Crystalloids

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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.

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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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