Massive Perioperative Hemorrhage: Considerations in Clinical Management

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10.1 Introduction

There is no universally accepted definition of massive hemorrhage. The British Committee for Standards in Haematology has consensus but arbitrary definition, "Bleeding which leads to a heart rate of more than 110 beats/min and/or systolic blood pressure less than 90 mmHg" [1]. Massive transfusion in an adult has commonly been defined as ten or more units of packed red blood cells (PRBC) in a 24-h period, which almost replaces one blood volume based on the total blood volume of a 70-kg male [2]. Massive transfusion can also be defined if one of the following conditions is satisfied: blood loss exceeding circulating blood volume within a 24-h period, blood loss of 50% of circulating blood volume within a 3-h period, blood loss exceeding 150 ml/min, and blood loss that necessitates plasma and platelet transfusion [3]. Hemorrhage is the main cause of death in major trauma patients surviving to the hospital admission [4]. In this review, we will discuss the risk factors for massive perioperative hemorrhage, clinical manifestations and evaluations, and various management strategies.

10.2 Etiology of Massive Perioperative Bleeding

Perioperative massive hemorrhage can be caused by various etiologies, as illustrated in Table 10.1.

10.2.1 Trauma

Major trauma is one of the leading causes of perioperative massive hemorrhage, and hemorrhage is the main cause of death following major trauma in patients surviving to hospital admission with the highest incidence in 1–3 h after admission [4]. Etiology of major trauma includes motor vehicle accidents, bullet injuries, blunt trauma injuries, fall from certain heights, glass injuries, blast injuries, etc. These traumatic injuries are potentially associated with major vascular laceration(s) or organ rupture (spleen injury) leading to extensive blood loss. Most of the patients expire on their way to hospital because of massive hemorrhage. So, hemorrhage/hemorrhagic shock is still the leading cause of death in all major traumatic injuries worldwide [4].

10.2.1.1 Surgical Procedures

1. Liver transplantation: In 1963, Starzl and colleagues performed the first liver transplantation procedure in human beings. The first five patients all died of bleeding complications. Liver transplantation has usually been associated with massive hemorrhage and requires considerable amount of blood transfusion. The etiologies of liver transplantation-associated bleeding can be multifactorial including preoperative (liver failure, cirrhosis, cholestasis, and splenomegaly), intraoperative (transection of the fragile collateral vessels, release of heparin-like factors from the allograft, coagulopathy), and postoperative (leaks at vascular suture lines, graft-versus-host disease, thrombocytopenia, coagulopathy, etc.) [5]. Intraoperative management-related issues such as massive volume load and subsequent hypothermia and hypocalcemia secondary to citrate toxicity can also significantly worsen the preoperative coagulopathy, thus further increasing the perioperative hemorrhage [6]. Excessive blood loss and large quantity

Table 10.1 Etiologies of massive perioperative bleeding

Major trauma	Surgical procedures	Coagulation abnormalities	Obstetric diseases
Major trauma	Liver transplantation	Acute traumatic coagulopathy	Placenta previa/accreta
	Cardiac/major vascular surgery	Clotting factor deficiencies	Embryonic emboli-associated DIC
	Major cancer surgery	Drug-induced acquired factor deficiency	
		An undiagnosed inherited bleeding disorder	
		Dilutional coagulopathy	

of blood transfusion during orthotopic liver transplantation are unfortunately associated with significantly decreased graft survival and dramatically increased episodes of sepsis and therefore prolonged ICU stay [6]. In principle, the degree of hemorrhage can be estimated based on the severity of preoperative liver disease and coagulation function, quality of the donor liver, recipient's overall clinical status, and surgical skills and experience of the transplantation team [7]. There is a strong correlation between MELD score and transfusion requirements in patients undergoing orthotopic liver transplantation. Higher MELD scores (>30) was found to be significantly associated with increased bleeding and transfusion requirements when compared to patients with lower MELD scores (<30) [8]. Massive bleeding can have multiple clinical consequences, as illustrated by ► Box 10.1.

2. Major cancer and spine surgery: Reconstructive and multilevel procedures like spine surgery and spine fusion procedures are potentially complicated by significant intraoperative blood loss and the need for allogeneic blood transfusion. The unique prone position (knee-chest) for spine surgery likely leads to increased intra-abdominal pressure which increases epidural venous pressure and consequently exacerbates intraoperative surgical bleeding. Raised intra-abdominal pressure is measured via a urinary bladder catheter [9]. The total blood loss is proportionate with the intra-abdominal pressure, also proportionate with patient's body mass index (BMI) [9]. In another study, the effects of prone versus jack-knife position on intra-abdominal pressure and intraoperative bleeding during lumbar disc herniation surgery were conducted, and intra-abdominal pressure came out to be significantly higher in prone position [10]. Certain anesthetic agents in spine and cancer surgeries play an important role in exacerbating intraoperative blood loss like sevoflurane results in significantly greater intraoperative blood loss than propofol [11]. Certain cancer surgeries also cause massive perioperative bleeding due to extensive intra-tumor blood vessel networks that lead to unpredictable internal bleeding during surgery. A case study is presented on metastatic prostate adenocarcinoma in which patient develops hyper-fibrinolysis leading to widespread ecchymosis and disseminated intravascular coagulation (DIC). Any surgical attempt to resect this type of cancer can potentially lead to massive perioperative hemorrhage and other complications [12].
3. Cardiac/major vascular surgery: In cardiac or major vascular surgeries, surgeons deal with main blood vessels like the aorta, coronaries, and femoral, tibial, brachial, or vertebral arteries. So, there are higher chances of intraoperative and postoperative hemorrhage leading to severe consequences.

Box 10.1 Consequences of Liver Disease on Coagulation

- Thrombocytopenia
- Accelerated or decreased fibrinolysis
- Qualitative defects in platelets function
- Predisposition to fibrinolysis

10.2.1.2 Coagulation Abnormalities

1. Acute traumatic coagulopathy: It could mainly be an iatrogenic or secondary coagulopathy, a condition in which various elements are thought to play a role, including consumption of clotting factors, hemodilution from large quantity of crystalloid infusion, acidosis, and hypothermia. The exact mechanism of coagulopathy is still unknown. One theory believes that actual injury causes release of certain tissue factors that lead to thrombin and fibrin generation and utilization leading to DIC [13]. Another theory describes that trauma-induced hypoperfusion and ischemia lead to release of activated protein C, which leads to consumption of plasminogen activator inhibitor, inhibition of the clotting cascade, systemic anticoagulation, and hyper-fibrinolysis [14]. A high fresh frozen plasma to RBCs ratio is the current treatment of choice for acute traumatic coagulopathy [15].

   Clotting factors deficiencies: Clotting factors deficiencies may be congenital or acquired. Congenital deficiency includes factor VIII deficiency called hemophilia A disease and deficiency of factor IX called hemophilia B. Another congenital bleeding disorder is von Willebrand's disease caused

by deficiency of von Willebrand factor (vWF). Acquired clotting factors deficiency also develops in selective individuals because of the autoantibodies affecting the activity or accelerating the clearance of clotting factors [16]. Such antibodies are usually directed against factor VIII and vWF. These acquired antibodies are basically IgG4 type targeting several epitopes of clotting factors [17].

An undiagnosed inherited bleeding disorder: Some individuals have congenital deficiency of coagulation factors like factor VIII and vWF. These patients do not have bleeding symptoms initially. If such patients are never being diagnosed with congenital coagulation factors deficiency and yet they present for any elective surgery or emergency trauma surgery, then bleeding is profuse and unpredictable [18]. Diagnosis is difficult in these patients unless some family members with some type of bleeding disorder or in some cases these patients are found to have large multimers of vWF [16]. Common bleeding sites are the skin, mucosa, and muscles. Hemarthrosis is rare. Recombinant factor VII and prothrombin complex concentrate are the first line of management.

2. Drug-induced acquired factor deficiency: Warfarin, an oral vitamin K antagonist, is used to prevent arterial and venous thromboembolism in variety of clinical conditions. It is one of the leading drugs causing emergency room visits for adverse drug reactions. Annually the frequency of bleeding complications associated with over-anticoagulation is 15% to 20%, with fatal bleeds accounting for as high as 1% to 3% [19]. Assessment of warfarin-induced anticoagulation is typically done using the international normalized ratio (INR). The INR levels and their management are summarized in Table 10.2. The authors recommend the use of 3-factor prothrombin complex concentrate (PCC) with vitamin K and a judicious amount of rVIIa as the treatment of choice for over-anticoagulation, although the risk of thromboembolism is still there. Selective serotonin receptor inhibitor (SSRI) is a group of antidepressant drugs most commonly used for depression all over the United States. Studies show that

10

Table 10.2 Guidelines for the reversal of anticoagulation therapy [22]

INR	Clinical scenario	Management
<4.5	No bleeding	Hold warfarin until INR in therapeutic range
	Rapid reversal required	Hold warfarin Consider vitamin K 2.5 mg oral
4.5–10	No bleeding	Hold warfarin until INR in therapeutic range Consider vitamin K 2.5 mg oral
	Rapid reversal required	Hold warfarin Give vitamin K 2.5 mg oral or 1 mg IV infusion
>10	No bleeding	Hold warfarin until INR in therapeutic range Give vitamin K 2.5 mg oral or 1–2 mg IV infusion over 30 min, and repeat q24h as needed
	Rapid reversal required	Hold warfarin Give vitamin K 1–2 mg IV infusion over 30 min, and repeat q6–24 h as needed
Any INR	Serious or life-threatening bleeding	Hold warfarin Give vitamin K 10 mg IV infusion over 30 min Give 4 units FFP/plasma *Consider 4-factor PCC (Kcentra) (preferred for life-threatening bleeding)* *INR 1.5–3.9: 25 units/kg (maximum 2500 units)* *INR 4.0–6.0: 35 units/kg (maximum 3500 units)* *INR >6.0: 50 units/kg (maximum 5000 units)*

there is a risk of postoperative hemorrhage with SSRI use only when used along with NSAIDs or warfarin [20]. Cessation of SSRIs before surgery is still under investigation because cessation of SSRI before surgery may potentially precipitate a discontinuation syndrome, which may exacerbate depression and increase sensitivity to postoperative pain [21]. So, the internists, surgeons, and anesthesiologists should be aware of potential perioperative SSRI-associated bleeding risks.

3. Dilutional coagulopathy: Dilutional coagulopathy is defined as a coagulation abnormality due to "loss, consumption, or dilution of coagulation factors that occurs when blood is replaced with fluids that do not contain adequate coagulation factors" [23]. This hemostatic disturbance is further deteriorated by continuous fluid administration, acidosis, fibrinolysis, and hypothermia. It is a multifactorial change that affects thrombin generation, clot firmness, and fibrinolysis. Acquired fibrinogen deficiency is considered the leading cause of dilutional coagulopathy [24]. High molecular weight dextrans are also linked to severe disturbances of clot formation [25]. This impact on clot formation was significantly reduced by introducing new low molecular weight starches, but depending on the amount of fluid given, a marked impairment of hemostasis can still be observed. Rotation thromboelastometry is the test of choice to evaluate perioperative coagulation status. FFP transfusion 30 ml/kg is the treatment of choice for dilutional coagulopathy and in massive transfusion scenarios [26].

10.2.1.3 Obstetric Diseases

1. Placental anomalies: Definition of massive obstetric hemorrhage include a fall in hemoglobin concentration of >40 g/L or blood loss of >2500 mL or transfusion of > four units of RBCs [27]. Postpartum hemorrhage (PPH) means more than 500 mL blood loss from the genital tract within 24 h of birth. PPH is subdivided into minor (500–1000 mL), moderate (1000–2000 mL), and severe (>2000 mL) [2]. Common etiologies include uterine atony, placenta previa, placenta accreta, abruptio placenta, uterine rupture, or embryonic emboli associated DIC. In parturient, fibrinogen levels are 4–6 g/L, almost twice the level when compared to nonpregnant females. And the concurrent drop in protein C and S promotes prothrombotic state resulting in shorter PT and aPTT values. So, the combined results may come out normal in massive hemorrhage [28]. A retrospective study shows that there is no association between the method of placenta removal and postpartum blood loss in cesarean section deliveries. Placenta removal can occur spontaneously by massaging on the uterine fundus and applying gentle traction on the umbilical cord, or it can be removed manually by placing surgeon's dominant hand in the uterine cavity and removing the placenta by detaching it from the uterine wall [29].
2. Embryonic embolic event-associated DIC: Amniotic fluid embolism leading to DIC usually occurs at term or immediate postpartum. Amniotic fluid contains surfactant and various pro- and anti-anticoagulants. Surfactant, a lipoprotein produced by fetal lungs and present in increasing amounts in amniotic fluid with increasing gestational age, is structurally like tissue thromboplastin and possesses significant thromboplastic activity. It also contains cysteine protease that directly activates factor X, and it directly inhibits the platelets too [29]. Newborns may develop tachypnea and cyanosis. Patient shows signs of hypotension, brief generalized seizures, and profuse vaginal bleeding followed by unconsciousness. PT, aPTT, and bleeding time all are prolonged, and fibrinogen level falls drastically. Treatment strategy comprises of blood component replacement, including PRBC, FFP, platelets, cryoprecipitate, and possibly fibrinogen concentrate. Recombinant factor VIIa use is associated with increased mortality as compared to the patients who do not receive rFVIIa.

10.3 Clinical Manifestations

10.3.1 Vital Signs Changes

Perioperative massive bleeding is categorized as compensated, mild, moderate, and severe, as shown in ◘ Table 10.3.

Table 10.3 Vital sign changes in various severity of hemorrhage [30]

Stage	I (compensated)	II (mild)	III (moderate)	IV (severe)
Blood loss	<15% 750–1000 ml	15–<30% 1000–1500 ml	30–<40% 1500–2000 ml	>40% 2000 ml or more
Blood pressure	Normal Vasoconstriction redistributes blood flow, slight rise in diastolic BP seen	Orthostatic changes in BP Vasoconstriction intensifies in noncritical organs (skin, muscles, and gut)	Markedly decreased SBP <90 mmHg vasoconstriction decreases perfusion to vital organs like the liver, spleen, and kidneys	Profoundly decreased SBP <80 mmHg decreased perfusion affects the brain and heart
Respiration	Normal	Rate mildly increased	Moderate tachypnea	Marked tachypnea, respiratory collapse
Heart rate	Normal (<100 bpm)	Tachypnea (>100 bpm)	Tachycardia (120 bpm)	Tachycardia (140 bpm)
Urinary output	>30 ml	20–30 ml/h	<20 ml/h	Anuria
Capillary refill	Normal <2 s	>2 s Clammy skin	>3 s Cool, pale skin	>3 s Cold mottled skin
Mental status	Normal or slightly anxious	Mildly anxious or irritated	Confused and agitated	Obtunded

10

10.3.2 Vital Organ Perfusion-Related Presentations

All ASA members and consultants strongly agree to the monitoring of vital organ's perfusion using standard ASA monitors (Table 10.4) (Fig. 10.1).

Table 10.4 Perfusion monitoring parameters

Organs	Perfusion monitoring parameters
Heart	Blood pressure, heart rate, oxygen saturation, EKG, and echocardiography
Brain	Cerebral oximetry and NIRS
Kidneys	Urine output and arterial blood gas analysis

10.4 Evaluation and Diagnostic Checklist

10.4.1 Prothrombin Time and Activated Partial Thromboplastin Time

PT is used to test factor VII (extrinsic factor pathway). aPTT measures the integrity of intrinsic system (factor VIII, IX, XI, XII). Using the cutoff value of international normalized ratio of more than 1.5 times normal, PT demonstrates a sensitivity of 88% and a specificity of 88% in detecting at least one non-hemostatic coagulation factor level after trauma, whereas aPTT (more than 1.5 times normal) demonstrates a sensitivity of only 50% and a specificity of 100% because factor VIII is often increased as an acute phase reactant in trauma and surgical patients [31]. The limitations of PT and aPTT are summarized in ▶ Box 10.2.

Thromboelastography (TEG) and Thromboelastometry (ROTEM) Since PT/aPTT tests are usually performed in central/core laboratories of the hospital, there is substantial time delay in getting the results. So TEG/ROTEM can be performed as a point-of-care hemostasis monitoring test. Both tests evaluate the speed and strength of clot formation as well as clot stability; both help to evaluate hemophilia, fibrinogen deficiency, factor XIII deficiency, and fibrinolytic state [33]. Reference ranges can vary from institution to institution. Clinical results of both tests can be similar, but the two results are not interchangeable [34]. Systemic fibrinolysis is suspected when clot breakdown is observed within 1 hour [35].

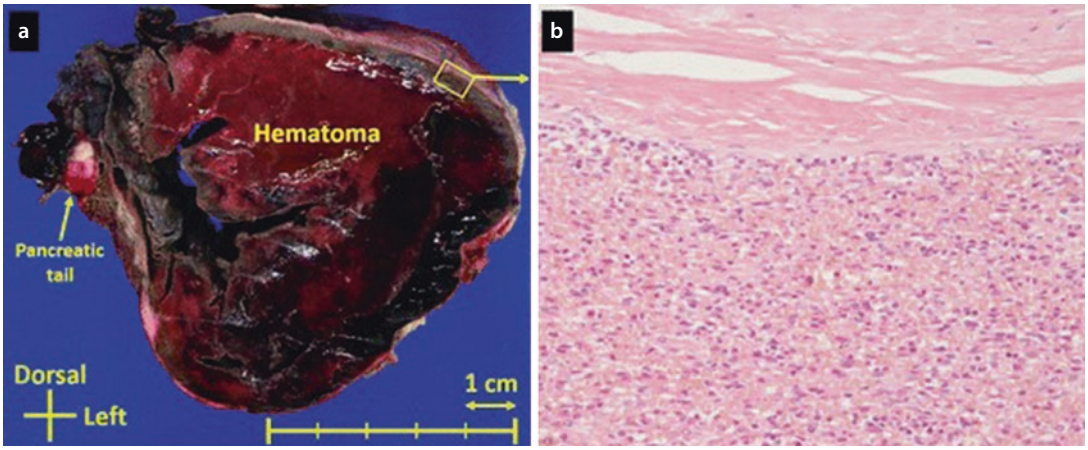

Fig. 10.1 **a** The excised specimen was grossly 9cm in diameter, had a giant hematoma surrounded by gray hrad parenchyma witha smooth capsule. **b** The specimen microscopically showed normal splenic tissue with a firm capsule [60]

Box 10.2 Limitations of PT/aPTT [32]

- PT and aPTT do not provide any clue about in vivo interaction of platelets with coagulation factors.
- PT and aPTT remain prolonged even if thrombin generation is improved because of antithrombin or protein C deficiency.
- PT/aPTT does not tell about the overall stability of a hemostatic thrombus because both tests are terminated at very low thrombin levels and before fibrin is polymerized.

10.4.2 Electrolytes Alterations

Serum calcium: Since massive hemorrhage is accompanied with massive blood and blood products replacement, electrolyte alterations are common consequences particularly serum calcium levels as it plays an important role in coagulation cascade and has an inotropic effect on cardiac myocytes. RBCs are stored in citrate, a calcium-chelating agent. So, massive transfusion leads to potentially severe hypocalcemia [36].

Serum magnesium: Citrate also binds magnesium like calcium, so patient may develop hypomagnesemia resulting into certain fatal cardiac manifestations as well.

Serum potassium: Hypokalemia or hyperkalemia may also occur because of release of stress hormones or reentry of potassium ions into transfused RBCs or higher potassium concentration in stored RBCs [37].

Table 10.5 Advantages/disadvantages of POC testing [39]

Advantages of POC testing	Disadvantages of POC testing
Only a small volume (1–5 ml) of blood is needed for testing	No single POC coagulation test covers the functioning of the entire hemostatic system
Rapid availability of results	Hypo- and hyperthermia affect the results
Lab transportation of blood sample is no longer necessary	Total cost of POC exceeds that of conventional coagulation testing
Can be carried out without specialized training	Pre-existing coagulopathies can alter the results

10.4.3 Point-of-Care Testing

It includes basic electrolytes, serum glucose level, lactate measurement, arterial blood gas analysis, and Hb/Hct ratio. Timely measurement of these parameters facilitates assessment of occurrence and severity of any disturbance and helps its management accordingly. Currently POC testing is usually suggested in most of trauma patients who have significant injuries but not enough to activate a massive transfusion protocol (MTP) [38]. The advantages and disadvantages of POC are summarized in Table 10.5.

10.5 Anesthetic Management of Massive Perioperative Hemorrhage

Anesthetic management strategies of massive perioperative hemorrhage are summarized in Table 10.6.

10.5.1 Non-pharmacologic Management

10.5.1.1 Transfusion

Blood products transfusion is generally considered for massive perioperative hemorrhage [40], except in those patients with unique religious believe such as Jehovah's Witness which prohibits any blood product infusion (▶ Box 10.3).

Table 10.6 Management strategies of massive perioperative bleeding

Management of massive perioperative hemorrhage	
Non-pharmacologic	**Pharmacologic**
Transfusion	Desmopressin
Temperature management	Tranexamic acid
Patient positioning	Aminocaproic acid
Acid-base balance	Aprotinin
Damage control resuscitation	Vasopressors
Other non-pharmacologic measures	

Box 10.3 Currently Available Blood Products for Massive Perioperative Hemorrhage

Therapeutic agents generally considered for massive perioperative hemorrhage:

- RBCs
- Fibrinogen
- Fresh frozen plasma (FFP)
- Cryoprecipitate
- Albumin
- Prothrombin complex concentrates
- Recombinant factor VII

Packed Red Blood Cells (RBCs)

For many decades, the decision to transfuse RBCs has been based upon the "10/30 rule" that means transfusion was used to maintain a blood hemoglobin concentration above 10 g/dl (100 g/L) and a hematocrit above 30% [41]. These guidelines were revised by the National Institutes of Health Consensus Conference in 1988 and many times afterward. Basically, there is no universally accepted single criterion for RBC transfusion. It varies with patient's clinical status and oxygen delivery needs and from institution to institution.

Oxygen delivery = cardiac output × arterial oxygen content

In healthy subjects, oxygen delivery is increased by increasing cardiac output, but in critically ill patients, oxygen delivery becomes more dependent on arterial oxygen content [42]. So, the higher hematocrit, the more oxygen will be delivered to tissues. Following is the blood transfusion guidelines for hemodynamically stable patients without active bleeding (Table 10.7).

For patients with massive bleeding or hemodynamically unstable, blood transfusion should be guided by the ability to achieve hemostasis and the rate of bleeding, rather than by the hemoglobin level alone. Therefore, the decision of transfusion

Table 10.7 Blood transfusion guidelines [41]

Hemoglobin Level	Comments
<6 g/dl	Transfusion recommended except in exceptional circumstances
6–7 g/dl	Transfusion generally likely to be indicated
7–8 g/dl	Transfusion may be appropriate in patients undergoing orthopedic surgery or cardiac surgery
8–10 g/dl	Transfusion generally not indicated but should be considered for some populations such as those with symptomatic anemia, ongoing bleeding, acute coronary syndrome with ischemia, and hematology/oncology patients with severe thrombocytopenia who are at risk of bleeding
>10 g/dl	Transfusion generally not indicated except in exceptional circumstances

in acutely hemorrhaging patients cannot rely on thresholds. Another concern is whether administration of fresher blood improves clinical outcome or not. One study demonstrated that fresher blood did not improve clinical outcomes as compared to stored standard-issue blood [43]. Without any doubt, RBC transfusion during surgical hemorrhage can potentially improve outcome and even be lifesaving in bleeding patients. However, it is challenging we may not be able to completely delineate the relative contributions of hemodynamic instability, systemic inflammatory reaction, and the transfusion-related side effects to the adverse clinical outcomes associated with surgical blood loss [44].

Fibrinogen

Fibrinogen provides a matrix and mesh network essential for clot strength, thus an important therapeutic product for bleeding control in perioperative settings. Following massive hemorrhage, hypofibrinogenemia occurs because of hemodilution from volume replacement and consumption by clotformation. So, the clot strength is evaluated by thromboelastography, and fibrinogen is administered along with other clotting factors to control perioperative bleeding [45]. Four fibrinogen precipitates are currently available and used all over. It is important to note that high fibrinogen levels can lead to high thrombin generation and ultimately thromboembolic events. Also of note, fibrinogen concentrate must be reconstituted by adding water and agitating for several minutes and has a somewhat limited shelf-life. To raise the serum fibrinogen level by of 1 g/L, 60 mg/kg of fibrinogen administration is required [46] (Table 10.8).

Table 10.8 Suggested bleeding management with focus on fibrinogen repletion strategy [46]

Suggested bleeding management with focus on fibrinogen repletion strategy		
1	Fibrinogen level is <1.5–2 g/l	Fibrinogen concentrates 25–50 mg/l Cryoprecipitate 8–10 units
2	Platelets are <100,000/mm	Platelet concentrate 8–10 units
3	INR >1.7 OR hypovolemia	FFP 20–30 ml/kg

Plasma

Plasma is extensively transfused in surgical and trauma patients, but research shows there is no benefit for most of the clinical conditions except trauma [47]. Some studies showed that the risks of excessive plasma transfusion might outweigh the benefits, hence proving to be harmful [48]. Plasma has three different preparations as illustrated in ▶ Box 10.4.

FFP contains all the components in donor plasma, including albumin and immunoglobulins and procoagulant, anticoagulant, and antifibrinolytic factors. If thawed, FFP is kept at 1–6 °C for 5 days, and such plasma can be used in acute emergencies for massive transfusion. There are some safety concerns as well with this FFP use: first being the transfer of viral infection that can be reduced in the future with use of viral-free plasma products [49] and second being fluid overload and multiple organ failures because a large volume of FFP is required to meet required serum coagulation factors level [50]. It should be kept in mind that these plasma preparations are never a good source of fibrinogen as fibrinogen concentration can vary 1–3 g/l. A large volume of plasma is required to replenish required fibrinogen level that can lead to volume overload instead [51]. The ideal choice for fibrinogen replacement is fibrinogen precipitate or cryoprecipitate.

Cryoprecipitate

Cryoprecipitate contains factor VIII, fibrinogen, fibronectin, von Willebrand factor (vWF), and factor XIII used widely for congenital and acquired coagulopathies. In 2007, the first version of the European guidelines on the management of bleeding after major trauma recommended treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by a plasma fibrinogen level <1 g/L; updates to these guidelines were in 2010 [52]. Generally, 1 unit of cryoprecipitate per 10 kg of body weight will increase the fibrinogen level by about 0.5 g/L. The target threshold of 1.0 g/L has been pushed up to 1.5 g/L in many

Box 10.4 Types of Plasma Preparations

Different plasma preparations
- Fresh frozen plasma (FFP)
- Plasma frozen within 24 h of collection
- Thawed plasma (used within 5 days of initial thaw)

institutions (2.5 g/L in obstetric hemorrhage) [53]. The following are indicationsfor three recommendations of cryoprecipitate use: congenital fibrinogen deficiency, bleeding patients with von Willebrand's disease, and the correction of microvascular bleeding in massively transfused patients with fibrinogen concentrations less than 80–100 mg/dl [54, 55]. In a randomized controlled trial, efficacy of FFP infusion was compared with cryoprecipitate supplement; the result suggested FFP were more efficacious, and FFP produced a significantly greater improvement in INR and activated partial thromboplastin time (aPPT) and resulted in less exposure to blood products than cryoprecipitate [56].

Albumin

During surgery, circulation is usually supported by crystalloids or colloid as a temporizing measure when there is an impending need for blood transfusion. Colloids such as albumin and hydroxylethyl starch (HES) are advantageous since they may remain in the intravascular compartment longer than crystalloid [57]. A meta-analysis found increased perioperative bleeding and need for transfusion with the use of albumin compared to administration of hydroxyethyl starch. Albumin may reduce the platelets activation and release of inflammatory mediators. Another randomized controlled trial compared the effect of albumin administration and Ringers' lactate (LR) during a major surgery and found similar blood loss in the two groups of patients yet increased need for transfusion of blood in the albumin-treated group [58]. A randomized clinical trial studied the impact of albumin on coagulation competence and hemorrhage during a major surgery. Resultsshowed that the perioperative use of 5% albumin compared to LR to support the circulation during cystectomy reduces the postoperative volume surplus but affects coagulation competence and has no impact on postoperative complications or hospital stay [59].

Prothrombin Complex Concentrates (PCC)

Prothrombin complex concentrate (PCC) is a term to describe pharmacological products that contain lyophilized, human plasma-derived vitamin K-dependent factors II, II, X, and X and various amounts of proteins C and S. PCC is administered at bedside irrespective of blood group and usually given to patients using oral anticoagulants [61]. It is also effective for warfarin reversal or deficiency of vitamin K in patients requiring urgent surgery, i.e., within 6 h. Generally, it is not recommended for massive transfusion and coagulopathy associated with liver dysfunction. Patients with heparin-induced thrombocytopenia (HIT) are the absolute contraindication [62]. FDA has approved PCC use only in warfarin-related bleeding because only vitamin K-dependent factors are affected in it, while perioperative coagulopathy involves deficiency of multiple coagulation defects like thrombocytopenia, hypofibrinogenemia, and hyper-fibrinolysis [63]. There is a risk of thromboembolic events with use of these PCC as well, first reported many years ago. In 1990s many activated factors were removed from PCC to improve its safety. In today's PCC, factor II called prothrombin is identified as the main culprit causing thrombogenicity. That's why it is recommended that PCC should be labelled according to prothrombin content as compare to Factor IX [63]. Three retrospective clinical studies have shown that although PCC alone can attenuate bleeding, it is more effective when used combined with FFP [45, 64]. In another study in a rabbit model of hemostasis, four-factor prothrombin complex concentrate administration significantly decreased edoxaban (oral anticoagulant)-associated hemorrhage, and edoxaban-induced factor Xa inhibition and anticoagulant effect have been shown to be similar in rabbits and humans [64].

Recombinant Factor VIIa

Recombinant activated factor VIIa is approved in Europe for the management of hemophilia A or B with inhibitors, acquired hemophilia, inherited factor VII deficiency, and Glanzmann thrombasthenia with antibodies to glycoprotein IIb/IIIa and/or human leucocyte antigens and refractoriness to platelet transfusion. It is also recommended in massive perioperative hemorrhage in those patients who do not have already existing coagulopathy. It is effective in reversing the coagulopathy but is associated with widespread arterial thrombosis too. So, recombinantfactor VIIa is not the priority until the last option [64].

10.5.2 Massive Blood Transfusion Protocol

While most institutions have developed their own massive transfusion protocol (MTP) involving multidisciplinary committee, the common

theme of all such protocols is determining specific triggers for activation of MTP, transfusion end targets, and the logistics of blood product and adjunct availability [65]. A sample MTP is shown in ► Box 10.5.

Generally, MTP is activated after replacement of total blood volume in 24 h needing ≥10 units of packed RBCs, replacement of >4 units of packed RBCs in 1 h with the anticipation of continuous need for blood products, or replacement of 50% of the total blood volume within 3 h and blood loss of up to 1.5 ml/kg/min for more than 20 min. In children, this is activated after transfusion of 4–10 units [68]. MTPs may have a predefined ratio of RBCs, FFP/cryoprecipitate, and platelet units in each pack (e.g., 1:1:1 or 2:1:1 ratio) for transfusion [69]. It is recommended to use the following MTP checklist.

Box 10.5 Sample Massive Transfusion Protocol from the National Blood Authority [66, 67]

Massive transfusion protocol (MTP) checklist:

- Is raising the patient's legs possible? (Avoid head-up position.)
- Inform transfusion medicine doctor "on call" that the MTP has been activated.
- Call for help (e.g., anesthesia clinical assistant [ACA] or second anesthesiologist), or assign a nurse or ACA to check blood products and do charting.
- Start arterial catheter after large-bore intravenous access has been established at two sites (14–16G peripheral intravenous lines preferred; consider large-bore sheath introducer or dialysis-type catheter).
- Is cell salvaging an option? Call the perfusionist "on call."
- Send baseline blood work (type and screen, CBC, INR, fibrinogen, electrolytes/biochemistry).
- Has systemic anticoagulation been reversed?
- Is salvage surgery (i.e., packing and revisiting later) an option?
- Ask the surgeon: "Should we call a vascular surgeon or other assistance for you?"
- Fluid/blood warmer (rapid infuser set up?).
- Forced air heater or other warming device (if <37 °C).
- Should calcium administration be considered?
- Consider intravenous tranexamic acid (15–30 mg·kg^{-1}).
- Consider NaHCO3 or THAM for a pH <7.2.
- Change blood filter every four transfusions if possible (and change the 3-L reservoir every 4 h).

MTP can lead to some complications such as acid-base disturbances, electrolyte abnormalities, and hypothermia, in addition to acute trauma coagulopathy, which are reviewed in the table below.

10.5.2.1 Temperature

Hypothermia is associated with significant coagulopathy. Hypothermia is defined as 35 °C or below since enzyme denaturalization occurs at this temperature [70]. The following are the effects of low temperature on coagulation, as shown in ► Box 10.6.

10.5.2.2 Patient Positioning

Performing a straight leg raise or exaggerated lithotomy position has been shown to increase cardiac output and to increase coronary and cerebral perfusion pressure, respectively, for between 5 and 10 min. In case of sudden severe blood loss when leg raising or exaggerated lithotomy position is not possible, then 5 degrees of Trendelenburg position or keeping the patient in a level position is recommended [71].

10.5.2.3 Acid-Base Balance

Maintenance of acid-base balance is critical in massive perioperative hemorrhage. In trauma patients, acidosis is usually induced by tissue hypoperfusion leading to anaerobic respiration and lactic acid production. This metabolic acidosis impairs almost all components of coagulation. At pH <7.4, platelets change their shape and structure. Impaired thrombin generation due to reduced activity of coagulation factor complexes on the cell surface is a major cause of coagulopathic bleeding. Furthermore, acidosis leads to increased degradation of fibrinogen which further aggravates the coagulopathy. Therefore, maintaining a delicate acid-base balance in a massive perioperative hemorrhage is mandatory for the anesthesiologists.

Box 10.6 Effects of Hypothermia on Coagulation [66]

- Increase in fibrinolysis
- Reduced synthesis of coagulation factors
- Activation of clotting cascade is slowed down
- Direct inhibition of platelets through sequestration

10.5.2.4 Damage Control Resuscitation

This concept was first proposed in the mid-2000s as an alternative approach to manage the hemorrhagic shock. Damage control resuscitation components are shown in ► Box 10.7 [72, 73].

10.5.2.5 Other Non-pharmacologic Management

Other non-pharmacologic measures are outlined in ► Box 10.8.

1. *Piggyback technique*: Instead of two end-to-end anastomoses in the classic technique, piggyback involves anastomosing the donor retrohepatic vena cava directly to the recipient inferior vena cava to help patient better tolerate the hypovolemic state [74].
2. *Low CVP level*: A CVP of less than 5 mmHg is required to reduce intraoperative bleeding. However, there are the risks associated with maintaining a low CVP including cardiovascular instability and air embolism [75].
3. *Intraoperative blood salvage technique*: Autologous blood transfusion and intraoperative blood salvage are useful techniques for the special patient population like Jehovah's Witnesses and patients with rare blood types, undergoing surgery with high risk of intraoperative blood loss and transfusion. Cell salvage may be used in obstetric, cardiac, vascular, orthopedic, pediatric, and oncologic surgeries. Cell salvage with the use of leukocyte-depleting filters removes nearly all cancer cells. Randomized trials suggest that the use of intraoperative cell salvage (ICS) with LDFs results in no difference in long-term survival or tumor recurrence. Nevertheless, the use of cell salvage techniques in cancer surgery remains controversial [76].
4. *Intraoperative normovolemic hemodilution*: In this technique, whole blood is withdrawn from a patient by venesection and is replaced by other isotonic fluids. This blood is then re-transfused intraoperatively and postoperatively as required. This preserves the integrity of RBCs and clotting factors [74].

Box 10.7 Components of Damage Control Resuscitation

- Rapid control of surgical bleeding
- Early and increased use of red blood cells, plasma, and platelets in a 1:1:1 ratio
- Hypotensive resuscitation strategies
- Prevention and treatment of hypothermia, hypocalcemia, and acidosis
- Limitation of excessive crystalloid use

Box 10.8 Other Non-pharmacologic Measures

- Piggyback technique
- Low central venous pressure
- Intraoperative cell salvage
- Intraoperative normovolemic hemodilution

10.5.3 Pharmacologic Management

1. *Desmopressin*: Desmopressin enhances platelet activation and thrombus formation and thus restores hemostasis perioperatively. It does not change whole blood thromboelasticity and coagulation times. Adverse effects may include transient hypotension or tachycardia due to endothelial release of nitric oxide potentially induced by desmopressin [77].
2. *Tranexamic acid*: The use of tranexamic acid in massive postpartum hemorrhage seems to be promising. A randomized, multicenter clinical trial enrolled 20,000 obstetric patients and showed that tranexamic acid reduces death due to bleeding in women with postpartum hemorrhage with no adverse effects. Tranexamic acid should be given as soon as the onset of bleeding to achieve the maximal benefits. Patients in tranexamic acid group were administered 1 g tranexamic acid intravenously, while patients in control group received normal saline [78]. Another study was conducted in pediatric patients undergoing scoliosis surgery in 2005. The benefits of tranexamic acid in controlling perioperative bleeding were investigated. Intraoperative blood loss was 41% lower in patients receiving tranexamic acid (1230 +/− 535 ml) compared with the placebo group (2085 +/−1188 ml, $P < 0.01$) [79]. Tranexamic acid has also been documented to safely reduce the need for blood transfusion in surgery

and improve important health and economic implications in high-, middle-, and low-income countries [80].

3. *ε-Aminocaproic acid*: Meta-analysis of placebo-controlled randomized clinical trials indicate that ε-aminocaproic acid administered before and/or during a procedure is effective in reducing total blood loss and the total number of patients transfused in major orthopedic, cardiac, or liver surgery. Aminocaproic acid administration also lowers the requirement of blood transfusion perioperatively as demonstrated by randomized clinical trials in knee replacement surgery [81]. The 2015 American Society of Anesthesiologists' (ASA) guidelines on perioperative blood loss management suggest the intraoperative antifibrinolytic therapy in the perioperative setting to decrease blood loss and blood product transfusions in major cardiac, liver, and orthopedic surgery [82]. The dosing of ε-aminocaproic acid varies considerably in the literature; commonly reported is a loading dose ranging from 25 to 150 mg/kg followed by a maintenance dose of 12.5 mg–30 mg/kg/h [83]. Side effects include seizures and renal dysfunction. Being a structural analogue of neurotransmitter: GABA, ε-aminocaproic acid has lower seizure complications as compared to tranexamic acid [84].
4. *Aprotinin*: It is a small peptide extracted from bovine tissues which belongs to the SERPINS family. It can neutralize a variety of peptides like trypsin, plasmin, and tissue and plasma kallikrein. Due to its antiplasmin activity obtained at low concentrations, aprotinin is often used as an antifibrinolytic agent perioperatively. Aprotinin also inhibits thrombin-induced platelet activation by unknown mechanisms. Aprotinin was discontinued due to potential increase in long-term mortality in coronary artery bypass surgery patients. There are ongoing investigations attempting to bring it back to clinical utilization in selective groups of patients.
5. *Vasopressors*: Certain vasopressors are of clinical benefits in reducing hemorrhage associated with liver transplantation. The use of low-dose vasopressin (0.04 U/min) infusion during the dissection phase of liver transplantation was associated with reduced blood loss when compared with control group in a retrospective nonrandomized study of 110 patients[85].

10.6 Conclusions

This chapter highlights a very important topic in the field of anesthesia practice. Managing the massive perioperative bleeding is a very challenging task, both for surgeons and anesthesiologists. We discussed the possible etiologies of massive perioperative hemorrhage including trauma, major cardiothoracic, spine surgery, liver transplantation, obstetric complications, and several congenital coagulation anomalies. Incidence and mortality of perioperative hemorrhage varies with different causes. The most common cause is major trauma. The clinical presentation of massive hemorrhage depends upon the severity and rate of blood loss. Amniotic fluid embolism-induced disseminated intravascular coagulation has a very high mortality rate that should be addressed very seriously by both obstetricians and anesthesiologists. Prothrombin time, activated partial prothrombin time, and international normalized ratio were the traditional laboratory tests used for diagnostic purposes for many decades, while TEG and ROTEX revolutionized the diagnostic techniques for hemostasis by providing results quickly and accurately, which helps clinical management of patient in massive hemorrhage tremendously. Serum electrolytes also provide very useful information which helps in management decisions. Treatment strategies can be non-pharmacological measures including massive blood and blood product transfusion, surgical hemostasis, and maintenance of normothermia and electrolyte and acid-base balance. And pharmacologic management includes desmopressin, antifibrinolytic agents, and some vasopressors.

10.7 Review Questions

? 1. What point-of-care techniques can you use to measure fibrinogen in the surgical bleeding patient?

? 2. What are the sensitive electrolyte alterations in massive perioperative hemorrhage in trauma?

3. What is the ideal transfusion option for patients already using oral anticoagulants?

4. What is the treatment of choice for dilutional coagulopathy?

5. What is the relationship between MELD score and blood transfusion in a patient of liver transplantation?

6. What is piggyback technique?

10.8 Answers

1. Thromboelastometry (ROTEM; TEM International, Munich, Germany) and thromboelastography (TEG; Haemonetics Corp., Braintree, MA) are increasingly used as point-of-care devices in perioperative settings.

2. Hypocalcemia and hypokalemia are two sensitive electrolytes disturbances seen in massive perioperative hemorrhage due to trauma.

3. Prothrombin complex concentrate (PCC) is the ideal transfusion option for patients already on warfarin therapy.

4. FFP transfusion 30 ml/kg is the treatment of choice for dilutional coagulopathy and in massive transfusion scenarios.

5. High MELD scores (>30) was found to be significantly associated with increased bleeding and transfusion requirements compared to patients with low MELD scores (<30).

6. Piggyback technique involves anastomosing the donor retrohepatic vena cava directly to the recipient inferior vena cava to make patient better tolerate the hypovolemic state in liver transplantation.

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