome measures in critically ill patients [18]. All the studies except 3 showed that RBC transfusion was more riskier than beneficial and it increased the possibility of mortality [OR 95% CI, 1.7 (1.4–1.9)], nosocomial infections [OR 95% CI-1.8 (1.5–2.2)], development of multiorgan dysfunction or acute respiratory distress syndrome [OR 95% CI-2.5 (1.6–3.3)]. Two studies included in the meta-analysis were neutral in their assessment of the effect of blood transfusion on outcome measures, while one study demonstrated a positive effect of RBC transfusion on outcome measures in elderly patients with cardiovascular disease (acute myocardial infarction) and low hematocrit less than 30%. Though the studies included in the meta-analysis were observational studies and not randomized controlled trials, the authors acknowledged the limitations of the data available and recommended the evaluation of the risk–benefit ratio in individual patients prior to RBC transfusion.

RBC Transfusions Specifically in Septic Patients

A retrospective analysis of patients with hematologic malignancies admitted to ICU with sepsis and/or septic shock studied the effect of RBC transfusion received in the first 48 h of ICU admission on mortality of patients. It found that transfusion within 2 days of ICU admission was associated with increased hospital mortality [19]. Another study specifically focused on general surgical ICU patients (excluding cardiac surgery patients) with sepsis to study the possible associations between anemia, RBC transfusion, and long-term (90 days) outcomes of these patients. Patients who were anemic and therefore required RBC transfusion had higher 90 days mortality as compared to patients who did not receive RBC transfusion [20]. Another prospective descriptive study from Turkey, comprising of adult patients admitted to the ICU with sepsis and/or septic shock studied the relation between RBC and platelet transfusion, and ICU and hospital outcomes. They found higher mortality in patients' transfused blood or blood products [21].

A propensity matched analysis of a multicentric prospective observational database of around 1000 patients with community-acquired sepsis and/or septic shock. Patients who received a transfusion had higher 28 day and in-hospital mortality and also stayed in hospital significantly longer. They were also sicker (higher SOFA and APACHE II scores). However, on propensity matched analysis of 152 pairs of patients, transfused patients were less likely to die after 7 or 28 days or in hospital [22]. A single center, retrospective cohort analysis of patients admitted with sepsis who received RBC transfusion within the first 24 h of hospitalization was performed in Taiwan. On propensity score matching, RBC transfusion within the first 24 h of hospitalization was not associated with increased mortality [23]. The SOAP study

was a multicentric, European epidemiologic study of sepsis in acutely ill patients and grouped the patients on whether they received RBC transfusion or not. In multivariate analysis, blood transfusion was not significantly associated with a worse mortality rate. In fact, in the propensity matched pairs of patients, there was a higher 30-day survival rate in the transfusion group than in the other patients ($P = 0.004$) [24].

At What Level of Anemia Should We Transfuse RBCs?

Triggers for transfusion have traditionally been Hb values though there have been some suggestions for physiological triggers. Generally, the 10/30 rule has been followed as a transfusion trigger (Hb < 10 gm/dl and hematocrit <30%) [25]. A consensus conference in 1988 suggested the presence of physiological factors [such as tachycardia, postural hypotension, neurologic symptoms, mixed central venous saturation (ScvO2) less than 60, elevated serum lactate] in addition to anemia as triggers for RBC transfusion [26]. Though the suggestions appear good in theory there is no evidence regarding the use of these physiological factors as transfusion triggers. Hence, Hb value continues to be most commonly used factor to decide regarding initiation of blood transfusion.

RBC Transfusion in General Critically Ill Patients

The TRICC study was a large (838 patients) prospectively randomized controlled trial (RCT) evaluating the effect of a so-called restrictive and liberal (transfusion trigger 10 gm/dl) transfusion strategy in ICU patients [27]. Thirty-day mortality rates in both group were similar, but there was better survival in certain groups of patients, notably patients with lower disease severity and younger patients, in the restrictive strategy group. However, patients with acute cardiovascular diseases [acute myocardial infarction (AMI), unstable angina) did not have better survival with the restrictive strategy.

RBC Transfusions Specifically in Septic Patients

The early goal-directed study (EGDT) by Rivers et al., presented an algorithmic approach to resuscitate patients with sepsis and septic shock [28]. It used the 10/30 transfusion trigger for RBC transfusion to increase DO2. Application of a sepsis bundle comprising several interventions, including RBC transfusion and EGDT could decrease mortality significantly in patients with septic shock.

However, the individual contribution of the intervention related to RBC transfusion could not be evaluated as the effect of the whole sepsis bundle was seen. In fact a single center, retrospective study in patients with septic shock and who received EGDT showed, RBC transfusion was associated with worse clinical outcomes (longer ICU and hospital LOS and more days on mechanical ventilation) [29].

The TRISS trial was a large (998 patients) multicentric, Scandinavian, RCT evaluating the effect of higher (<9 gm/dl) and lower (<7 gm/dl) threshold for blood transfusion in patients admitted with septic shock [30]. There was no difference in mortality or in occurrence of ischemic events.

The TRICOP trial was a single-center RCT in adult patients with cancer presenting with septic shock. It evaluated the effect of a liberal and restrictive transfusion strategy in these very sick patients (overall mortality 50%, mean APACHE II score 57, mean SOFA score 7). There was a better 90 days survival in the liberal strategy group as compared to the restrictive strategy group [31].

Meta-analysis of Trials Using Hb as a Transfusion Trigger

A systematic review and meta-analysis of 37 RCTs with around 19,000 patients (adults as well as children/medical plus surgical ICU) compared liberal versus restrictive strategies for RBC transfusion. The meta-analysis did not find any difference in 30-day mortality, hospital or ICU LOS,

complication rate (including the risk of infection and AMI), and functional recovery [32].

A different meta-analysis used a context-specific approach (based on patient and clinical type) to evaluate 31 trials to compare the liberal versus restrictive RBC transfusion strategy in surgical and critically ill patients. They concluded that restrictive strategy may be harmful in patients undergoing cardiac or vascular surgeries and elderly patients undergoing orthopedic surgeries. These patients had more complications related to inadequate O2 supply (organ-specific ischemic events, cardiac arrhythmias, or unstable angina). These complications were not found to be increased in critically ill patients [33].

What Should Be Our Approach to RBC Transfusion in Patients with Sepsis Considering All the Above Evidence?

Patient blood management (PBM) program should incorporate appropriate evidence-based multidisciplinary interventions but also allow adequate space to incorporate prudent clinical judgement-based decision-making to optimize patient care [34]. Decisions to transfuse a patient should not only be based on Hb values alone but should be individualized to incorporate patient clinical characteristics including symptoms and physiological factors [35]. This leeway for clinical judgement to decide whether this individual patient with this Hb trigger should be transfused or not at this particular moment is an extremely important part of PBM. The restrictive Hb threshold (Hb less than 7 gm/dl) is an appropriate trigger in most patients with sepsis/septic shock. Caution should be exercised in patients who have associated underlying ischemic heart disease and may be in seriously ill cancer patients.

Conclusion

Anemia in critically ill patients is associated with increased morbidity and mortality due to its deleterious effects on oxygen delivery. But the correction of anemia by RBC transfusion is not always beneficial. A restrictive approach to RBC transfusion has been shown repeatedly and in different clinical settings (including sepsis and septic shock) to be more appropriate. Clinical Guidelines of various societies have endorsed the same approach.

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Part XI

Blood and Blood Products: Complications

Neurological Complications of Anticoagulation

Mauricio Giraldo and Luis F. Botero

Abstract

Anticoagulation is a medical therapy indicated in diseases such as deep vein thrombosis and atrial fibrillation. The reduction of thrombotic events associated with the implementation of anticoagulation is widely well demonstrated in clinical practice with large-scale studies in populations at risk. Despite the benefit of this treatment, bleeding complications are frequent and intracranial hemorrhage is one of the most serious that can occur. Anticoagulation can be achieved with different medications including warfarin, heparin, and the new direct Factor IIa anticoagulants with different levels of evidence and also associated with bleeding complications.

Knowledge of these agents and their pharmacology, their indications, correct dosification, patient's risk factors for central nervous system bleeding, and their treatment, either medical with the specific reversal of the anticoagulant agent involved—when available—or surgical if it is necessary, are the most important interventions in the management of this complication.

The emergence of new drugs with safer profiles and high effectiveness requires, as well, epidemiologically strong studies to demonstrate their superiority compared to traditional drugs.

Unfortunately, until today, the mortality associated with cerebral hemorrhage, both spontaneous and associated with the use of anticoagulant drugs, continues to be very high and the sequelae of patients who survive in many cases are devastating.

Keywords

Anticoagulants · Warfarin · Heparin
Rivaroxaban · Apixaban · Complications
Intracerebral hemorrhage

M. Giraldo (✉)
Western University and Schulich Medicine and Dentistry School, Anesthesiologist London Health Science Centre, London, ON, Canada
e-mail: mauricio.giraldo@lhsc.on.ca

L. F. Botero
Clinica Las Americas, Medellin, Colombia

Neuroanesthesia Coordinator Neurological Institute of Colombia, Medellin, Colombia

Pontificia Bolivariana University, Medellin, Colombia

UPB and CES University, Medellin, Colombia

Introduction

Blood anticoagulation and antiplatelet therapy have been used for decades in modern medicine to treat several problems related to abnormal thrombosis of the blood vessels, the migration of these thrombi to other organs such as the lung, brain, or gastrointestinal tract, prevention associated with events such as myocardial infarction

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and stroke, as well as for patients who benefit from anticoagulation such as those with connective tissue diseases or hypercoagulable states [1].

The use of these drugs in clinical practice is consistently associated with a reduction in the number of patients who suffer thrombotic events each year; for example, up to 64% of patients with atrial fibrillation (AF) are treated with warfarin [2].

On the other hand, bleeding complications associated with the use of these medications can occur frequently and, in some cases, even lead to death [3].

The hemorrhagic complications of anticoagulation associated with higher morbidity and mortality are those that affect the central nervous system (CNS) and the gastrointestinal tract (GI).

In this chapter, we will focus on the description of the main medications used in current medical practice for the anticoagulation of patients at risk of thrombotic events, we will discuss their safety profile and their relationship with bleeding complications focused on the central nervous system as well as some important aspects in the prevention and medical and surgical management of cerebral hemorrhages.

Isolated antiplatelet therapy with aspirin is related to hemorrhagic events in the brain of approximately 0.4 events per 100 patients per year, but as it is not an anticoagulant drug per se, so it will not be considered in this discussion [4, 72].

Indications for Anticoagulation Therapy

Anticoagulation began in clinical practice in 1941 as part of the management of thromboembolic disease [5] and by 2011, in the United States alone, more than 35 million of these prescriptions were issued [6].

The most common indications are unprovoked deep venous thrombosis (DVT) and pulmonary embolism (PE), [7] atrial fibrillation related to both: valvular and non-valvular origin [8], antiphospholipid syndrome [9] and some patients with cancer, mainly affecting pancreas, stomach, lungs, and brain [10].

In recent years, the indications and drugs used for anticoagulation have increased substantially, new drugs with a better safety profile with efficacy similar to or even superior to previously well-established drugs by numerous studies done in the previous decades, have changed the outlook and management of the blood anticoagulation.

The use of these anticoagulant drugs, in combination or not with antiplatelet therapy in such diverse clinical settings, the choice of the appropriate medication and the duration of therapy, among others, have made this topic one of the most important for all clinicians, surgeons, and anesthesiologists who actively participate in the management of these patients.

Table 1 shows the indications for anticoagulation therapy in medical practice.

Anticoagulant Drugs

The drugs used for blood anticoagulation in clinical practice are warfarin [11], both unfractionated heparin, with more than 90 years of use in medical practice [12], the newer low molecular weight heparin agents (LMWH), and a series of new drugs with different brand names such as direct oral anticoagulants (DOAC) or non-vitamin K dependent drugs.

These new drugs are divided into two categories: selective thrombin inhibitors (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban, and betrixaban) inhibitors [13]. In general, they are characterized by not requiring periodic control to establish their level of activity and effectiveness.

Table 1 Indications for anticoagulation therapy

Chronic atrial fibrillation
Congestive heart failure
Mechanical prosthetic valves
Myocardial infarction
Deep venous thrombosis
Pulmonary embolism
Stroke
Antiphospholipid syndrome
Cardioversion

Furthermore, they have fewer drug and food interactions, which is why they have been displacing the use of traditional anticoagulants and step by step being used in more clinical scenarios [14].

We are going to describe each one of them and define their risk profile for bleeding complications in the CNS.

Warfarin

Warfarin is widely used in the medical practice for short- and long-term anticoagulation in patients with medical and/or surgical indications [15].

Its mechanism of action is through competitively inhibiting the vitamin K epoxide reductase complex one (VKORC1), an essential enzyme for activating the vitamin K available in the body. Through this mechanism, warfarin can deplete functional vitamin K reserves and therefore reduce the synthesis of active clotting factors. The hepatic synthesis of coagulation factors II, VII, IX, and X, as well as coagulation regulatory factors protein C and protein S, require the presence of vitamin K [16] (Fig. 1).

The effectiveness of warfarin is out of any discussion and generally has a very good safety profile in most patients [15]. However, this effectiveness has been questioned for some subgroups of patients such as Hispanics, blacks, and people over 90 years of age, whose numbers in most studies are far below the white Anglo-Saxon population [17].

The main problem with warfarin is related to the need to frequently monitor its activity level using the international normalized ratio (INR). After administering the drug the earliest changes in INR are typically seen 24 to 36 h after administration of the dose. The antithrombotic effect of warfarin is not present until approximately the fifth day of therapy, which is dependent on the clearance of prothrombin [18].

The normal range of the INR is between 0.9 and 1.2. The therapeutic range of warfarin is INR between 2 and 3.5 depending on the patient's problem as shown in Table 2.

Warfarin has a large number of synergistic interactions with its anticoagulant activity; anticoagulants such as heparin or non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin

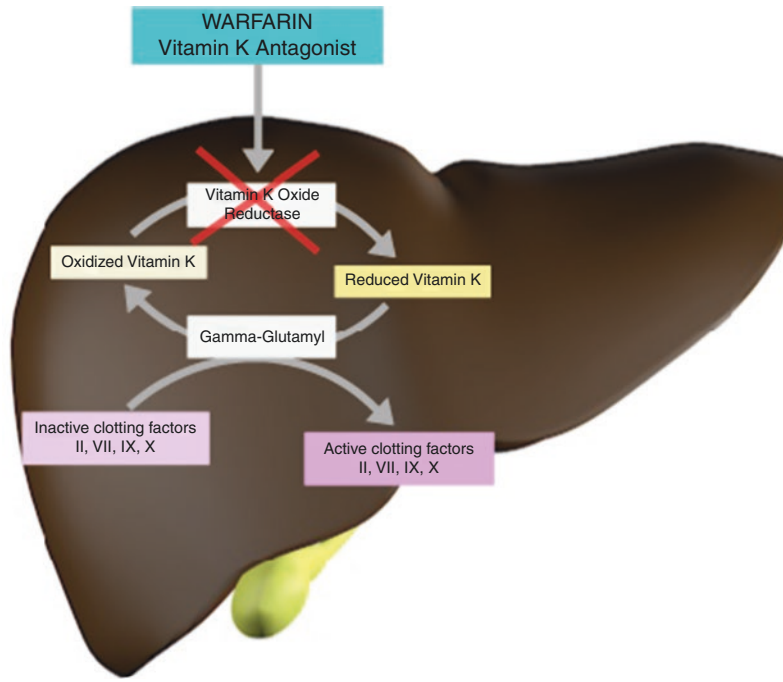

Fig. 1 Mechanism of action of warfarin. Being a vitamin K antagonist, warfarin inhibits conversion of oxidized vitamin K to reduced vitamin K, resulting in a depletion of the last one. Carboxylation of reduced vitamin K is fundamental for the activation of the inactive form of coagulation factors in the liver

Table 2 INR therapeutic ranges

Therapeutic ranges	
Clinical conditions	INR
DVT prophylaxis	2.0–2.5
Treatment of DVT/PE	2.0–3.0
Systemic embolus	
Atrial fibrillation	
TIAs	
LV mural thrombus	
Mitral valve repair	
Tissue heart valves	2.5–3.5
Mechanical prosthetic heart valves implanted after 1990	
Recurrent DVT/PE	
DVT/PE with lupus anticoagulant (a lower range may be sufficient)	3.0–3.5
Mechanical prosthetic heart valves implanted before 1990	

(ASA), serotonin [19] reuptake inhibitors, antibiotics such as metronidazole, ciprofloxacin, rifampin, and the sulfa-20 group, phenytoin [20], alcohol [21], and other medications including some herbal ones may alter the effect of warfarin, the INR values and its anticoagulant potency [22]. Factors that have been associated with a high variability of the INR are advanced age, poor adherence to treatment, and some foods of vegetable origin [23] although the latter has not been demonstrated in any previous study.

The main complications of warfarin are those of the hemorrhagic type and can range from mild (cutaneous hematomas, epistaxis, abnormal vaginal bleeding) and relatively common to the most severe such as intracerebral hemorrhage (ICH) that can sometimes cause the death of the patient [24].

ICH associated with the use of warfarin, both for AF and for stroke prevention, has an absolute incidence of 1% per year, however, due to the large number of patients treated with this drug worldwide, ICH cases are not uncommon in the emergency services and are sometimes associated with devastating neurological consequences or patient's death [25]. Mortality associated with ICH is close to 50% in its initial phase and up to 62% at 3 months, consistently higher in patients receiving warfarin than in those presenting with ICH without anticoagulation [26].

A large number of risk factors for presenting ICH have been listed during the use of warfarin mainly in patients with AF and as prevention of DVT and the most important of these factors is inadequate to control INR with over anticoagulation effect and INR values greater than three [27].

Uncontrolled hypertension, aged over 70 years, concomitant use of antiplatelet drugs [28] and leukoaraiosis (Leukoaraiosis is a common MRI finding seen in stroke and ICH patients, and has been strongly associated with risk of presenting dementia) [29], are among other important risk factors frequently associated with this complication.

Since the 1990s, Fihn et al. have described that the first three months of treatment and the inability to stabilize the INR value during this initial phase were consistently related to bleeding complications in patients treated in anticoagulation clinics with experienced doctors in anticoagulated patient management, neither age nor hypertension was negatively associated with these bleeding complications.

One of the most controversial aspects of the management of these patients is whether or not warfarin therapy should be restarted after a bleeding event in the central nervous system in patients at high risk for an ischemic embolic episode. Yung evaluated the impact of restarting anticoagulant therapy with warfarin in patients with ICH and mechanical cardiac valves, finding that restarting warfarin did not translate into higher mortality or rebleeding at one year in these patients [30].

Restarting anticoagulation is therefore based on the criteria of the clinician and the absolute risk of an embolic event in these patients with CNS bleeding [31].

The treatment of ICH associated with the concomitant use of warfarin is the complete reversal of anticoagulation and normalization of the INR with the use of prothrombin concentrate complex (PCC) if available or fresh frozen plasma (FFP) [30]. Although some have suggested that in high-risk patients (e.g., mechanical cardiac valves) the mere suspension of warfarin without reversing its effect has not been shown to be associated with worse results [32].

The details of treatment and the reversal of anticoagulant drugs in the management of ICH will be discussed later in this chapter.

Unfractionated Heparin (UFH) and Low Molecular Weight Heparins (LMWH)

Unfractionated heparin has been a widely used drug for several decades in a wide variety of clinical settings [33].

Its dose has a great variability depending on the circumstances in which it is used and the characteristics of the patient. Unlike other drugs, the dosage of heparin does not depend on the renal function [34].

Its indications are varied and are summarized in Table 3.

The mechanism of action of heparin is complex but it is focused on two basic aspects, the inactivation of thrombin and the inactivation of factor Xa.

The inactivation of thrombin has as a consequence the impossibility of fibrinogen to pass to fibrin and therefore prevents the formation of clots [35]. The clinical effect of heparin is monitored by measuring the partial thromboplastin time (PTT) and the activated clotting time (ICT) [36].

The main side effects of heparin are bleeding and thrombocytopenia in up to 30% of patients and should be discontinued if the platelet count is less than 100 thousand per mm^3 [35]. Other less frequent are hypokalemia, alopecia, and osteoporosis with prolonged treatment [37].

Table 3 Indications for anticoagulation with unfractionated heparin

PE, DVT, and AF treatment and prevention
Mechanical prosthetic valves
Anticoagulation in cardiac surgery
Thrombosis prevention in vascular surgery
Dialysis
Myocardial infarction and PCI
Cardioversion

PCI: Percutaneous Coronary Intervention

The risk of bleeding is related to treatment intensity. Major bleeding episodes occur more frequently with full-dose than with low-dose UFH therapy and have been reported more frequently with intermittent intravenous injection than with continuous intravenous infusion of the drug. The risk of UFH-induced hemorrhage is increased by the presence of concomitant bleeding risks such as the use of other anticoagulant or antiplatelet drugs, previous bleeding, malignancy, renal or hepatic failure, associated trauma, people above 65 years of age, or a low hemoglobin value at the beginning of therapy [38].

On the other hand, Low Molecular Weight Heparins (LMWHs) comprise a large group of drugs used as preventive therapy for thrombosis associated with immobility and its prevention within the hospital environment. Its mechanism of action is similar to that of unfractionated heparin, but its half-life is longer as well as fewer side effects, including thrombocytopenia [39].

ICH associated with the use of high doses of heparin has been described for several decades, mainly in patients with anticoagulation for ischemic stroke [40, 41].

In cardiac surgery, embolic phenomena are much more frequent [42] (due to the use of the extracorporeal circulation pump and the residual air in the cardiac chambers or the circuit). The requirement of high doses of heparin to maintain the ICT above 400 s is associated with a risk of between 1 and 2% of demonstrable bleeding phenomena on CT scan in patients who undergo cardiac valve surgery [43] and can range from mild to catastrophic events in very rare cases.

On the other hand, the use of low doses of heparin as prophylaxis for DVT has not been associated with increased bleeding or other complications in patients with spontaneous ICH or associated with the use of anticoagulant drugs [43].

LMWHs are not associated either with worse results in relation to the growth of the hematoma in patients with ICH when administered at prophylactic doses in DVT [44].

The use of enoxaparin was recently evaluated in patients with spontaneous ICH, demonstrating

its safety and the absence of an expansion of the cerebral hematoma [45].

The use of LMWH in patients with high-grade gliomas at prophylactic doses for DVT also did not increase the risk of intracerebral bleeding at one-year follow-up [46].

Dabigatran

Dabigatran is an oral anticoagulant that is part of a new group of drugs that acts by directly inhibiting free thrombin (Factor IIa) and by reversibly binding to the thrombin's active site, reducing the effectiveness of its active form and therefore the fibrin production [47].

In 2009, the RE-LY results were published showing the effectiveness of dabigatran in patients with AF; its bleeding complications were directly related to the dose, being lower with 110 than with 150 mg and being just a third of those that occur with the use of warfarin [48].

Its use was approved by the US Food and Drug Administration in 2010 [49] for the prevention of embolic events in patients diagnosed with non-valvular atrial fibrillation. In Canada, in the same year, it was approved for the prevention of deep vein thrombosis and pulmonary embolism after hip or knee arthroplasty and for the prevention of cerebrovascular accidents and systemic embolism in patients with non-valvular atrial fibrillation.

Dabigatran is still indicated as an alternative therapy to warfarin and is, to date, as effective as warfarin in preventing embolic events in patients with non-hemorrhagic stroke and AF.

Routine laboratory monitoring of anticoagulant response is unnecessary, but patients on anticoagulant therapy should be evaluated periodically for clinical signs of bleeding as well as their hemoglobin and creatinine levels.

The biggest adverse effect of dabigatran is of course bleeding. The incidence of bleeding episodes found in RE-LY was 2.7% with 110 mg and 3.1% with 150 mg, which was a statistically significant difference, mainly in the gastrointestinal tract with three fatalities [48].

There are few reports of the incidence of intracranial bleeding related to dabigatran in the literature, but in the subgroup analysis of the RE-LY study, the rate of intracranial bleeding was 0.2 to 0.3% per year with doses of 220 mg and 300 mg per day. The location of intracranial hemorrhages was 46% intraparenchymal hemorrhage, 45% subdural hematoma, and 8% subarachnoid hemorrhage. The intracranial bleeding rate was significantly lower compared to warfarin [50].

This drug is not indicated in patients with creatinine clearance less than 30 mL/min, however, in a meta-analysis of more than 12 thousand patients with AF, Kimachi found that there were no more complications or embolic events in patients treated with direct anticoagulants (including dabigatran) compared with those taking warfarin in the presence of chronic kidney disease [51].

The use of this drug may also be associated with interstitial nephritis [52], acute hepatitis [53], myocardial infarction [54], erosion of the esophagus walls [55] (some have recommended accompanying this drug with proton pump inhibitors), and infrequent allergic reactions [56].

So far, its use has not yet been approved in pregnancy or lactation.

In October 2015, the FDA and in 2016 Health Canada approved Idarucizumab as the first specific reversal agent for dabigatran, indicated for patients with life-threatening or uncontrolled bleeding, as well as in cases where rapid reversal is needed for urgent and emergent procedures [57].

Apixaban Rivaroxaban Edoxaban and Betrixaban

This group of drugs has the same mechanism of action that consists of the direct inhibition of Factor Xa and does not require permanent monitoring of its activity.

These drugs have been evaluated in AF patients' clinical settings and compared with traditional therapy, finding a similar incidence of embolic events and CNS bleeding episodes lower than found with warfarin [58].

Table 4 Intracranial hemorrhage with non-vitamin K antagonists

Oral anticoagulant and dose	Study	Intracranial hemorrhage %/year
Apixaban 5/2.5 mg bid	ARISTOTLE	0.33
Dabigatran 150 mg bid	RE-LY	0.30
Dabigatran 110 mg bid	RE-LY	0.23
Edoxaban 60/30 mg od	ENGAGE AF	0.39
Edoxaban 30/15 mg od	ENGAGE AF	0.26
Rivaroxaban 20 mg od	ROCKET-AF	0.57

Taken together, the reduction in bleeding complications with direct coagulation inhibitors (including dabigatran) is about 30% less than with the use of warfarin [59], however many authors have expressed mistrust of these results and recommend greater care with the use of these drugs, patient follow-up and larger-scale studies that conclusively demonstrate their superiority are still needed [49].

Table 4 summarizes the incidence of ICH with the use of the various direct anticoagulants used most frequently in clinical practice.

Rivaroxaban presents an incidence of 0.57% evaluated in the ROCKET-AF trial [60, 61] showing an efficacy similar to warfarin (not inferior) and a lower absolute number of bleeding complications.

Apixaban was evaluated in the ARISTOTLE study, in the context of patients with AF and compared with warfarin. A dose of 5 mg showed better results in the prevention of thromboembolic phenomena and a reduction in bleeding complications [62], especially in patients without diabetes. However, this study has found detractors due to its limited follow-up time (less than two years) and the noninclusion of patients with renal failure, which may have increased the number of bleeding complications associated with its use in this study [63].

Lastly, edoxaban was evaluated in the ENGAGE AF trial and showed that it was not inferior to warfarin in the prevention of abnormal embolism in FA with fewer bleeding complications associated with its use [64]. We must emphasize that this has been up today, the study that has evaluated the greatest number of patients and the one that has faced the fewest design and follow-up problems [65].

Presentation, Management, and Prognosis of Intracerebral Hemorrhage Associated with Anticoagulant Drugs

Intracerebral hemorrhage (ICH) including intraparenchymal (lobar or deep), epidural, subdural, and subarachnoid (with ventricular compromise or not), is a medical-surgical condition with high morbidity and mortality for patients who suffer from it and it is associated with the use of anticoagulant drugs in many of their cases.

As for stroke, the hemorrhagic type corresponds to 10% to 15% of all cases and is incontrovertibly associated with the use of anticoagulant drugs [66]. ICH associated with anticoagulation has been recognized as a problem associated with this therapy since its beginning in medical practice [67].

Warfarin is the cause of 9–14% of all ICH every year [68], and its incidence in patients who take it chronically is close to 2.1 per 100 patients per year [69].

Considering that the patient suffering this event might not be the most reliable source of information, all data regarding the use of the anticoagulant drug, indication for use, dose, last time taken, and other medications such as antiaggregants, NSAIDs, and aspirin should be collected from the closest and most trustful sources possible, generally relatives or caregivers, will be able to provide this information [3].

Although there is no evidence, these patients could benefit from high-flow mask oxygen, some of them will require intubation due to the compromise of consciousness and the impossibility of protecting the airway from secretions, vomit, or blood.

Supportive therapy is accompanied by judicious crystalloid infusion and intravascular volume replacement, red blood cells if necessary, and vasopressor and inotropic drugs in the event of hypotension and refractory shock.

The administration of red blood cells in the neurocritical patient is still a controversial issue and there is no consensus in this regard in cases of ICH. However, the minimum hemoglobin value between 8 and 9 g/dL is accepted for transfusion in the majority of neurosurgical or neurocritical patients [70, 71].

The administration of the anticoagulant drug should be discontinued, the heparin infusion suspended and in the event of an accidental oral overdose of any of the oral agents within the first two hours of the onset of bleeding, gastric lavage with activated charcoal could be a good alternative to reduce the absorption and plasma levels of the ingested drug [3].

Coagulation, INR, PT, PTT, or ACT tests can help direct the administration of reverse agents and verify the effectiveness of the established medical therapy; however, this would only have some utility in the case of warfarin or unfractionated heparin. The other direct anticoagulants can be evaluated with thrombin time [72], anti-Xa activity 85, or more recently recommended thromboelastography [73].

It is important to mention that the correction of the INR within 5 h of the onset of symptoms was not associated with a reduction in mortality or fewer neurological sequelae, so it is essential to initiate an early reversal and avoid the expansion of hematoma 3.

Managing blood pressure is still a controversial topic. It is accepted that a greater than Systolic Blood Pressure (SBP) > 200 mmHg is associated with a greater expansion of the hematoma and therefore greater mortality. Keeping the systolic pressure below 180 mmHg seems to be adequate, although the safe lower limit of this reduction in blood pressure is not clear [74].

Many medications have been evaluated for SBP management including nicardipine and labetalol but there is not sufficient evidence to recommend a medication on top of the others.

Performing a CT scan quickly helps us to assess the severity of the bleeding and its extent. The volume of the hematoma can be calculated in cm^3 and is generally associated with the intensity of anticoagulation [75]. Expansion of the hematoma despite medical therapy is one of the factors that is consistently associated with a worse prognosis [76, 77].

Tranexamic acid should be administered to all these patients based on the good results of this drug in other clinical settings [78] although in the case of ICH there is no evidence to recommend its use [79].

The administration of PCC is the first option in the reversal of anticoagulation caused by warfarin. The effectiveness of this treatment has been demonstrated in numerous studies, both retro and prospective, [80, 81] and it is the only one that rapidly reverses the effects of this drug compared to other options.

The administration of vitamin K is recommended intravenously from 5 to 15 mg in 30 min together with PCC or, in the PCC absence, using FFP for reversal of anticoagulation [36].

Heparin and LMWH can be reversed with the use of protamine, with a greater effect and predictability for the unfractionated molecular form. Protamine should be administered at a ratio of 1 mg per 100 units of heparin and should be done with caution in patients who have previously received the drug [82].

Idarucizumab is the specific reversal agent for dabigatran [57]. Its administration produces a rapid reversal of the anticoagulant effect of this drug. In the absence of this agent, PCC and/or FFP must be used.

Andexanet is the FDA approved reversal agent for the specific reversal of apixaban and rivaroxaban. It is expected to be approved soon for edoxaban, fondaparinux, and LMWH. The reversal of the anticoagulant effect is quick and effective in most patients, although unfortunately, like the rest of the reversal agents, it increases the probabilities of thrombotic events, therefore planning the reinitiating of anticoagulant therapy, especially in high-risk patients should be considered early within the comprehensive management that these patients should receive [83].

Surgical evacuation of a hematoma in cases of ICH should be performed when the patient has been reversed and does not present obvious coagulation problems as recommended by current guidelines [84].

At last, the cost related to these new medications including those used for anticoagulation and their specific reversal agents is quite high. Warfarin is so far, the cheapest option that we still have to manage anticoagulation in the general population and reduce the embolic events incidence in high-risk populations such as AF patients.

Conclusions

Anticoagulation is necessary and required for patients at high risk of thrombotic events, especially those with AF. Although frequent, the bleeding episodes related to this therapy are usually mild. Some patients, unfortunately, will present with serious complications including intracerebral hemorrhage.

The management of this complication must be rapid and focused on the specific reversal of the agent involved in this problem and although warfarin is still the most widely used agent, new drugs with the same effectiveness and lower risk of side effects are taking their place in the current clinical practise.

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Complications Related to Blood Products

Mayank Tyagi and Charu Mahajan

Abstract

Complications related to blood products mainly present as unintended responses occurring in a patient during or after transfusion of whole blood or its components, for which no other reason can be found. These untoward effects may vary in severity from trivial to life-threatening and require rapid recognition and management. Application of evidence-based practice and hemovigilance (before and after the transfusion) has helped to decrease the complications associated with blood transfusion. This chapter highlights the clinical presentation, pathophysiology, and management of transfusion reactions that we commonly deal with during our clinical practice.

Keywords

Adverse events · Blood transfusion · Complications · Hemovigilance · Non-infectious · Reaction

Introduction

Blood transfusion is carried out with a purpose to increase the oxygen-carrying capacity of blood but may also be associated with adverse reactions. This is the reason that it should be used prudently to avoid possible undesirable complications [1]. The stringent testing modalities have decreased the incidence of infectious complications; however, noninfectious adverse transfusion reactions (NIATRs) still account for substantial morbidity and mortality [2]. The estimated incidence of acute blood transfusion reactions is 0.2–10% with a mortality of around 1 per 250,000 [3]. The World Health Organization (WHO) regularly updates information about the global status of blood transfusion services, assesses country needs and helps in formulating recommendations for improving blood safety, plans and implements activities and evaluates progress [4]. Various countries have formulated their own committees like the British Committee for Standards in Haematology (BCSH) and the American Association of Blood Banks for developing guidelines for safe blood transfusion. Hemovigilance is an essential component of blood safety system, for monitoring, identifying, reporting, investigating, and analyzing unforeseen or undesirable adverse events and reactions to prevent their occurrence and recurrence [5].

Transfusion reactions can be defined by reaction type, timing (acute or delayed), and severity.

M. Tyagi · C. Mahajan (✉)
Neuroanaesthesiology and Critical Care, All India Institute of Medical Sciences, New Delhi, Delhi, India

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Table 1 Classification of blood transfusion reactions

A. Immune-mediated transfusion reactions (TRs)	
Acute transfusion reaction	Delayed transfusion reaction
1. Acute hemolytic TR 2. 3. Allergic TR (Anaphylactic/ Urticarial) 4. Febrile non-hemolytic TR 5. Transfusion-related acute lung injury	1. Delayed hemolytic TR 2. Transfusion-associated immunomodulation 3. Transfusion-associated graft versus host disease 4. Alloimmunization 5. Post-transfusion purpura
B. Non-immune-mediated TRs	
Acute transfusion reaction	Delayed transfusion reaction
1. Transfusion-associated circulatory overload (TACO) 2. Air embolism 3. Bacterial contamination 4. Metabolic citrate toxicity 5. Hyperkalemia 6. Hypothermia	1. Iron overload 2. Transfusion-related sepsis

The acute and delayed adverse reactions are further categorized according to their etiology into immune-mediated and non-immune-mediated subtypes (summarized in Table 1). These include hemolytic, non-hemolytic, allergic, infectious, transfusion-related acute lung injury and circulatory overload reactions.

Hemolytic Transfusion Reactions

The hemolytic reactions can be acute (occurring within 24 h) or delayed (after 24 h till 30 days post-transfusion). Acute, immune hemolytic transfusions reactions occur due to incompatibility of the donor's red blood cell antigens with the recipient's preformed antibodies resulting in immediate destruction of the transfused red cell and initiation of the inflammatory cascade. Clinical symptoms become apparent within minutes of commencing transfusion and include fever, rigor/chills, nausea/vomiting, chest/abdominal pain, dyspnea, hypotension, oliguria/anuria, and diffuse bleeding. Common laboratory findings include decreased hemoglobin, hemoglobinaemia, reduced serum haptoglobin, hemoglobinuria, unconjugated hyperbilirubinemia, elevated serum glutamic-oxaloacetic transaminase and Lactate dehydrogenase levels [6]. Transfusion of ABO mismatch platelets or plasma can rarely results in lysis of the recipients' red blood cells, especially if transfused plasma has a high titre of ABO antibodies. Patients may develop even disseminated intravascular coagulation (DIC) and renal failure after the initial acute reaction. Risk of mortality increases in direct proportion to the volume of incompatible blood transfused and occurs at approximately one in 1.8 million units transfused with an estimated prevalence of approximately one in 70,000 per unit transfused [7, 8].

Delayed hemolytic transfusion reactions (DHTRs) occur 3–10 days after the transfusion. It is apparently caused by antibody-mediated removal of recently transfused RBCs due to an amnestic immune response generated from antibodies against an incompatible minor red blood cell antigen (Rh, Kidd, Duffy, Kell, MNS) to which the patient had been exposed to, in the past. The estimated incidence of DHTRs is about 1 in 6000 units transfused [9]. Clinical symptoms and laboratory findings may occur days to weeks (up to 28 days) after a transfusion. Acute renal failure, hemoglobinuria, and DIC are rare manifestations as hemolysis is primarily extravascular [10]. Sometimes recipient demonstrates new antibodies against red blood cells after transfusion without exhibiting any clinical or laboratory evidence of hemolysis; this is known as delayed serologic transfusion reaction (DSTR) [11]. Patients with a history of clinically significant red blood cells alloantibodies should receive crossmatch compatible, antigen-negative RBC to decrease the risk of development of DHTRs or DSTRs. Recognition and management of acute transfusion reactions have been summarized in Tables 2 and 3 [12].

Non-immune Hemolytic Reactions

Red cell destruction may occur by co-administering hypertonic or hypotonic solutions, concurrent administration or mixing of drugs, temperature-induced (improper storage temperature, or improper warming of blood mechanical-related causes (as in cardiopulmonary bypass pumps), physically (using inappropriate small bore size needle, use of rapid pressure infuser) or chemically induced transfusion reactions (hyperkalemia, hypothermia, diminution, or dilution of coagulation factors). Management regimen includes immediate cessation of transfusion, maintenance of hemodynamics and renal output and to induce diuresis by administration of diuretics along with intravenous fluids.

Table 2 Transfusion reaction categories and manifestations

Category	Symptoms for recognition
Category 1 (Mild reaction)	Localized dermal reactions, rash, urticaria, pruritus
Category 2 (Moderately severe)	Flushing, rigors, urticaria, restlessness, anxiety, headache, fever, tachycardia, palpitations, pruritus, mild dyspnea
Category 3 (Life-threatening)	Fever, rigors, restlessness, anxiety, fall of ≥20% in systolic BP, rise of ≥20% in heart rate, dyspnea, chest pain, respiratory distress, hemoglobinuria, unexplained bleeding (DIC), loin/back pain, pain near the infusion site

Febrile Non-hemolytic Transfusion Reactions

Febrile non-hemolytic transfusion reactions (FNHTRs) are defined as a rise in temperature of at least >1 °C or 2 °F from baseline during or shortly after transfusion, often associated with chills and rigors. The presence of chills and rig-

Table 3 Guidelines for managing acute transfusion reactions[a]

Category	Management plan
Category 1	Immediately decrease the transfusion rate Check and monitor vital signs (HR, BP, UO, oxygen saturation) Order antihistamines IM (e.g., chlorpheniramine 0.1 mg/kg) Treat as category 2: If within 30 min, no clinical improvement occurs or if signs and symptoms worsen
Category 2	Action: Stop the transfusion immediately Check and monitor vital signs Recheck identification of patient and blood bag Do not flush the existing line and use a new IV line if required Notify your Medical Officer and Hospital Transfusion Service Investigation: Send freshly collected blood and urine sample (from vein opposite infusion site) along with blood pack and infusion set Send Reaction form/Grouping/Antibody screen/Compatibility testing to transfusion lab Send investigations (ABG, CBC, renal and liver function, direct antiglobulin test) Send (LDH, bilirubin, haptoglobin, blood culture, coagulation screening, urine analysis) in case of an acute hemolytic transfusion reaction or bacterial contamination Management: Administer antihistamine and antipyretic Avoid aspirin if patient has thrombocytopenia In case of anaphylactoid features, administer IV corticosteroids and bronchodilators If clinical status improves, restart transfusion slowly with a fresh blood unit and observe carefully If no clinical improvement observed within 15 min or if signs and symptoms worsen, treat as category 3

(continued)

Table 3 (continued)

Category	Management plan
Category 3	Action: Same as category 2 Call for immediate medical help Initiate resuscitation-ABC Investigation (same as category 2) Management: Maintain airway and supplement high flow oxygen by mask Hemodynamic support: Infuse normal saline 0.9% (initially 20–30 mL/kg) to maintain SBP. If hypotensive, give over 5 min along with legs raised Administer adrenaline (1:1000 solution) 0.01 mg/kg, slow IM injection Administer IV corticosteroids and bronchodilators (in case of anaphylactoid features) Administer frusemide 1 mg/kg IV Analyze for abnormal bleeding from puncture sites or wounds: In case of clinical or laboratory evidence of DIC: administer blood products (use virally-inactivated plasma coagulation products) Urine analysis (red/pink urine) for signs of hemoglobinuria Strict intake and output charting Maintain proper fluid balance Re-evaluate. If hypotensive- • Administer normal saline 20–30 mL/kg over 5 min • Start inotrope support If laboratory evidence of acute renal failure (rising potassium, urea, creatinine) or falling urine output: • Preserve fluid balance • Give furosemide • Consider infusion of dopamine, • Seek expert help: The patient may require renal dialysis If suspicion of bacteremia (fever, rigors, collapse, no evidence of a hemolytic reaction), start with broad-spectrum antibiotics

HR: Heart rate; BP: Blood pressure; UO: Urine output; DIC: Disseminated intravascular coagulation; IM: Intramuscular; ABC: Airway, breathing, circulation; ABG: Arterial blood gas; CBC: Complete blood count; LDH: Lactate dehydrogenase; IV: Intravenous, SBP: Systolic blood pressure

[a] Adapted from WHO guidelines use of blood in surgery and anesthesia [12]

ors in absence of fever is called as an "atypical" or "afebrile" FNHTR. FNHTRs are commonly seen after platelet transfusion, with a higher incidence in patients with prior history of multiple transfusions.

Storage of blood products stored at room temperature results in the generation of pro-inflammatory substances like cytokines from the white cells which, contaminate red blood cells, and platelet concentrates and are implicated in the development of FNHTRs [13]. Treatment of FNHTRs is usually symptomatic. Routine use of premedications (acetaminophen) is unnecessary and should only be administered in neutropenic patients and in those with a history of clinically significant FNHTRs. Leucoreduction (LR) is a procedure of removing and filtering white blood cells from a blood product before transfusion and has been shown to minimize the risk of FNHTRs. LR also prevent transmission of leucotropic virus (CMV and EBV), minimizes the risk of platelet refractoriness and HLA-alloimmunization in multiple times transfused patients [14]. Prestorage leucoreduction of red cells with help of special (polyurethane) filters is more effective than bedside leucoreduction. Other causes such as septic transfusion reactions, acute hemolytic transfusion reactions, and some underlying diseases may present as isolated fever only [6].

Allergic Transfusion Reaction

Most of the allergic reactions manifest within seconds or minutes of starting transfusion but at times, may appear several hours later. The sever-

ity may vary from a single lesion to extensive urticaria along with edema and pruritis. It may be associated with nausea, vomiting, mild upper respiratory symptoms, or abdominal cramps. Allergic transfusion reactions complicate 1–3% of all transfusions. Urticaria (hives) is considered the mildest form of an allergic reaction attributed to hypersensitivity (recipient IgE antibody) to a foreign plasma protein in the donor product. As soon as an allergic reaction is suspected, transfusion should be discontinued immediately. Intravenous hydrocortisone 5 mg/kg (maximum of 200 mg) can be used as an adjuvant. For the prevention or treatment of allergic reactions, first-generation antihistamines (diphenhydramine)counteract smooth muscle and vascular-related symptoms. However, there is no evidence that long-acting second-generation antihistamine (cetirizine) premedication prevents allergic reactions, although they do reduce the severity if they occur. In case of mild urticarial reaction, transfusion may be resumed with observation, once clinical manifestations subside and the patient feels well. Severe allergic reactions may be associated with the development of angioedema [8, 15].

Systemic immediate hypersensitivity reaction (anaphylaxis) can also occur with severe hypotension, cough, bronchospasm, severe hypotension, cough, bronchospasm and loss of consciousness, and are relatively rare with an incidence of about 1:20,000–1:50,000 transfusions [8]. Severely IgA deficient (<0.05 mg/dL) patients who have antibodies against donor IgA may develop moderate to severe anaphylactic reactions. IgA/anti-IgA workup is technically challenging and is suggested to be performed only in patients with anaphylactic reactions [16]. Quantitative haptoglobin may be used as one of the screening test, as haptoglobin deficiency can also cause anaphylactic reactions [17]. Management of severe anaphylaxis (patient is unconscious or in shock) post transfusion includes administration of intramuscular adrenaline injection (1:1000). However, in a hospital setting and in patients having pre-existing intravenous access, bolus of intravenous adrenaline (20–40 mcg) followed by an infusion titrated to blood pressure is beneficial. This should be accompanied by close hemodynamics and cardiac monitoring [18]. Steroids for the prevention of biphasic response and antihistamines may be used as adjuvants. In known IgA-deficient patients, prevention of subsequent anaphylactic reactions involves transfusion of IgA-free plasma washed blood products.

Acute Hypotensive Transfusion Reaction

It is a severe but, less recognized reaction predominantly manifesting as an abrupt decrease in systolic blood pressure of ≥30 mmHg or to below 80 mmHg, in absence of other causes of hypotension [6]. It resolves quickly once transfusion is stopped and responds well to supportive treatment. The pathogenesis appears to be related to the disturbances in the metabolism and production of bradykinin in plasma that is incited by the negatively charged surface such as blood filters used for LR. Angiotensin-converting enzyme inhibitors delay the bradykinin breakdown, thereby prolonging its effect and increasing the severity of reactions [6, 19]. For prevention of hypotensive transfusion reactions, it is recommended to use prestorage LR blood products rather than bedside filtration [20].

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is a potentially lethal complication of blood product transfusion and accounts for a significant number of all transfusion-related deaths [21]. All plasma-containing components (whole blood, RBCs, platelets, fresh frozen plasma and cryoprecipitate) have been involved in TRALI. The estimated occurrence of TRALI is approximately 0.81 per 10,000 transfused blood components

[22]. It is mainly a clinical diagnosis, and laboratory investigations may be used to only support the diagnosis. TRALI is of two types [23]:

TRALI Type I:

a. Criteria:
   i. Acute onset
   ii. PaO2/FiO2 ≤ 300 or SpO2 < 90%
   iii. Bilateral pulmonary edema evident on, chest radiograph, or CT, or ultrasound
   iv. No evidence of left atrial hypertrophy
b. Onset during or within 6 h of transfusion
c. No temporal relationship to major ARDS risk factor
d. New-onset ALI after transfusion

TRALI Type II

Patients having risk factors for ARDS or with mild ARDS (PaO2/FiO2 of 200–300), but whose respiratory status deteriorates (based on clinical judgement along with other respiratory parameters and PaO2/FiO2 deterioration) and is judged due to transfusion based on:

i. Findings as described in categories a, b, and d of TRALI Type I, and
ii. Stable respiratory status 12 h prior to transfusion

The lung injury mostly lasts for a brief period, and majority of affected patients gradually recover within 2–4 days, once the transfusion is stopped [8]. Patients develop non-cardiogenic edema and it does not improve by diuretic therapy.

Two different pathophysiologic mechanisms have been proposed: the antibody hypothesis and the neutrophil priming hypothesis [21, 24]. Both mechanisms result in pulmonary edema despite absence of circulatory overload. In the antibody hypothesis, passive transfusion of anti-leucocyte antibodies in plasma-containing blood components reacts with neutrophil antigens in the recipient [21]. This triggers the recipient's neutrophils resulting in capillary leakage of intracellular mediators which eventually causes pulmonary edema. Patients having an underlying infection, shock or surgical stress are prone to endothelial activation and neutrophil priming. In the neutrophil priming hypothesis, transfusion of plasma containing components, the primed neutrophils are activated resulting in pulmonary endothelial damage, capillary leakage, and pulmonary edema [21].

With symptomatic respiratory support, patients may improve within 2–4 days [25]. Practice of evidence-based transfusion guidelines may reduce needless transfusions and related morbidity. Moreover, several transfusion medicine professionals and the American Association of Blood Banks TRALI working group recommend temporary disqualifying donors known to be at risk for HLA alloimmunization. As anti-neutrophil and anti-HLA antibodies are more prevalent in females than in male donors, the removal of multiparous female donors from plasma donation has resulted in a decrease in the incidence of TRALI [26]. However, only plasma-rich products and not RBC transfusions from female donors is implicated in the development of TRALI. Washing of cellular components helps remove antibodies and lipids from the transfused plasma containing component. Transfusing blood for <14 days and platelet concentrates for <2 days may obviate several unwanted effects.

Management of TRALI

To minimize the risk of complication, early recognition and rapid clinical assessment is essential. Treatment is mainly immediate discontinuation of transfusion and treatment of complications with specific supportive measures. Effective steps for reducing the incidence include the employment of mainly male donor plasma and apheresis platelets [10]. Diuretics are not indicated in the absence of signs of cardiogenic pulmonary edema or acute volume overload. There is no existing evidence pertaining to the effectiveness of corticosteroids or antihistamines. A better understanding of the blood components and patient risk factor is essential for novel treatment and preventive strategies. TRALI manage-

ment primarily involves averting adverse reactions during future transfusions [27]. Early reporting to the National Blood Bank (in whom TRALI is suspected) for a serological workup of the recipient and the involved donors for the presence of HLA and HNA antibodies should be done. Incompatibility is assessed by cross-matching donor plasma against the recipient's leucocytes. Rigorous donor selection should be consistently applied with an aim to exclude further donations of blood from a donor with antibodies that are incompatible with the patient.

Transfusion-Associated Circulatory Overload

Transfusion-associated circulatory overload (TACO) is a vastly underreported complication resulting from hydrostatic transudate accumulation in the lungs [6]. It includes any four of the following features occurring within 6 h of blood transfusion. These include tachycardia, increased blood pressure, acute respiratory distress, acute or worsening pulmonary edema and evidence of a positive fluid balance [28, 29]. Patients with compromised cardiopulmonary status who are unable to tolerate acute blood volume expansion are considered to be at the highest risk of TACO, particularly elderly patients, infants, patients with renal failure, patients having hypoalbuminemia, anemia, fluid overload or congestive heart failure [28]. It is seen in <1% of transfused patients. The absence of hemoglobinemia, hemoglobinuria and the absence of a positive post-transfusion direct antiglobulin test (DAT) distinguish it from that caused by immune hemolysis. Similarly, the absence of fever, chills, or urticaria helps to differentiate it from the febrile/allergic reactions [6]. Blood should be infused slowly unless there is a life-threatening shock or severe hemorrhage. It is managed by stopping the transfusion immediately, placing the patient in a head-up position, and treating symptomatically with oxygen inhalation, fluid restriction and diuretics Mechanical ventilation and appropriate treatment in the intensive care unit (ICU) may be required in serious cases.

Transfusion-Related Sepsis

Transfusion-related sepsis is uncommon, but at times, can lead to serious sequelae or even be fatal. Bacterial contamination of stored blood poses a serious threat to the recipient. Bacteria contamination may occur during blood collection, component preparation or due to occult bacteremia in the blood donor. Platelet-related sepsis is more common than RBCs as they are stored at room temperature, and risk of contamination is most significant with pooled platelet when compared to apheresis units (single donor platelet). Single donor platelet (SDP) also outperforms platelet concentrate by limiting the risk of transfusion reactions and reduced the rate of alloimmunization [30]. Hence, the shelf life of stored platelets should not exceed 5 days. The diagnosis is rested on the occurrence of at least one of the following clinical features: (1) temperature ≥39 °C or rise of ≥2 °C; (2) heart rate >120/min, or an increase of >40/min; (3) chills and (4) greater than 30 mmHg increase or decrease in systolic BP within 90 min of transfusion [31]. Severe cases may advance to shock with consequent disseminated intravascular coagulation (DIC) and renal failure. Blood transfusion should be stopped immediately after a reaction is suspected. Blood samples should be sent immediately to the blood bank for bacterial culture/gram stain. Samples for testing of DAT and hemolysis should also be sent. Other steps of management include the use of broad-spectrum antibiotics and hemodynamic support along with other standard care for sepsis. Risk reduction strategies involve screening of platelet units for bacterial contamination, culture at the blood collection site before product release, and adopting "diversion technique" during blood collection [32]. Multiple studies have documented a substantial reduction in bacterial contamination by diversion technique which involves diverting an initial 15–30 mL of whole blood that is contaminated by the donor's skin commensals into another pouch away from the blood collected in the main container [33, 34].

Transfusion-Associated Immunomodulation

Transfusion-associated immunomodulation (TRIM) is defined as a recipient's cellular immunosuppressive response caused by the transfusion of "by-products" contained in the allogenic stored blood [35]. These "by-products" comprise elements of the storage solution such as adenosine and by-products of the stored RBCs such as oxidized lipids, lactate, hemoglobin, heme, and "free" iron) [35]. The deleterious effects are increased risk of postoperative bacterial infections, activation of latent viral infection, tumor recurrence and death due to cancer recurrence. TRIM has also been associated with changes in immune functions such as decreased natural killer cell activity, reduced helper to suppressor T-lymphocyte ratio, defective antigen presentation, decrease in cell-mediated immunity and macrophage function [10, 36]. The use of prestorage leucofiltered blood or autologous blood can attenuate the adverse effects of TRIM.

Metabolic and Hemostatic Derangement

Acute hemostatic and metabolic abnormalities may occur during a massive blood transfusion. The common changes observed in massive transfusion include circulatory overload, hypothermia, dilutional coagulopathy, hyperkalemia, deranged liver and platelet function, hypoglycemia, and rarely, citrate-induced transient hypocalcemia and hypomagnesemia. Viscoelastic hemostasis assays such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are the point of care tests for evaluating coagulation status and blood component requirement.

Citrate toxicity is a frequent complication after massive blood transfusion usually evident in patients with liver failure and/or severe hypothermia, where citrate metabolism is reduced. Stored blood components containing citrate binds to calcium ions resulting in clinically significant hypocalcemia in these patients. This can usually be addressed by reducing the infusion rate. Calcium replacement protocols vary in the literature but are indicated to avoid dangerous decrease in levels of ionized calcium, particularly in those with severe liver disease [37]. Transfusion of four units of PRBC and FFP are associated with severe hypocalcemia [38].

Potassium levels may reach about 50 meq/L in a single RBC unit stored for around 42 days due to leakage of potassium into the supernatant and a decrease in ATP production. Thus, blood transfusion, especially of old blood, can lead to potential complications of hyperkalemia. High potassium level (>5 mEq/L) or ≥1.5 mEq/L net increase within an hour of transfusion is categorized as transfusion-associated hyperkalemia [1, 39].

Patients suffering massive hemorrhage may have coagulation disorders related to trauma-induced coagulopathy or due to infusion of a large amount of fluids and blood products [40]. Bleeding subsequent to massive transfusion can occur due to dilutional coagulopathy, hypothermia, fibrinolysis, platelet dysfunction, consumptive coagulopathy, and hypofibrinogenemia [41].

Infusing large volume of inadequately warmed blood and blood products decreases the core temperature and may cause hypothermia. This exposes the patients to adverse effects like dysrhythmias, decreased cardiac output, platelet dysfunction, decreased coagulation kinetics, hypothermic coagulopathy, increased insulin resistance and increased systemic vascular resistance [40, 42]. Blood warmers may be used to check hypothermia. Approved blood warming device should be used to avoid thermal damage to blood cells and proteins.

Air Embolism

Air embolism is a rare, serious complication associated with rapid infusion of blood using pressurized devices. Caution should be taken to avoid air entrainment while infusing a large volume of warmed blood. Similarly, pressurized infusion of blood from cell saver should be discouraged as it contains significant amount of air which is difficult to remove [40, 43].

Alloimmunization

Red blood cell (RBC) alloimmunization is an immune response against antigen-positive red cells; this usually occurs after sensitization due to previous blood transfusions, organ transplantation or feto-maternal hemorrhage during pregnancy. The prerequisite for the development of alloimmunization is exposure to the donor erythrocyte antigens that are not present in the recipient; these antigens initiate the formation of antibodies against erythrocytes resulting in potentially serious transfusion reactions. The incidence increases in transfusion-dependent patients, such as with sickle cell disease (9–30%) and severe thalassemia syndromes (9%) [44]. Acute, life-threatening anemia can occur in some thalassemia and sickle cell patients when they are transfused multiple times [45]. The alloimmune-mediated platelet transfusion refractoriness is majorly observed in patients with a history of multiple transfusions, multiparity, or who have received non-leucocyte depleted transfusion which can produce alloantibodies to HLA antigen [10, 46]. The risk of bleeding in such patients can be reduced by transfusion with HLA/HPA-matched platelets [47].

Post-transfusion Purpura

Post-transfusion purpura (PTP) is a relatively rare, yet serious complication characterized by thrombocytopenia happening 5 to 10 days after transfusion, in patients who lack a specific human platelet antigen (HPA). Although alloantibodies directed against HPA-1a is the main etiology; antibodies directed to other platelet-specific antigens (HPA-1b) are also involved. These patients have a history of sensitization with previous transfusions, transplants, or pregnancies. About 85% of cases occur in females. Differentiating between Heparin-induced thrombocytopenia (HIT) and PTP can be challenging due to similar clinical presentations. Severe thrombocytopenia (platelet counts often <10,000/μL) is a common feature in PTP (counts <20,000/μL rarely seen in HIT) which sometimes results in significant bleeding from the urinary and gastrointestinal tract or mucous membranes whereas HIT is associated with thrombosis [48]. Thrombocytopenia is usually severe and sudden in onset and frequently resolves in two weeks. This severe thrombocytopenia can help distinguish it from heparin-induced thrombocytopenia. The predominant cause of mortality is intracranial hemorrhage. Immunomodulation remains the treatment of choice by administering intravenous immunoglobulin (0.5 mg/kg IVIG for 5 days) with or without corticosteroids. The use of plasma exchange for PTP treatment is controversial [49].

Transfusion-Associated Graft Versus Host Disease

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare, complication wherein donor lymphocytes mount an immunodestructive response against the immunocompromised transfusion recipient [1]. It is defined as a clinical syndrome occurring 2 days to 6 weeks post-transfusion characterized by fever, watery diarrhea, maculopapular rash (develops centrally and spreads to extremities), liver dysfunction, pancytopenia and characteristic histological appearances on liver or skin biopsy [50]. Treatment is supportive, and the emphasis is placed on the prevention of TA-GVHD by gamma irradiation (2500 cGy per unit for 1–5 min) of lymphocyte-containing blood components (red blood cells, granulocytes, and platelets), especially in situations like congenital immunodeficiencies, HLA-matched platelet transfusion, patients receiving fludarabine therapy, granulocyte transfusions or those undergoing hematopoietic stem cell transplantation [51]. Response to therapy is poor, with an estimated mortality of 90–100%. HLA typing and other molecular studies can discern chimerism and assist in the diagnosis.

Iron Overload

Iron overload can develop among transfusion-dependent patients (sickle cell disease, hereditary hemochromatosis, thalassemia, aplastic anemia, myelodysplasia, and refractory sideroblastic anemias) receiving red blood cells over a long period. Regular transfusion (2–4 units of blood per month) in most transfusion-dependent patients may increase the iron load by 5–10 g per year (one unit of transfused red blood cells contains approximately 250 mg of iron) [10]. The body has no natural way to for removing excess iron, and the majority of it is stored in internal organs as ferritin and hemosiderin causing progressive tissue damage to the liver, heart, and endocrine organs. It may present as growth failure in children, heart failure, delayed onset of puberty, liver dysfunction, endocrine dysfunction (hypothyroidism and diabetes) and skin pigmentation if a chelating therapy is not introduced (such as deferoxamine, deferiprone, and deferasirox) [52].

Conclusion

Blood and blood component transfusions are life-saving but have an inherent risk of causing most serious adverse reactions or events. Hence, it is essential to be recognized promptly by the medical team and blood bank personnel such that suitable measures can be instituted quickly. Covering surveillance procedures through hemovigilance system and following restrictive strategy of blood transfusion may reduce unwanted transfusions. This will help improve clinical outcomes as well as avoid reactions that expose the patient to serious infectious and noninfectious risks.

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Part XII

Total Parenteral Nutrition

Basics of Total Parenteral Nutrition

Vanitha Rajagopalan and Hemanshu Prabhakar

Abstract

Nutrition is an essential requirement of all individuals for the sustenance of life. The phrase "total parenteral nutrition" (TPN) describes the delivery of nutrition entirely by the parenteral route. It has been used in clinical practice for over five decades and has revolutionized the management of the potentially life-threatening condition in both adults and children where enteral feeding is not possible for optimizing nutrition and energy status in these patients. Parenteral nutrition has evolved tremendously with mastery of concepts of human nutrition and metabolic processes which have led to safer and accessible formulations to suit specific conditions. Further, the invention of modern catheters and delivery systems along with refinement in techniques and improvements in formulation have made parenteral nutrition a safer option. This chapter will provide a basic overview of total parenteral nutrition in modern medicine.

Keywords

Parenteral nutrition · Enteral nutrition · Nutritional admixtures · Nutritional formulae Macronutrients · Micronutrients

V. Rajagopalan (✉) · H. Prabhakar
Neuroanaesthesiology and Critical Care, All India Institute of Medical Sciences, New Delhi, Delhi, India

Introduction

Parenteral nutrition (PN) is a means of supplying nourishment to the body that requires the delivery of nutrients through the intravenous route. It is also popularly known as total parenteral nutrition or TPN. Intravenous nutrition and artificial nutrition are other commonly used terms for the same. Recent years have seen a progressive increase in the early use of parenteral nutrition once again [1].

PN is only indicated when one cannot get going with the oral, or enteral route of nutrition, or it is inadequate for the continuation of the patient's nutritional needs in relation to his/her clinical status. Partial parenteral nutrition (PPN) is the simultaneous intravenous administration of nutrients together with oral or enteral nutrition for the same therapeutic goal.

The macronutrients (protein or amino acids, carbohydrate, and lipids or fats), the electrolytes, and the micronutrients (trace elements, and vitamins) and water constitute the basic elements of a standard PN regimen, carbohydrate (glucose or dextrose), and lipids being the primary energy sources.

Historical Perspective

The hypothetical concept of providing nutrition to patients using methods other than the gastrointestinal tract, by intravenously administer-

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ing nutrient substances or fluids was prescribed and tried for many decades before its victorious accomplishment [2–4]. The fulfilment of this supposedly imaginative ambition spanned over hundreds of years of elementary investigation and learning, concurrent with scores of technological evolution and prudent practices which stem from as early as the seventeenth century. The understanding of the anatomy and physiology of the circulatory system; comprehension of the biochemical character of nutrient substrates; the correlation of these active and potent substrates with microbiology, immunology, asepsis, and antisepsis; and some command of the complex interactions of food substances with metabolism, numerous pharmacologic agents, and the series of pathophysiologic processes are imperative to logical clinical studies in this demanding yet essential domain [5–15]. Though available as a practical and potent clinical adjunct for almost 50 years, it is the determined and committed research of Elman in the late 1940s that has led to the recent development of this approach of treatment [16, 17]. However, its effective clinical utilization did not transpire until the 1960s. The salient research that has been crucial to the subsequent establishment and expansion of TPN are outlined in Table 1.

Table 1 Salient epoch-making research resulting in the subsequent establishment and expansion of PN [3]

Year	Event	Investigator
1616	Discovery of the circulation of blood	Harvey
1628	First published report of circulation of blood	Harvey
1658	First intravenous injection in animals (ale, wine, and opium)	Wren
1678	Intravenous infusion of olive oil, vinegar, salts, and urine into a dog	Courten
1818	Transfusion of blood from human to human	Blundell
1870	Aseptic and antiseptic techniques for surgery in humans	Lister
1876	Subcutaneous injection of milk in humans for nutrition	Whittaker
1877	Discovery of microbes and the microbial relationship to infection	Pasteur
1887	Intravenous infusion of sucrose in humans for treatment of shock	Landerer
1891	Intravenous infusion of saline solution in humans for treatment of shock	Matas
1895	Discovery of colloid osmotic functions of plasma proteins	Starling
1896	Intravenous infusion of glucose in humans	Biedl/Kraus
1901	Discovery of first 3 of the 4 human blood groups	Landsteiner
1904	Subcutaneous injection of peptone, fat, glucose, and electrolytes in humans for parenteral nutrition	Friedrich
1905	Development of methods for analysis of urea, creatinine, and other nitrogenous fractions useful for nutritional assessment	Folin
1907	Discovery of fourth blood group and classification of 4 blood groups	Jansky
1911	Intravenous infusion of glucose postoperatively in humans for nutrition	Kausch
1912	Discovery of vitamins (vital amines) as essential nutrients	Funk
1915	Demonstration of rate of use of intravenous glucose in humans (0.85 g of glucose/kg/h)	Woodyatt/Sansum/Wilder
1920	Intravenous infusion of emulsified fat in humans	Yamakawa
1924	First continuous intravenous drip infusion of glucose in humans	Mata
1932	Transfusion of human serum in humans	Kunz
1932	Description of increased nitrogen losses in urine resulting from catabolic response to major limb trauma in animals and humans	Cuthbertson
1935	First intravenous infusion of cottonseed oil emulsions in humans	Holt
1938	Identification of the essential amino acids and their requirements in humans	Rose
1939	Demonstration of use of amino acids in hydrolyzed casein infused intravenously in humans	Elman/Weiner

Table 1 (continued)

Year	Event	Investigator
1940	Demonstration of use of crystalline amino acids infused intravenously in humans	Shohl/Blackfan/Dennis
1944	Infusion of hypertonic dextrose, insulin, and plasma protein by peripheral vein in high-risk surgical patients	Dennis
1945	Intravenous infusion of fat emulsions, dextrose, and protein hydrolysate by peripheral vein in humans	McKibbin/Hegsted/Stare
1945	Development of first polyethylene catheters for intravenous infusions in humans	Zimmermann
1946	Intravenous infusion of plasma proteins in humans with demonstration of positive nitrogen balance	Albright/Forbes/ Reifenstein
1947	First intravenous protein hydrolysate available commercially in Europe	Wretlind
1952	First description of subclavian percutaneous venipuncture to achieve rapid transfusion in severely injured war victims	Aubaniac
1959	Demonstration of optimal nonprotein calorie: nitrogen ratio as 150:1 in humans	Moore
1961	Development of first safe, standardized, and stable intravenous fat emulsion (soybean oil stabilized by egg phosphatides)	Schuberth/Wretlind
1962	Diuretics as an adjuvant in disposing of extra water used as a vehicle in parenteral nutrition	Rhoads
1965	Achievement of positive nitrogen balance by infusing high-volume nutrient solutions and diuretics by peripheral vein in humans	Rhoads et al.
1968	Normal growth and development in an infant nourished entirely by central venous total parenteral nutrition; first use of in-line intravenous filter	Dudrick/Wilmore
1968	First comprehensive technique for long-term total parenteral nutrition in humans	Dudrick/Wilmore/Vars/ Rhoads
1968	First patient supported entirely by total parenteral nutrition at home for 6 months	Dudrick/Steiger

Indications for PN

A critically ill patient with unattainable enteral feeding is the chief indication for TPN. It is also used to complement insufficient oral intake or enteral nutrition when caloric targets are not achieved and the patient is severely malnourished [18]. Effective TPN use requires the selection of correct patients, sufficient expertise with the process, and knowledge of its untoward effects. Certain indications of TPN are listed below [19, 20]:

1. New-borns with gastrointestinal anomalies (tracheoesophageal fistula, complicated meconium ileus, intestinal atresia, diaphragmatic hernia, gastroschisis, omphalocele or cloacal exostrophy, and untended pyloric stenosis)
2. Failure to thrive infants with bowel anomalies, enzyme deficiencies and chronic diarrhoea resulting in malabsorption
3. Necrotizing enterocolitis, intestinal fistulae, severe trauma, burns, postoperative infections and malignancies in children
4. Adults with short bowel syndrome resulting from gross small-bowel resection or enteric fistulae
5. Malnutrition due to high intestinal obstruction
6. Protracted ileus
7. Malabsorption syndromes
8. Functional gastrointestinal disorders
9. Hypercatabolic states
10. Patients with malignancies in whom therapy may be jeopardized by malnutrition.

Contraindications for PN

TPN when not indicated is contraindicated. Definite contraindications to TPN include:

1. Where enteral feeding is possible as it is the best route to provide nutrition to the patient [21].
2. Short-term TPN support in patients with adequate nutrition
3. Patients lacking a specific therapeutic goal [22]
4. Severe cardiovascular instability or metabolic derangements
5. Infants with less than 8 cm of small bowel

Decisions and Considerations to Start PN

Considering the patient's condition, the decision to start parenteral nutrition depends on how long the patient has been or is likely to be unable to maintain adequate enteral nutrition and whether this period can be managed without parenteral nutrition. The lack of a functioning gastrointestinal tract for more than about a week has conventionally been the main indication for switching from clear intravenous fluid regimens to parenteral nutrition. This is an important decision and must not be rushed or taken lightly.

Prior to the institution of TPN, the patient's nutritional status must be assessed in order to plan the treatment and to work out precise therapeutic endpoints [19]. If appropriate then PN should be initiated without delay and before malnutrition worsens. The initiation of PN is a collective decision of the nutrition team comprising of a doctor, a specialist nurse, a pharmacist and a dietician.

Nutritional Assessment

Traditional methods of nutritional assessment include clinical history, anthropometry, biochemical and immunological criteria. Antecedent illness, ≥10% weight loss, debility and fluid retention are important points to be noted in history and examination [23]. Triceps skinfold thickness is the most important indicator for nutritional assessment apart from other clear-cut signs of malnutrition, while height-weight ratio and total body surface area are the other commonly used anthropometric measures. Biochemical parameters (serum albumin and transferrin levels), immunological status (total lymphocytic count) and visceral reserves (retinol-binding protein and thyroxin-binding globulin) are also evaluated. A combination of these parameters may be used for prognostication of morbidity, mortality or survival. The Prognostic Nutritional Index (PNI) is useful in predicting the risk of septic complications and death:

$$\mathrm{PNI}(\%) = 158 - 16.6(\mathrm{ALB}) - 0.78(\mathrm{TSF}) - 0.20(\mathrm{TFN}) - 5.8(\mathrm{DH})$$

where ALB is the serum albumin in gm/dL, TSF is triceps fold thickness in mm, TFN is serum transferrin level in mg/dl., and DH is delayed cutaneous hypersensitivity.

A PNI ≤ 40% is associated with low rates of complication and death in critically ill patients, while a PNI ≥ 50% is associated with about 33% mortality [24].

When devising the parenteral nutrition regimen, the following points have to be taken into consideration:

i. Fluid volume
ii. Energy requirement
iii. Nitrogen requirement
iv. Proportion of macronutrients (fat, protein, and carbohydrate)
v. Type of intravenous access available—central vs peripheral
vi. Suitability of standard regimen as therapy
vii. Electrolyte and trace elements requirement

Fluid Volume

The fluid volume required by the patient and that which can be safely tolerated must be considered while devising the PN regimen. In the absence of any other intravenous fluid intake, around 2–3 L of fluids per day would be adequate for most adult patients. But most patients may be receiving other fluids in the form of intravenous antibi-

otic infusions, blood and blood products. Some patients with heart and renal failure may require fluid restriction while some others with burns, diarrhoea and vomiting, and intestinal fistulae and stoma may require excessively higher fluid intake. These volumes must be considered when calculating the PN regimen volume.

Energy Requirement

The total energy requirement of a patient is calculated considering the age, gender, height, weight and clinical condition of the patient. The recommendations for adults are total of 25–35 kcal/kg/day from parenteral nutrition [25]. Energy requirements are calculated to ensure appropriate energy intake and avoid both over and underfeeding [26]. Indirect calorimetry is the gold standard for the assessment of resting energy expenditure but is limited in use due to restricted availability and technical issues involved. Hence, Harris–Benedict equation or Long's Modification of it is used to calculate energy requirements [27]. Table 2 shows the formulae for energy requirement calculation.

Multiplying the patient's weight by kilocalories is the simplest way to calculate the energy requirements. A modified approach can be used in obese (decrease of kcal per kg) or severely malnourished (increase of kcal per kg) patients (Table 2).

Table 2 Energy requirement calculation

Indirect Calorimetry and Energy expenditure calculation
EE(kcal) = 3.9VO2(L) − 1.1VCO2(L) − 2.17 urinary nitrogen (g)
Weir equation used to calculate
REE = (3.94 × VO2) + (1.1 × VCO2)
EE = energy expenditure, NM = nitrogen excretion, REE = resting energy expenditure, RQ = respiratory quotient, VCO2 = carbon dioxide production, VO2 = oxygen consumption
Harris–Benedict Equation for calculation of resting energy expenditure
In males:
HB = (66.5) + (13.7 × W) + (5 × H) – (6.8 × A)
In females:
HB = (65.5) + (9.6 × W) + (1.8 × H) – (4.7 × A)
HB = Basal metabolic rate, W = weight in kg, H = height in cm, A = Age in years
Caloric Requirement Calculation
Basal energy requirement is the ramification of the individual's
• weight
• age
• gender
• activity level
• disease process
The components of energy output are
• major—resting energy expenditure, physical activity
• minor—energy cost of metabolizing food, shivering thermogenesis
Total energy expenditure (TEE) = resting energy expenditure (70% of TEE) + thermic effect of food (10% of TEE) + energy expenditure of physical activity (20% of TEE)
Average energy intake is about 2600 kcal/d for men and 1900 kcal/d for females, though these estimates vary with body size and activity level
For males, REE = 900 + 10m, and for females, REE = 700 + 7m, where m is mass in kilograms
Calculated REE is the adjusted for physical activity level (multiplying by 1.2 for sedentary, 1.4 for moderately active and 1.8 for very active)
TEE = REE + Stress Factor + Activity Factor
Rest Energy Expenditure
• Adults (18–65) 20–30 kcal/kg
• Elderly (65+) 25 kcal/kg
• Burns Patients 30–35 kcal/kg
• Other factors: Pregnancy: Add 300 kcal/day; Lactation: Add 500 kcal/day; Obese or Super obese 15–20 kcal/kg
Stress Factor
• Peritonitis + 15%
• Soft tissue trauma + 15%
• Fracture + 20%
• Fever (per °C rise) + 13%
• Moderate infection + 20%
• Severe infection + 40%
• <20% BSA Burns + 50%
• 20–40% BSA Burns + 80%
• >40% BSA Burns + 100%

BMI (kg/m^2)	Energy requirement (kcal/kg/d)[a]
15	35–40
15–19	30–35
20–24	20–25
25–29	15–20
30 and >30	<15

[a] These values are recommended for critically ill pts and obese pts; add 20% of total calories in estimating energy requirement in non-critically ill pts

Patients should be underfed initially to avoid metabolic complications due to PN, especially if they are malnourished or in acute physiological stress due to illness. High-risk patients may have to be started on as low as 10 kcal/kg/day and increasing slowly over several days till their full needs can be met.

Dextrose: Dextrose is the major carbohydrate and primary source of calories. It is readily available, inexpensive and can be administered with commercially available solutions. It is available in concentrations range from 5% to 70% [28]. Only a part of energy needed of the patient is supplied in the form of dextrose to avoid complications like hyperglycaemia, hypercapnia, fatty liver and acidosis. Insulin resistance should be considered during critical illness and Insulin should be given to maintain normoglycemia.

Lipids: Similar to normal nutrition intake, lipids should provide 25–40% of the total energy requirement. In patients with respiratory failure and good fat tolerance up to 50% of total energy can be given as lipid emulsion. Some centres restrict fat intake to 15–20% of total energy in order to cover the daily requirement for essential fatty acids (EFA) due to higher cost of lipid emulsion. In order to avoid EFA deficiency, at least 4% of calories should be in the form of lipids.

Lipids in parenteral nutrition solutions are an oil-in-water emulsion, containing a mixture of egg phospholipids (emulsifier), water, and safflower or soybean oil (polyunsaturated fatty acids source). Glycerol may also be added to the solution. Lipid emulsions conventionally use widely are long-chain triglycerides (LCT). Recently, a mixture of medium-chain triglycerides (MCT) and LCT has been developed as these are less likely to derange liver functions. The MCT/LCT containing fat emulsions supply only half the EFA compared to same volume and concentration of LCT emulsion. In critically ill patients and those with marked hypertriglyceridemia, considering impaired lipid utilization, the intake of lipid emulsion should be modified.

Proteins: Protein requirements are calculated based on the patient's body weight and his/her clinical condition. The minimum recommendation for a healthy adult is about 0.8–1 g/kg/day, with higher amounts being recommended in severe catabolic states, extensive protein loss or severe malnutrition. In patients with renal failure or hepatic insufficiency, the protein intake needs to be modified.

Amino acids are the source of protein in parenteral nutrition formulas, with standard solutions containing approximately 40% essential and 60% nonessential amino acids [29]. Patients with renal failure benefit from more concentrated amino acid preparations. Solutions with higher concentrations of branch-chained amino acids (BCAA) may be required for patients with end-stage liver disease [30].

Amino acid solutions of discrete concentrations (5–15%) and composition are available commercially. Amino acid solutions commonly used in adults contain a mixture of all the essential amino acids and the solutions with a complete amino acid spectrum are preferred. Electrolytes containing amino acid solutions are also available and their electrolyte content must be considered for the calculation of daily allowance.

The proteins can be used effectively only when sufficient non-protein energy is provided. The majority of stable patients require 100–150 kcal: 1 g nitrogen.

Electrolytes: The amount of carbohydrates present in the parenteral nutrition solution determine the need for electrolytes like magnesium, phosphorus, and potassium; whose need increases directly as the amount of carbohydrates increases [31]. Standard solutions contain chloride, calcium, potassium, phosphorus, and magnesium. The patient's diagnosis and metabolic requirements also influence the types and amounts of electrolytes added to the solution. For example, additional chloride may be required in patients with high gastric output, and reduction in magnesium, phosphorus, and potassium may be needed in patients with renal failure.

Recommended dietary allowance (RDA) of sodium are 1–2 mEq/kg; potassium 1–2 mEq/kg; chloride 1.5–2 mEq/kg; calcium 0.2 mEq/kg, phosphate 20–40 mmol and magnesium 0.35–0.45 mEq/kg.

Micronutrients: Trace elements and vitamins mixtures formulated to meet the basic daily

requirement are available. However, these multivitamins preparations may be insufficient in some patients, who may require higher dosage or additional single vitamins supplements. Trace element admixtures must be provided in some clinical situation (e.g., burn patients or patients with GI fistulas). The dosage must be further modified as per changes in excretion; e.g., in obstructive jaundice or renal failure.

Zinc 5 mg, copper 1 mg, chromium 10 mcg, manganese 0.5 mg, iron 1–2 mg, iodine 75 mcg and selenium 0.5–1 mcg/kg of protein are required daily. Vit K 10 mg and folic acid 5 mg should be administered once a week. Water-soluble vitamins should be given daily.

Proportion of Macronutrients (Fat, Protein and Carbohydrate)

TPN formulation without lipid (2-in-1 solution) should have 20–25% calories from amino acids and the remaining 70–80% from dextrose. The formulation with lipid (3-in-1 solution) should have 20–25% calories from amino acids, 15–40% from lipids and 35–50% from dextrose. Practically, it is started with 25 kcal/kg/day with 20% protein, 30% fats and 50% carbohydrates, where proteins and carbohydrates produce 4 kcal/g and fats provide 9 kcal/g.

Type of Intravenous Access Available—Central Versus Peripheral

The site for administration of PN, the available vascular access, and the duration of therapy will determine the choice of PN solution. The duration of therapy (short term versus long term), helps in deciding which type of vascular access device to use. Certain considerations to be taken into account prior to intravenous access include:

- Patient's activity level
- Vascular access device care that can be provided by patient or caregiver
- Concerns regarding body image
- Need for additional therapies
- Past history of vascular access devices

The accurate placement and utilization of vascular access are essential components of PN. Commonly used intravenous access sites for PN are:

- Internal jugular vein
- Subclavian vein
- Cephalic vein
- Basilic vein

via

- Peripherally inserted central catheter (PICC)
- Tunnelled central venous catheter
- Subcutaneous port

Choices for vascular access include tunnelled vascular access devices (VADs) with an anchoring cuff, implantable ports, and PICC [32]. PICC lines are used for short-term PN therapy lasting less than a few weeks [32]. Their advantages include decreased risk of catheter complications, economical, and ease of removal. A major disadvantage of PICCs is the greater risk of thrombosis present with their use [33].

Tunnelled catheters are the best option for long-term PN therapy due to the simplicity of self-care and a reduced risk of thrombosis [30]. Subcutaneous ports implanted beneath the skin are another feasible option for long-term PN with almost nil chances for unexpected pulling or removal of the device.

PN Formula

The composition of the PN should be modified according to the patient's clinical and metabolic profile with basic recommendations remaining common for majority of them.

Peripheral formula—should have low osmolarity usually less than 1000 mOsm/L to be suitable for infusion via peripheral veins. The volume and amount of fat are increased and the amount of electrolytes is kept to a minimum to enable this.

Standard formula for central venous catheter—available as two or three chamber ready-to-use bags given to most patients.

Patients with moderate stress require increased protein intake.

Patients in severe stress may require glutamine and increased amounts of zinc and selenium.

Renal patients require individualization of the dosage of water, electrolytes, trace elements and sometimes vitamins, depending on the degree of renal failure and renal replacement therapy. Patients on dialysis have usual protein requirements and the protein intake is influenced by the presence of other clinical conditions.

Patients with hepatic encephalopathy require reduction in the dose of amino acids which should be predominantly in the form of BCAA. Only zinc and selenium must be used in these patients instead of a mixture of trace elements as excretion of copper and manganese is impaired in them.

Cardiac failure patients should receive restricted fluid and sodium to prevent overload.

Severely malnourished patients are at risk of refeeding syndrome because of depletion of intracellular electrolytes. They should receive additional amounts of potassium, magnesium, vitamins and especially phosphate along with a gradual increase in energy input.

Patients suffering from respiratory failure gain from limited intake of dextrose and increased amount of lipids.

Diabetic patients may have altered metabolism and require increased amounts of potassium and phosphate.

Patients with severe hyperlipidaemia are not candidates for the usual lipid emulsions and their lipid intake should be restricted just to cover for the EFA.

Patients requiring long-term PN have very different nutritional needs due to short bowel depending on their physical activity, absorption capacity of the remnant gut and increased GI losses of some nutrients. They also have higher calcium requirement compared to short-term fed patients, as they often suffer from metabolic bone disease.

Patients with postoperative fistulas have higher need for protein, water and electrolytes influenced by fistula losses.

Preparation and Prescription of PN

Once a choice on initial nutritional and fluid requirements has been made, all the ingredients are combined into a single all-in-one (AIO) bag that simultaneously supplies all the nutrients and requires only a single change per day [34, 35]. The use of these systems prevents component handling, reduces chances of contamination and has significant advantages in terms of lowering rates of bloodstream infection and thereby length of hospital stay [36].

Standard solutions as well as those formulated specific to the patient's requirement are available in the market for use as PN. Under strict aseptic technique using a laminar-flow filter PN solutions are prepared in the pharmacy.

Commercial manufacturers provide a variety of "multi-chamber" semi-prepared bags for ease of composition, which typically contain amino acids, dextrose and lipids in separate compartments. These are mixed together by exerting pressure by kneading or wringing gently to break out one compartment into another. The uncombined commercially available bags have a long shelf-life. AIO systems provide simpler prescriptions, save time, and reduce workload and costs [37].

Administration

PN is typically administered over 24 h, simultaneously providing all the nutrients, thus permitting effective utilization by the body. Long-term or stable patients who require only partial nutrition can be given the infusion over shorter durations usually overnight permitting routine activities during the day time.

Many higher osmolality PN bags require a large calibre, high flow vessel to minimize vessel irritation and damage. Some regimen has low osmolality to enable administration via peripheral vein. A glyceryl trinitrate patch may be put on the infusion site and left for 24 h to reduce the risk of thrombophlebitis in the vein used for administration by causing vasodilatation.

Complications and Monitoring

Multiple meta-analyses have shown that though PN is associated with more infectious complications [38, 39], the caloric targets are better attained using this method [40]. Due to several short-term and long-term problems, PN warrants monitoring especially in new as well as severely ill patients [41–44]. This is discussed in detail in the following chapter.

PN in Special Situations

PN has proven efficacy as adjunctive treatment in the management of some specific situations like cancer patients, paediatric patients, critically ill patients, etc. This too is elaborated in the subsequent chapter.

Weaning from PN

Other methods of providing nutrition should be established prior to completely stopping PN. Discontinuation of TPN should be considered when at least 75% of the caloric and protein needs of a patient can be met with oral intake or enteral feeding. PN should never be abruptly stopped for fear of the development of hypoglycemia [45]. PN infusion may be slowly reduced once the patient has started attaining the nutritional requirements by other routes. Laboratory parameters are studied to assess fluid and electrolyte stability when the infusion is reduced. Once the requirements for PN are reduced to a minimum of three days per week, the patient's PN therapy is stopped for one week, carefully monitoring the patient's weight and enteral intake along with laboratory parameters. If all are found satisfactory, the PN can be discontinued.

Conclusion

PN is a vital part of continuing nutrition for patients who are unfit for enteral feeding (primary) and as an adjunctive treatment for a multitude of clinical conditions. In some situations, this rescue therapy combined with enteral nutrition helps sustain patients.

A multidisciplinary team approach is employed to guarantee that accurate solutions are delivered with reference to each patient's unique set of needs. Meticulous surveillance and rigorous monitoring are pivotal to diminishing the odds of complications associated with PN therapy. Recent advances in technology have made PN a fairly safe procedure. Further developments in the form of reducing PN-associated complications and preparation of clinical situation-specific formulations are warranted.

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Monitoring and Complications of Total Parenteral Nutrition

Jaya Wanchoo

Abstract

Early start of nutrition in neurocritical care should be the goal in order to prevent malnutrition. Enteral route is always the first choice, usually well tolerated and is associated with a lower incidence of complications. Parenteral route of feeding should be reserved for those subset of patients who for some reason cannot tolerate enteral feeds. It is not without its complications and requires a proper assessment of the patients keeping in mind their metabolic needs. The intensivist should be aware of the risks associated with the parenteral route of feeding namely infection, thrombotic complications and the long-term metabolic side effects. The aim should be to switch over to enteral route as soon as feasible.

Keywords

Parenteral nutrition (PN) · Vascular complications · Catheter sepsis · Central venous catheter (CVC) · Catheter-related blood steam infection (CRBSI) · Metabolic complications · Refeeding syndrome

J. Wanchoo (✉)
Department of Neuroanaesthesia and Critical Care, Medanta the Medicity, Gurgaon, India
e-mail: jaya.wanchoo@medanta.org

Introduction

Parenteral nutrition is an alternative source of energy when the gastrointestinal tract cannot be used. A non-functional enteral route is labelled as an intestinal failure and was originally defined by Fleming and Remington as 'a reduction in the functioning gut mass below the minimal amount necessary for adequate digestion and absorption of food' [1]. Some examples of intestinal failure are intractable diarrhoea, impaired absorption as in short bowel syndrome, high output enterocutaneous fistula, intestinal obstruction, ischaemic bowel or prolonged ileus. In a neuro ICU, the usual causes of inability to feed through the enteral route are massive gastrointestinal haemorrhage or severe haemodynamic instability due to hypovolemic or septic shock. Malnutrition is commonly seen during severe trauma, major surgery and in hypercatabolic states where parenteral route of nutrition may be used temporarily till enteral feeding is resumed. Both American (ASPEN) and European (ESPEN) guidelines support an early (24–48 h) start of enteral nutrition but ASPEN suggests withholding parenteral nutrition for one week if enteral nutrition is not feasible, while ESPEN advocates combining both the enteral and parenteral nutrition if the nutrition targets are not achieved within 3 days [2].

PN formulations must furnish adequate energy and proteins to preserve lean muscle mass and to support metabolic activities. The macronutrient

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base of all PN regimens consists of protein, carbohydrate and fat. The ideal nutrition should provide 25 kcal/kg/day, with an adequate proportion of protein (0.8–1.5 g/kg/day), glucose (2 g/kg/day), fat (<1.5 g/kg/day), vitamins, trace elements and water [3]. In the presence of acute stress and hypercatabolic state, the estimated requirements may be multiplied by a factor of 1.3–1.5 [4]. PN is not without its side effects, some of which may be life-threatening. Careful selection of patients, individualizing patients' needs, prevention of complications and regular monitoring of patients on PN plays an important role in providing safe and effective nutrition and optimizing outcomes.

Monitoring During TPN

All patients who receive PN should be closely monitored to detect warning signs of complications. The monitoring should include anthropometric data, clinical and laboratory monitoring. In addition, the access route should be checked regularly to look for signs of infection, the gut should be assessed for initiation of enteral feeding and medications should be checked for any drug -PN interactions. The frequency of monitoring may vary in different centres and can be decided jointly by the intensivist and nutritionist.

1. Anthropometric Data—This includes regular monitoring of patient's weight, height, BMI, mid arm circumference, triceps skinfold and grip strength. Use of a particular method of estimation has not been shown to improve patient outcomes and thus this process depends on institutional preferences. Patient weight should be monitored and calories subsequently adjusted to target ideal body weight.
2. Clinical monitoring—Patients' vitals are to be measured closely to look for signs of underfeeding or overfeeding. The monitoring should include pulse, blood pressure, temperature, respiratory rate, fluid balance and urine output. Early signs of complications should be looked for like metabolic acidosis, fluid or sodium overload or deficiency, electrolyte imbalance, renal or hepatic dysfunction, early signs of bloodstream infection or thrombophlebitis.
3. Laboratory data—Initially whole blood counts and renal functions with electrolytes should be measured daily. The liver functions, coagulation profile, triglyceride levels should also be monitored at regular intervals. Infection markers like white blood cells, CRP and blood cultures should be done. Some of the other parameters that need regular monitoring are arterial blood gas analysis to detect metabolic acidosis, blood glucose levels, micronutrients (iron, zinc, copper, B12), Vitamins A, E and D as well as international normalized ratio. Bone density wherever feasible is measured at baseline [5].
4. Monitoring of trace elements is important because they are essential components of multiple enzymatic reactions in the body and their requirement varies in different pathological conditions. Their requirement increases in stress and hypercatabolic states and decreases in multiorgan dysfunction leading to their toxicity. Consequences of their excess or deficiency are not easy to detect clinically, hence monitoring their levels is extremely important in the unstable ICU patient. In 1979, the Nutrition Advisory Group of the American Medical Association (NAG-AMA) published guidelines that were submitted to the Food and Drug Administration (FDA) highlighting the list of daily trace elements considered essential for human health in parenteral nutrition [6]. Among these were zinc, copper, manganese, chromium, selenium, iron, iodine, molybdenum and fluorine [7].

Vascular Complications

Delivery of parenteral nutrition into the central venous circulation is the preferred route though, in some special circumstances, the peripheral route can be used. Peripheral PN is most useful as a bridge therapy during transition periods when oral/ enteral intake is suboptimal but is expected to return to near normal in 3–4 days or in circum-

Table 1 List of catheter-related complications of TPN

During catheter placement	Pneumothorax, hydrothorax Arterial puncture Catheter embolism Arrhythmias
Catheter occlusion	Thrombotic causes Non-thrombotic causes External causes
Occlusion of the vessel	Phlebitis Catheter Thrombosis
Catheter-related infection	Colonization Exit site infection Tunnel infection Catheter-related bloodstream infection Infusate related bloodstream infection

stances that do not justify placing a central venous catheter. As expected, most of the vascular complications are related to the access used for the delivery of PN (Table 1).

Catheter-Related Complications [8]

During Catheter Placement

Complications during placement of a CVC are usually user-dependent. They may range from transient arrhythmias to life-threatening complications like pneumothorax, hydrothorax, arterial puncture or catheter embolism. A confirmatory chest X-ray should be done to rule out pneumothorax and to confirm the position of the catheter tip. Large pneumothorax may require the placement of a chest drain. The catheter should be placed in the superior vena cava just proximal to the right atrium. The risk of cardiac arrhythmias increases if the catheter tip crosses the right atrium.

Catheter Occlusion

Catheter occlusion is a common complication of TPN, the causes of which could be internal or external factors. Catheter occlusion may be partial, in which blood cannot be aspirated but infusions can be given, or complete in which neither blood can be aspirated nor infusions can be given. Preventive measures include saline or heparin flushes, low dose warfarin or unfractionated heparin, which have yet to prove their efficacy [9].

Thrombotic Catheter Occlusion

Most thrombotic occlusions occur due to thrombus formation around the catheter rather than within the catheter. Patient factors like hypercoagulable state, hypotension, dehydration, congestive heart failure, all lead to stasis and predispose to thrombus formation. Slow infusion rates, small lumen catheters, administration of blood or blood components and frequent blood sampling can also cause thrombus formation. Catheter patency can be compromised by the position of the catheter tip in relation to the vessel wall. The ideal position of the catheter tip should be parallel to the vessel wall. The tip should be floating freely in the lumen of the vessel. The superior and inferior vena cava are best suited for this purpose as they have high blood flow rates. Delivery of hypertonic parenteral nutrition in veins that have low flow rates like the innominate or femoral vein may cause sclerosis of their walls predisposing to thrombus formation.

Management includes early recognition, confirmation by Doppler ultrasound or contrast venography. Anticoagulation with heparin, warfarin, urokinase, streptokinase or tissue plasminogen activator may be used. Thrombotic occlusions are treated by instillation of alteplase with a concentration of 2 mg/2 ml. Alteplase catalyzes the conversion of clot-bound plasminogen to plasmin and initiates fibrinolysis. In the COOL trial (Cardiovascular thrombolytic used to Open Occluded Lines), one 2 mg dose of alteplase cleared the catheter occlusion after 120 min in 74% of patients, compared to only 17% of patients who received placebo. The safety and efficacy of alteplase has been confirmed in various studies. Use of a guide wire and fibrin sheath stripping are invasive methods that can be used if thrombolytics fail. Recombinant urokinase and Alfimeprase are newer drugs being used [10].

Non-thrombotic Catheter Occlusion

There are several causes for non-thrombotic occlusion of the TPN catheter. Risk factors that predispose to catheter occlusion by non-thrombotic materials include catheter material, composition of TPN, concomitant use of TPN catheters for infusion of other medications or use of the catheter for repeated blood sampling. There are some drugs that do not readily dissolve in water and require a vehicle for their delivery which may cause precipitation. The pH of many drugs makes them incompatible when mixed with other solutions. Formation of insoluble salts of calcium and phosphate can cause precipitation in the catheter. Precipitation also occurs due to the mixing of large organic cations and anions like heparin with aminoglycosides. Lipid emulsions are known to form precipitates or lipid protein layer which can cause catheter occlusion.

Management of catheter occlusion due to any reason requires attempts at flushing the catheter using heparin. Obstruction due to low pH medications or calcium phosphate crystals can be treated with 0.1% hydrochloric acid. Obstruction caused by medications that precipitate in an acidic environment can be treated with sodium hydroxide or sodium bicarbonate. Lipid precipitants can be cleared by 70% ethanol solution. If all treatment fails the catheter has to be removed and replaced taking care not to injure the vessel wall during the procedure.

Occlusion Due to External Causes

Pinch-off syndrome is a well-known complication of vascular devices in the subclavian vein. It is caused by the movement of the clavicle against the first rib. This could lead to partial fracture of the catheter resulting in leaking of the infusate around the catheter. In some cases, due to repeated friction there could be complete fracture of the catheter causing the catheter fragment to embolize into distal circulation. Catheters may also fracture due to pressure inside their lumen. The infusion pressure must be greater than the venous pressure to deliver the infusion but not more than the recommended tolerated pressure. The size of the syringe used for infusions or use of power injectors can also result in catheter fracture if excessive pressure is applied. Catheter emboli, migration or dislodgement are well-documented complications. Regular checks for catheter patency and function need to be done for early detection of these problems.

Occlusion of the Vessel

Phlebitis

Vessel occlusion can lead to serious consequences and the intensivist should keep a close watch to look for early signs of this complication. Phlebitis is caused by inflammation of the vessel wall and maybe a precursor to vessel occlusion. The delivery of parenteral nutrition through the peripheral route carries an increased risk for phlebitis due to the hyperosmolar nature of the formulations. Compared with central formulations, the peripheral parenteral nutrition formulations contain a lower concentration of nutrients, but the osmolarity of peripheral formulations often exceeds the 600 mOsm/l limit for peripheral infusion. Incidence of phlebitis may be lowered by measures such as limiting the duration of PPN, changing the catheter every 24 to 48 h, and administering lipid emulsion through the same vein or as a component of the PN admixture.

Catheter Thrombosis

Various factors predispose to thrombus formation and blockage of the central venous catheter. Virchow's triad lists the three causes of thrombus formation-changes in the vessel wall, alteration in the blood flow and changes in the chemical composition of blood. Presence of a foreign body within the vessel induces platelet aggregation and formation of a nidus for thrombus formation [11]. Injury to the intima of the vessel wall during catheter insertion also predisposes to thrombus formation. Hypertonic TPN is a potent inducer of human monocyte procoagulant activity which is

an initiator of coagulation [12]. Venous thrombosis can lead to serious complications like SVC or IVC syndrome. Pulmonary embolism is a rare complication and cases of intracardiac thrombosis have also been reported which is related to the position of the catheter tip in the right atrium. Right atrial thrombus should be suspected in a patient on TPN who develops new-onset dyspnoea, signs of right heart failure, new murmur or pulmonary emboli [13]. Catheter removal should be done cautiously in such patients as there is a risk of thrombus getting dislodged into the distal circulation [14].

Low dose warfarin that does not affect the prothrombin time has been found to be useful in decreasing the risk of thrombosis. There is still insufficient data to prove the efficacy of prophylactic anticoagulation for patient on TPN. Parenteral nutrition guidelines suggest various anticoagulant regimens for the prevention and treatment of catheter-related thrombosis during long-term parenteral nutrition [15].

Catheter-Related Infection

This is probably the commonest complication of long-term parenteral nutrition. Most of the catheter-related bloodstream infections are preventable but maybe life-threatening, so the focus should be on strict preventive measures and training of the staff handling these catheters. Risk factors that predispose to infections are diabetes, uraemia, steroids, immunosuppression, repeated puncture attempts, the use of multi-lumened catheters, use of the line for other infusions. Prolonged use of TPN in itself is a risk factor for developing sepsis [16]. Central venous catheters may get infected from various sites, most commonly from the skin flora at the time of insertion. The infection may also spread from the hub due to improper cleaning at the time of connection and disconnection. Infected infusate may be another source of infection or through haematological seeding from a distal site [17]. Infective endocarditis, though rare, is a known complication of right heart catheterization and has been reported with indwelling TPN catheters. The infection is usually confined to the tricuspid valve and the patient may present with recurrent pulmonary emboli [18]. Electron microscopy of the catheters shows a biofilm adherent to the lumen of the venous line. Bacteria colonizing the catheter lumen can be seen in two forms-sessile and free-floating. The common organisms are coagulase-negative staphylococci, staphylococcus aureus, Candida, Enterobacter, Enterococci. In long-term hospitalized patients, Gram-negative organisms may be the major cause of catheter-related sepsis like Pseudomonas, Klebsiella or E. Coli.

Preventive Measures to Reduce Catheter Sepsis

(1) Precautions should start at the time of insertion which include careful selection of the insertion site (higher incidence of bloodstream infection with femoral and internal jugular vein as compared to subclavian), use of ultrasound to guide venepuncture, use of maximal barrier precautions during insertion and tunnelling the catheters. Insertion site colonization can be prevented by cleaning the area with 2% chlorhexidine or povidone iodine and letting it dry before catheter insertion [19].
(2) Using peripheral access (PICC lines) and use of single lumen catheters whenever possible [20].
(3) Appropriate cleaning and dressing of the exit site, use of 2% chlorhexidine has been found to be superior to povidone iodine in its bactericidal properties [21].
(4) Hand washing and asepsis during handling of the infusions.
(5) Use of gauze dressing is preferable to transparent polyurethane dressings if the patient is diaphoretic or bleeding. Increased bacterial colonization is seen under transparent dressings probably due to accumulation of moisture or blood under such dressings. Frequency of dressing changes should be reduced and should only be done if the dressing is visibly soiled. Use of biopatch at the

insertion site, which is a chlorhexidine impregnated hydrophilic polyurethrane foam dressing, has been found to be useful for prevention of colonization. Irrespective of the type of dressing the skin at the entry point should be kept clean and dry.

(6) Disinfection of hubs and avoidance of using three-way stopcocks should be encouraged.
(7) Antiseptic impregnated catheters may reduce the risk of colonization, more so if the catheter is expected to be in use for more than 5–7 days. Chlorhexidine and silver sulphadiazine have been used for this purpose [22]. Minocycline and Rifampicin coated catheters reduce the risk of bloodstream infections but may be short lived as antibiotics are washed off with time [23].
(8) Regular change of administration sets is recommended (after every 24 h for TPN).
(9) In patients who have repeated bloodstream infections or are severely immunocompromised, prophylactic antibiotic lock solution (amikacin, gentamicin, vancomycin) in a volume only to fill the catheter may be helpful. Use of thrombolytics (urokinase) with antibiotics should theoretically break down the biofilm thereby releasing the microorganisms adherent to it but there is no definite advantage described so far.

The following interventions are not effective in reducing the risk of infection and should not be adopted:

(1) Use of in-line filters
(2) Routine replacement of central lines
(3) Defatting the skin with acetone or ether for disinfection of insertion sites of central venous catheters. This practice did not show any benefit, the reason being that fatty acids secreted by normal skin play an important role in regulation of the cutaneous microbial ecosystem. Paradoxically this practice may promote colonization by pathogenic microorganisms and also increase cutaneous inflammation and patient discomfort.
(4) Topical antibiotic ointment or cream at the insertion sites as they may promote resistance or damage the catheters
(5) Use of heparin and prophylactic antibiotics

Diagnosis of Catheter Sepsis

Obtaining a positive CVC tip culture was considered diagnostic. The procedure followed was described as the ‘Maki roll’. It involves rolling the catheter tip across an agar plate and thereby inoculating those organism’s adherent to the outer surface, >15 CFU being indicative of catheter colonization. A major disadvantage of this technique is that the catheter may be contaminated by commensals as it is pulled through the skin exit site. In addition, bacteria growing on the luminal surface of the catheter will not be detected. Another method was the ‘Cleri flush’ which required the tip of the catheter to be immersed in broth and the lumen flushed through. The microorganisms may be dislodged from the CVC tip using the sonication technique, giving a higher sensitivity of culture. However, a positive culture may still reflect only contamination of the outer surface of the catheter. Both the Maki roll and Cleri flush methods provide only retrospective confirmation of CR-BSI and inevitably involve catheter removal in up to 85% of cases where the catheter may not be infected. Whether or not colonization progresses to CR-BSI is unclear. The patient may exhibit signs and symptoms of infection namely fever, leucocytosis or erythema at the insertion site. Qualitative blood culture remains the most common diagnostic test for bloodstream infection, the drawbacks being that it does not rule out contamination nor does it quantify the organism. Paired quantitative blood cultures drawn simultaneously from a peripheral vein and from the catheter are diagnostic. A single bacterial count of >100 CFU/ml from the catheter or a colony count ratio of 4:1 (central versus peripheral blood) is diagnostic of catheter sepsis. A recent investigation in adult oncology patients compared the time to positivity of paired

blood cultures taken simultaneously from CVC and peripheral blood. CVC blood culture becoming positive at least two hours before the peripheral culture was found to be diagnostic of CR-BSI, with a specificity of 100% and a sensitivity of 96.4%. However, this technique is dependent on the patient not having received antibiotics and requires specialized laboratory automated blood culture equipment [24]. Infusion-related sepsis is another entity that is difficult to distinguish from CR-BSI and the role of the microbiologist is of paramount importance in guiding the physician here. All blood isolates should be identified to the species level with complete susceptibility testing [25].

Management

All patients with catheter sepsis should have an echocardiography done to rule out vegetations on the valves. Since most of the infections are caused by coagulase-negative staphylococci, patient should be started on vancomycin and continued for 4 weeks. Most cases of catheter sepsis can be treated successfully without catheter removal. The catheter should be removed in cases of tunnel infection, fungaemia, septic shock or failure to improve within 48–72 h from the start of antibiotic therapy [26].

Metabolic Complications

Metabolic complications, both acute and long term, are common with PN. In order to label any abnormality as a complication of TPN it should satisfy the following criteria: the abnormality is known to occur with TPN, is detrimental for the patient, appears after TPN initiation and subsides after appropriate adjustment of the TPN [27]. The acute and chronic complications are listed in Table 2, though the chronic complications may not be seen in the intensive care setting.

Table 2 List of acute and chronic metabolic complications of TPN

Acute	Chronic
Volume overload and electrolyte imbalance	Hepatic
Hyper/hypoglycemia	Biliary
Hypertriglyceridaemia	Renal
Hyperazotemia	Bone
Refeeding syndrome	Cardiac
Metabolic acidosis	

Volume Overload and Electrolyte Imbalance

Volume or fluid overload is a potential complication when high volumes are infused in a short duration, particularly in patients with cardiac or renal failure. It manifests as a weight gain of more than 1 kg per day. Ideally, the patient should be started with 50% of the calculated requirement, with a gradual increase to meet the full requirement in 4–5 days. Electrolytes that need to be monitored closely are sodium, potassium, magnesium, phosphate and chloride

Hyperglycemia

Hyperglycemia is seen in almost 50% of patients on TPN initiation. Patients who are at risk of developing hyperglycemia are those who have pre-existing diabetes mellitus or are on steroids. It also depends on the severity of the primary illness and the amount of glucose in the PN. The aim should be to maintain normoglycemia.

Hypertriglyceridaemia

This is seen commonly in 25–50% of patients receiving PN. It depends on various factors-presence of hyperglycaemia, renal insufficiency, steroid administration, amount of lipid infused. Severe forms of hypertriglyceridaemia can cause pancraeatitis.

Hyperazotemia

This is seen in patients with pre-existing renal dysfunction, catabolic states or infusion of high dose of proteins in the TPN [28].

Refeeding Syndrome

Refeeding syndrome is seen in severely malnourished patients, started on aggressive parenteral nutrition and occurs within first few days of initiation of parenteral nutrition. The cause of refeeding syndrome can be attributed to alteration in the metabolism. In starvation, energy is derived mainly from fats which does not require phosphate containing intermediates. When feeding is initiated in such a patient, carbohydrates become the main fuel source, and the patients' metabolism shifts to glycolysis with intracellular trapping of phosphate. Signs and symptoms may be mild like diarhhoea, nausea and vomiting. Severe manifestations may occur due to intracellular shift of electrolytes causing hypophosphataemia, hypokalemia and hypomagnesaemia. The electrolyte imbalance and generalized lack of ATP may cause widespread cellular dysfunction or death [29]. Clinically these changes may manifest as life-threatening tachy or bradyarrythmias, cardiac and pulmonary edema or acute respiratory failure. To prevent refeeding syndrome, it is always advisable to start TPN slowly with close monitoring of electrolytes [30].

Acute Metabolic Acidosis

Acute metabolic acidosis can occur due to multiple reasons in a patient on TPN. It is seen more commonly in patients who have diarrhoea, renal tubular acidosis or are in septic shock due to lactic acidosis. The causes of metabolic acidosis could be due to exogenous addition of acids in TPN namely cationic and sulphur containing amino acids, acetic acid and hydrochloric acid. Thiamine deficiency is another important cause of metabolic acidosis as thiamine is required for the conversion of lactate to pyruvate. Recent guidelines recommend addition of thiamine in doses of 100–300 mg/day in ICU patients who are at risk for developing thiamine deficiency [31]. Thiamine deficiency is known to cause cardiac Beri Beri. Hypophosphatemia is also responsible for the development of metabolic acidosis during TPN as phosphate along with bicarbonate and ammonium buffer help in the renal removal of non-volatile hydrogen ions [32].

Hepatic

The hepatic complications seen with long-term parenteral nutrition range from steatosis, steatohepatitis, cholestasis, phospholipidosis, fibrosis, micronodular cirrhosis and hepatic failure. The broad term used to label these complications are termed as Intestinal Failure associated Liver Disease (IFALD). The causes are divided into non-nutrient and nutrient-related factors. Non-nutrient causes could be sepsis, pre-existing liver dysfunction like biliary stones or biliary obstruction or concomitant use of hepatotoxic drugs. Nutrient causes implicated are increased calories in the form of glucose or lipid, manganese or aluminium toxicity, or nutrient deficiencies like essential fatty acids, taurine, carnitine and choline [33].

Steatosis

Steatosis is usually benign, irreversible and asymptomatic. Most sensitive indicators are increased gamma-glutamyl transpeptidase, alanine transaminase, aspartate transaminase and alkaline phosphatase. These enzymes peak in 1–2 weeks and then show a decline. Hyperbilirubinaemia is not very common.

Various factors known to cause steatosis are

(1) High concentration of glucose and amino acids promote hepatic fat deposition by stimulating release of insulin which promotes lipogenesis and synthesis of acyl glycerol from glucose.

(2) Carnitine deficiency may have a role in causing steatosis as it has an important role in lipid metabolism.
(3) Increase lipid in PN may cause direct deposition of exogenous fatty acids in the liver.

The incidence of steatosis can be decreased by cyclic parenteral nutrition or by using balanced glucose, amino acids, lipid solution.

Cholestatic Liver Disease

Cholestatic liver disease, usually seen with long-term parenteral nutrition, is not commonly seen in neurocritical care. Most of the times it is irreversible and may progress to cirrhosis and liver failure; for this reason, TPN should be discontinued once patient develops cholestatis. The key biochemical abnormalities seen are hyperbilirubinaemia, increases in gammaglutamyl transferase and alkaline phosphatase. Histologically there is cholestasis associated with periportal and portal infiltration and extensive fibrosis; cirrhosis is seen during the final state of the disease.

Various contributing factors could be

(1) A decrease in the enterohepatic cycle of bile acids as seen with short bowel syndrome or fistulas, can lead to depletion of bile acids and increase in lithogenicity of bile.
(2) Bacterial overgrowth with portal endotoxaemia can stimulate cytokine production and decrease bile transport.
(3) The content and composition of phospholipids may be responsible for liver injury connected with parenteral nutrition.
(4) Glucose overfeeding

The hepatic complications may be prevented by decreasing the number of macronutrients, providing cyclic PN and promoting early enteral nutrition. Certain amino acids like taurine may prove beneficial [34].

Biliary

Acalculous cholecystitis occurs because of decreased gallbladder emptying related to the decreased release of cholecystokinin due to insufficient oral intake. Narcotic use, bile stasis, and increased bile lithogenecity may also be contributing factors. Patients may develop massive gallbladder dilation and require percutaneous cholecystostomy for drainage. Most of the stones are calcium bilirubinate. These can be prevented by stimulating the gall bladder by cholecystokinin and by giving small amounts of oral or enteral nutrition. Rapid infusion of amino acids or lipids may also stimulate gall bladder contractions.

Renal

Short-term PN may lead to increased creatinine clearance, probably because of glomerular hyperfiltration. Patients on long-term PN are at risk of nephrolithiasis, glomerular sclerosis, decline in renal function and hyperoxaluria. Calcium oxalate stones are commonly seen as the unabsorbed fatty acids in the non-functional short bowel bind to calcium rather than oxalate. These are then absorbed in the colon leading to high urinary levels of calcium oxalate. The aetiology of PN associated nephropathy is unknown but risk factors include age, use of nephrotoxic drugs and bloodstream infections. No correlation has been found between the decline in renal function and intravenous amino acid intake but excessive chromium infusion (primarily in the form of contaminates in the TPN solutions) is associated with decreased renal function in children. Hyperoxaluria which is seen in adults could be related to endogenous production from vitamin C contained in TPN solutions or due to acidity of TPN solutions. Close monitoring of intravascular volume status and acid–base balance needs to be done to prevent renal complications.

Metabolic Bone Disease

This complication is seen with long-term use of parenteral nutrition and may not be of significance in neurocritical care. Potential causes of metabolic bone disease in patients on long term TPN include the underlying disorder like dehydration, primary hyperparathyroidism, hypoparathyroidism, magnesium deficiency from chronic diarrheal losses, vitamin D malabsorption, osteopenia due to steroids, long-term immobilization and bone demineralization, excess of sulphur-containing amino acids in PN. Aluminium toxicity is also a significant factor in TPN-related osteomalacia. Plasma fluoride concentration has been shown to correlate significantly with bone mineral density in children requiring long-term TPN. Patients may present with bone pains or fractures. The initial biochemical abnormality seen is hypercalciuria, hypercalcemia, high normal vitamin D levels and low parathyroid levels. Bone biopsy in these patients revealed decreased mineralization.

Cardiac

Cardiac changes seen with long-term PN are still under evaluation, being more structural in nature than metabolic. It was observed with regular transthoracic echocardiograms that there is an increase in right-sided heart pressures, though a cardiac MRI is a gold standard for this [35].

Most of the complications seen with PN administration are reversible and preventable. The intensivist should be aware of the need for close biochemical monitoring of such patients for best outcomes. Shift to enteral route should be done as soon as feasible to avoid long-term side effects.

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Special Neurologic Patient Population and TPN

Sritam S. Jena and Swagata Tripathy

Abstract

Functional disability during many neurological diseases impairs the ability of the affected individuals to fulfill their nutritional needs. The resultant nutritional deficiency further complicates the disease course and increases the associated morbidity and mortality. Clinicians often tend to focus on managing the primary pathology and other associated complications and ignore the nutritional aspects. Though early enteral feeding has been the preferred route of nutrition, there is a paucity of knowledge regarding parenteral nutrition when the enteral route is not feasible or sufficient to fulfill the nutritional goals. Parenteral nutrition is not free from complications, and this should be kept in mind while prescribing to patients. Good nutritional therapy ultimately contributes to a better prognosis.

Keywords

Parenteral nutrition · Neurological conditions
Brain injury · Neurocritical care

S. S. Jena · S. Tripathy (✉)
Department of Anesthesia & Critical Care, AIIMS, Bhubaneswar, India
e-mail: anaes_sritam@aiimsbhubaneswar.edu.in; anaes_swagata@aiimsbhubaneswar.edu.in

Patients admitted to the neurocritical care unit are frequently either in an unconscious state or have impaired swallowing ability because of motor dysfunction and neuropsychological disturbances. Unlike patients in other intensive care units (ICU), neurological patients often require sedatives, analgesics, anesthetics, muscle relaxants, and hypothermia to control intracranial pressure. Such interventions often decrease the nutritional needs. Also, neurologically ill patients frequently require prolonged ventilatory support. Such disabilities have a profound effect on their nutritional status. Malnutrition and dehydration contribute to morbidity and mortality in such patients. Though enteral nutrition is the first-line therapy in critically ill patients, the target goal of calories is not met consistently through the enteral route in certain circumstances. Sometimes enteral nutrition might not be feasible.

Patients with various neurological diseases are at risk of malnutrition in either acute or in the chronic phase as shown in Tables 1 and 2. Amyotrophic lateral sclerosis is a neurodegenerative disease characterized by progressive muscle weakness. Progressive bulbar paresis leads to dysphagia, and the oral route of nutritional supplementation is not feasible. Though enteral nutrition via early gastrostomy is preferred over parenteral nutrition, parenteral nutrition should be used in the acute setting whenever the enteral route is not feasible or contraindicated (e.g., gastrointestinal hemorrhage, failure to place gastros-

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Table 1 Neurological disorders with a risk of dysphagia in the acute phase

Central nervous system diseases	Neuropathies	Neuromuscular disorders	Myopathies	Trauma
Ischemic stroke Intracranial hemorrhage Meningitis Encephalitis Cerebral abscess Hypoxic-ischemic encephalopathy	Guillain–Barre syndrome Neoplastic cranial nerve involvement Diphtheria	Myasthenia Gravis Botulism	Inflammatory myositis Necrotizing myopathy	Craniofacial trauma

Table 2 Neurological diseases that may lead to malnutrition in the chronic phase

Central nervous system diseases	Neurodegenerative diseases	Myopathies	Others
Ischemic stroke Intracranial hemorrhage Tuberculosis Multiple sclerosis Cerebral palsy Hypoxic-ischemic encephalopathy	Amyotrophic lateral sclerosis Motor neuron disease Dementia Alzheimer's disease Parkinson's disease	Inflammatory myositis Dermatomyositis Hereditary myopathies Muscular dystrophies Mitochondrial myopathies	Myasthenia gravis Chronic polyneuropathies

tomy, development of ileus, malabsorption, entero-cutaneous fistula) [1].

Parkinson's disease is another neurodegenerative disorder in which dysphagia, dysarthria, gastroparesis, and impaired gastrointestinal motility develop as the disease progresses. Though there are no guidelines regarding starting parenteral nutrition in patients with Parkinson's disease, a case report implicates an association between total parenteral nutrition and precipitation of neurolept malignant like syndrome. The postulated pathophysiology is the total parenteral nutrition competing with levodopa absorption by the enterocytes [2].

Stroke is one of the most common acute neurological illnesses that lead to mortality and physical disability. Patients frequently suffer from malnutrition and dehydration because of impaired consciousness, dysphagia, and neurocognitive deficits. They are prone to aspiration pneumonia which is a risk factor for mortality. The presence of malnutrition at hospital admission leads to poor outcomes in such patients. In these patients, parenteral nutrition is indicated when enteral nutrition is not feasible or contraindicated. Even in well-nourished patients enteral nutrition may not meet the nutritional needs for more than a week, and switching over to parenteral nutrition may be considered. In the acute phase of stroke, hydration through the oral route may not be adequate and intravenous hydration may be necessary [3].

Providing adequate nutritional support following a traumatic brain injury can be challenging. The metabolic state following TBI is different from that of healthy individuals because of increased energy requirements caused by a stress-induced release of catecholamines, steroidal hormones, and inflammatory indicators [4]. Energy consumption is also affected due to decreased levels of consciousness, immobilization, analgesics, and sedatives. The parenteral route can provide calories, fluid, and electrolytes. The caloric goals can be achieved faster with this route than an enteral route. The amount of nitrogen provided by PN is higher and more efficient in preventing catabolism [5]. However, it leads to higher nitrogen excretion, ultimately making the nitrogen balance similar to enteral nutrition. Parenteral nutrition should be avoided for the first seven days in patients with low nutritional risk, and it should be started as soon as possible in cases with high nutritional risk or in cases with malnutrition. The additional recommendation is that if 60% or more of the energy requirements are not met by the end of 7 to 10 days, supplemental parenteral nutrition should be considered [6]. Patients in induced (barbiturate) coma may develop intolerance to enteral nutrition in the first

48 h [7]. Early parenteral nutrition may be indicated in such patients. Some of the earlier studies conducted on animals have demonstrated worsening intracranial tension following hyperosmolar dextrose solutions to severely brain-injured patients [8]. The postulated mechanisms being increased vasogenic edema and accumulation of lactic acid, causing injury to already hypoxic neurons. A randomized controlled trial by Young et al. has shown no difference in peak daily intracranial pressure in patients with severe traumatic brain injury randomly assigned to parenteral and enteral nutrition [9]. Wang et al. have analyzed 16 studies (RCTs and observational studies) for the timing and route of feeding traumatic brain injury patients. Early feeding was associated with a better outcome- a finding also emphasized by the Brain Trauma Foundation. Another observation was that the parenteral route was associated with better mortality and infectious complications though there was no statistical significance [10].

About 19% of patients suffering from cervical spinal cord injury suffer from neurogenic shock: the incidence is lower in thoracic and lumbar cord injury patients. Such patients may need high-dose vasopressor support to maintain hemodynamics. There is a theoretical risk of intestinal ischemia and necrosis because the blood is shunted away from the mesenteric vasculature. With poor tolerance of enteral feeds in such patients, parenteral nutrition may be considered.

Secondary injury following traumatic brain injury is a delayed response, and it consists of neurochemical and neurometabolic events which result in abnormal cell metabolism. This leads to hyperglycemia as well as protein wasting. The goal of nutrition in such a situation is to attenuate the catabolic response and to prevent hypermetabolism. Nutrients have a role in the cellular physiological response to injuries like oxidative stress, inflammation, repair, and recovery. However, there is very little evidence regarding the role of micronutrients and other food components that may ameliorate the symptoms related to brain injuries like cognitive deficits, somatic and affective disorders, and subsequent neurodegenerative disorders. Zinc is believed to have a role in neuroplasticity, immunity, and cell apoptosis. Urinary zinc excretion increases following traumatic brain injury, and a fall in plasma zinc concentrations correlates with injury severity. However, the pilot study by Young et al. (though underpowered) did not find any significant effect of supplemental zinc [11]. Vitamin E an antioxidant and has a role to play in inflammation, oxidative stress, and cellular apoptosis. In the trial published in 2011, traumatic brain injury patients treated with vitamin E had lower mortality at six months and better outcome scores than others [12], but the small sample size and methodological concerns made it insufficient to support a recommendation. There has been animal research on several antioxidants, iron, branched-chain amino acids, magnesium, vitamin D, creatine, and choline. Although some experimental studies have promising results, clinical trials confirming their beneficial role following a brain injury are awaited. Information related to micronutrients' role in neuronal metabolism and their effect on neuronal function needs to be updated. Further studies on micronutrient status, appropriate dose, and proper therapy timing following brain injury need to be done.

Parenteral nutrition has its own set of complications, refeeding syndrome being one of the most serious ones in extremely malnourished individuals. Weinsier and Krumdieck reported two rapidly evolving refeeding syndrome cases following aggressive dextrose-based parenteral nutrition that resulted in deaths [13]. Hypophosphatemia, sodium, and water retention are the proposed factors behind the pathophysiology of the syndrome. Apart from the prohibition of aggressive refeeding, identification of patients at risk is the key to prevention. Neuro-ICU patients at risk of chronic malnutrition should be evaluated for possible refeeding syndrome before initiating nutrition.

Neurologically ill patients, when they develop malnutrition during the course of their illness, are at higher risk of associated morbidity and mortality. While several factors may be attributed to malnutrition in these patients, cellular metabolism changes feature prominently. Providing nutrition via the enteral route is preferred as it is

more physiological, less expensive, and has less severe complications. The exact mechanism of failure of enteral feeds to achieve nutritional goals and the beneficial effects of parenteral nutrition in this regard is not clear. There is a paucity of literature regarding the use of parenteral nutrition in neurological patients. More research is needed to address this gap in knowledge.

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