Chapter 9

Blood and Transfusion

Megha K. Kanjia

A five-year-old patient with history of severe sickle cell disease presents to the operating room for a craniotomy after having suffered a fall from the roof of a home. His CT scan upon admission shows a midline shift and his last hemoglobin is 7 g/dL.

What Are the Considerations for the Perioperative Management in Patients with Hemoglobinopathies?

Common Hemoglobinopathies and Bleeding Disorders: The major hemoglobinopathies seen in the pediatric population are glucose-6-phosphate dehydrogenase deficiency, hemophilia, and sickle cell disease.

Sickle Cell Disease (SCD) is caused by a variant beta-globin gene on chromosome 11 where valine is substituted for glutamine, resulting in instability of the hemoglobin molecule when deoxygenated, causing sickling, hemolysis, and vaso-occlusive crises. Sickling can be caused by hypothermia, hyperthermia, acidemia, dehydration, and poor oxygenation. Vaso-occlusive crises are caused by a combination of inflammation, vascular endothelial adhesion, and platelet dysfunction. Sickled cells occlude microvasculature causing tissue ischemia. Chronic hemolysis is seen in SCD and results in a baseline hemoglobin of 5–9 g/dL.

Chronic SCD may affect a host of systems including pulmonary restrictive lung disease and pulmonary hypertension, stroke, chronic pain, renal abnormalities and avascular necrosis of the bone.

Treatment for severe chronic disease includes hydroxyurea, which increases the concentration of fetal hemoglobin, causing a leftward shift in the oxyhemoglobin dissociation curve (Figure 9.1). Preoperatively (except with minor, non-invasive procedures), most children with homozygous sickle type hemoglobin (HbSS) should receive a transfusion to correct their hemoglobin level to 10 g/dL and may likely require preoperative hydration, however follow up with the hematologist would be beneficial for specific recommendations.

Perioperative considerations in children with SCD include: Preoperative evaluation and management has been shown to reduce peri-anesthetic morbidity and mortality. Avoidance of hypoxia, acidosis, hyperthermia, hypothermia, and dehydration is paramount to minimizing vaso-occlusive crises. Recommendations for transfusions with most patients with SCD are to correct the anemia to around 10 g/dL. Regional anesthetics are beneficial in reducing pain which can promote sickling.

Thalassemia is a common genetic disorder resulting from a disturbance of the 1:1 alpha:beta polypeptide chains. Severity may range from an asymptomatic carrier to hydrops fetalis, resulting in death. Release of toxic agents causes an alteration of red cell membranes resulting in cells that are rigid and can disintegrate. Clinically, patients may need increased erythropoiesis and, transfusions, and may have iron overload as a result. Concomitantly, infections, splenomegaly, and bone abnormalities may be seen as a result of extramedullary hematopoiesis. Patients with chronic severe disease may require splenectomies, cholecystectomies, or vascular access placement for frequent transfusions.

von Willebrand Disease (vWD) is the most common bleeding disorder, seen in 1/10,000 people. The missing or poorly functioning glycoprotein vWF in this disease causes adherence of platelets to the subendothelium and inability to carry factor VIII properly. Typical symptoms include easy bruising, epistaxis, and menorrhagia. Type 1 (85% of cases) and type 3 (5% of cases) vWD are quantitative deficiencies, while type 2 (10% of cases) is both a qualitative and quantitative deficiency of vWF multimers.

https://doi.org/10.1017/9781108668736.010 Published online by Cambridge University Press

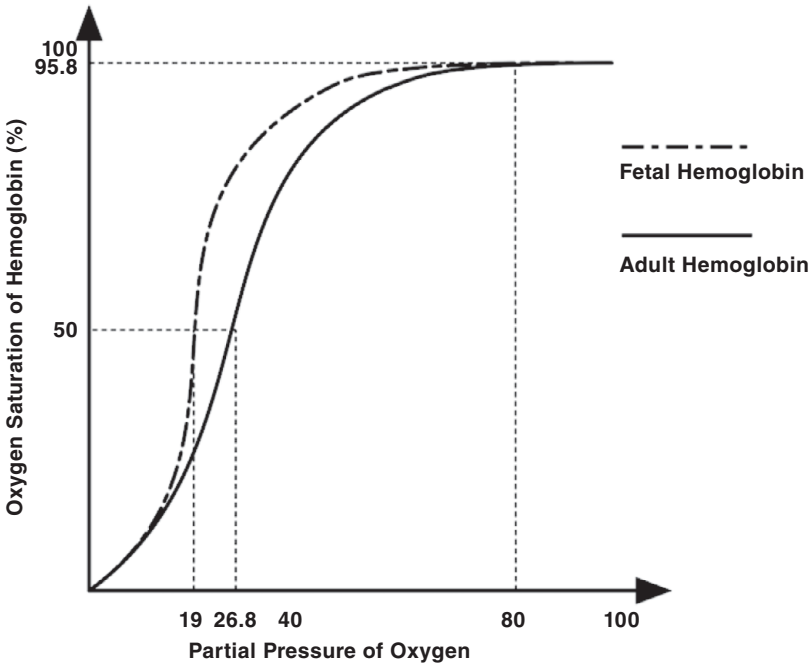

Figure 9.1 Oxyhemoglobin dissociation curve for fetal and adult hemoglobin. Illustration by Adam C. Adler, MD

Typical coagulation studies (PT/aPTT) may be normal in patients with vWF, especially if factor VIII is normal. DDAVP is effective in type I to stimulate the release of vWF; however, it can be deleterious in type II as it may increase the level of poorly functioning vWF. Intravenous fluid hydration should be minimized after administration of exogenous factors to avoid diluting the functional factor. Additionally, acquired vWF may be seen with lymphoproliferative disorders, chronic renal failure, Wilms tumor, hypothyroidism, and certain congenital heart diseases. Caution should be used when considering regional anesthesia, intramuscular injections, nasogastric tubes, and nasal intubations. Consideration may be given to use of antifibrinolytic agents such as aminocaproic acid and tranexamic acid.

Treatment can involve use of DDAVP to encourage release of endogenous stores (types 1 and 3 only) or through use of plasma-derived factor VIII-vWF concentrates (Humate-P).

Hemophilia: Hemophilia A is a congenital bleeding disorder caused by a deficiency in factor VIII, while Hemophilia B is caused by a deficiency in factor IX; each of these bleeding disorders has wide ranges of penetrance, so mild disease may not be noted unless severe trauma occurs, while severe disease may be seen spontaneously even with minor trauma. The degree of the disease depends on the percentage of functional factor. Because hemophilia is typically X-linked, female carriers have 50% of normal factor concentrations, so they are typically asymptomatic. DDAVP may be helpful in mild cases to increase the factor VIII availability, while recombinant factor VIII may be required in other situations. Recommendations from hematology should be obtained to identify the optimal perioperative management strategy. The goal of treatment in a patient with hemophilia undergoing a surgical procedure is to obtain a factor level of 0.8–1.0 units/mL (80–100%) prior to the surgical procedure.

Patients with mild to moderate hemophilia are generally only treated prior to surgical procedures. In general, for non-life-threatening bleeding, coagulation factor activity should be raised to 40–50% of normal. For life-threatening bleeding, coagulation factor activity is raised to 80–100% of normal.

Factor replacement is continued into the postoperative period; 2–3 days after a minor procedure and 7–10 days for major procedures, especially in situations where bleeding is highly detrimental

https://doi.org/10.1017/9781108668736.010 Published online by Cambridge University Press

(neurological surgery). Intermittent dosing or continuous infusion factor replacement can be used to accomplish this goal.

Table 9.1 Estimated blood volume in pediatric patients

Age	Estimated blood volume (mL/kg)
Premature infants	100
Term neonates (<1 month)	90
1–12 months	80
Older children	75
Adolescents/Adults	70

$$Dose\ of\ Factor\ VIII\ (Units) = Desired\ Rise\ in\ \%\ Factor\ Activity \times Weight\ (kg) \times 0.5$$

$$Dose\ of\ Plasma-derived\ Factor\ IX\ (Units) = Desired\ Rise\ in\ \%\ Factor\ Activity \times Weight\ (kg) \times 1$$

$$Pediatric\ dose\ of\ recombinant\ Factor\ IX\ (Units) = Desired\ Rise\ in\ \%\ Factor\ Activity \times Weight\ (kg) \times 1.4$$

$$Adult\ dose\ of\ recombinant\ Factor\ IX\ (Units) = Desired\ Rise\ in\ \%\ Factor\ Activity \times Weight\ (kg) \times 1.2$$

*Dosing for modified prolonged half-life products will depend on the specific product and the patient's pharmacokinetics.

What Are the Indications for Transfusion in the Perioperative Setting?

According to the American Society of Anesthesiology Task Force on Blood Component Therapy, there is evidence to suggest that transfusion at a hemoglobin above 10 g/dL is not indicated, and that transfusion is indicated for lab values below 6 g/dL. For hemoglobin between 6 and 10 g/dL, decision to transfuse should be made based on the child's clinical picture, including vital signs, efficiency of oxygenation and perfusion, as well as degree of blood loss. Transfusion may still be indicated in a child with a Hb >10 g/dL if the clinical picture drives an indication such as baseline increased Hb, increased oxygen demand, higher concentrations of Fetal Hb, or other surgical components.

TRANSFUSION FOR THE PRETERM INFANT

What Are the Risks of Transfusion for Preterm Infants?

Significant risks include hyperkalemia and hypocalcemia. Consideration should be made to receive the freshest blood from the blood bank to minimize hyperkalemia. Often a single unit is split into multiple units over a period of time for a preterm infant, so care should be taken to ensure that the split units are administered from the same "original unit" to minimize exposure of the baby to multiple donors.

For a preterm infant, acute blood loss risks include hypovolemia, hypotension, acidosis, apnea, and hyperkalemia.

TRAUMA AND INDICATIONS FOR TRANSFUSION

What Are the Implications of Major Trauma in a Pediatric Patient?

With their relatively small blood volume (on per kg basis), pediatric patients can become unstable, hypovolemic, and anemic with what is usually considered to be small blood volumes. Twenty percent of trauma deaths are a result of coagulopathy and this is likely related to tissue hypoperfusion. The triad of hypoperfusion, hemodilution, and hypothermia increases the existing coagulopathy for poor outcomes. Hyperfibrinolysis is seen frequently in trauma, but has been found to occur more frequently in the pediatric population than seen in adults. Reliable measurement is difficult in these patients and use of rapid tests, such as rTEG (rapid thromboelastography) is helpful to guide transfusion in a timely manner. Major bleeding should trigger the anesthesiologist to consider activation of a massive transfusion protocol. Additionally, administration of recombinant Factor VIIa has been shown to increase 30-day survival rates when used within two hours of initial bleeding in addition to administration of whole blood.

What Are the Indications for Plasma/Fresh Frozen Plasma Transfusion?

Indications include replacement of a specific factor that is deficient (especially if the factor is unavailable in a recombinant or separate form), iatrogenic

https://doi.org/10.1017/9781108668736.010 Published online by Cambridge University Press

coagulopathy after massive transfusion, immediate need for warfarin reversal, supportive therapy in disseminated intravascular coagulation (DIC), and for children requiring heparin therapy who have an antithrombin III deficiency. Transfusion of FFP has the highest risk as it is often used unnecessarily outside of the setting of Massive Blood Transfusion (MBT) and may result in TRALI (transfusion related acute lung injury), TACO (transfusion associated circulatory overload), or TRIM (transfusion related immunomodulation). TRALI is the most common cause of transfusion related mortality.

What Are the Indications for Cryoprecipitate?

Cryoprecipitate is indicated for active/anticipated bleeding in children with fibrinogen deficiencies (congenital or as a result of massive transfusion), or von Willebrand disease in the setting of poor response to DDAVP.

One unit of cryoprecipitate contains:

- 100 IU of factor VIII
- 250 mg of fibrinogen
- von Willebrand factor (vWF)
- factor XIII

What Is the Debate of 1:1:1 Component Therapy Versus Whole Blood?

Banked whole blood should contain normal levels of all clotting factors and proteins but has 20–50% of factors V and VIII. However, a coagulopathy secondary to a deficiency of a clotting factor typically occurs if there is $<$30% of a normal concentration. While many experts believe that transfusion should occur in a 1:1:1 ratio (plasma:platelet:RBCs), some feel that whole blood more appropriately replaces acute blood loss during surgery. This debate has been longstanding, but it is clear that in cases where transfusion of large volumes replace significant blood loss, such as MBT, clotting factors should also be replaced. Another criticism of whole blood is the difficulty with leukocyte reduction; however newer filters have the capability to save the platelets.

How Does Heparin Resistance Play a Role in the Perioperative Setting?

Heparin is a glycosaminoglycan that binds to antithrombin III to cause a conformational change, inactivating thrombin as well as factor Xa. This is significant in the setting of heparin resistance, which is often noted over time in patients with antithrombin III deficiency, which may be treated with FFP to restore the factor, or with a recombinant antithrombin III factor. As in adults, it should be suspected if appropriate activated clotting time (ACT) levels are not achieved prior to cardiopulmonary bypass.

How Does Hydroxyethyl Starch Play a Role in Platelet Function?

Hydroxyethyl starch primarily affects coagulation by dilution, specifically factor VIII and von Willebrand factor. Additionally, the reduction of glycoprotein IIb/IIIa availability will alter platelet adhesion. Direct movement into fibrin clots will also decrease coagulability; most of these scenarios are noted when $>$20 mL/kg are administered.

How Does ABO Compatibility Play a Role in Transfusion?

While RBCs must only be ABO isoagglutinin compatible, any component with large volumes of plasma (FFP, whole blood, and platelets) must be compatible with the A or B surface antigens. Whole blood must be ABO identical.

What Constitutes a "Massive Blood Transfusion"?

Massive blood transfusion (MBT) is defined as administration of greater than or equal to 1 blood volume in a 24-hour period, greater than or equal to 0.5 blood volume in 12 hours, or acute administration of greater than or equal to 1.5 estimated blood volume (EBV). The goal of MBT is to minimize hemodilution of coagulation factors by replacing factors and blood products lost rather than by replacing with crystalloid and packed red blood cells.

Activation of the massive transfusion protocol through the blood bank will rely on the expertise of the blood bank/transfusion experts to assist in transfusion guidance. This may also allow transfusion to be expedited by use of type O Rh negative blood without prior sample of a cross-match. Type O Rh positive blood can be utilized for male patients. Appropriate monitoring should be established prior to surgery to ensure that adequate baseline data is available.

https://doi.org/10.1017/9781108668736.010 Published online by Cambridge University Press

Additionally, a urinary catheter should allow for appropriate urine output monitoring. Arterial lines as well as central venous pressure lines will provide additional monitoring to guide transfusion as well.

How Does Hematopoietic Stem Cell Transplantation Affect Future Transfusion?

Following Hematopoietic Stem Cell Transplantation, irradiated, leukocyte reduced, cytomegalovirus (CMV)-negative blood should be used; coordination with the transplant team is prudent as the blood type of the patient may change from that of the recipient to that of the donor.

TESTS TO HELP GUIDE TRANSFUSION

How Is TEG (Thromboelastography) Useful for Guiding Transfusion?

TEG is a standardized method of quantifying the quality of a clot as well as providing information regarding fibrinolysis (Figures 9.2, 9.3, and Table 9.2). This tool is primarily used for liver transplantation and cardiac surgery as the information is more accurate and is obtained more quickly than sending prothrombin time/partial thromboplastin time/international normalized ratio (PT/PTT/INR) to the main laboratory. Some studies have found that TEG is an accurate tool for guiding transfusion of various blood products and assistance in choosing which product to transfuse.

How Is ROTEM Useful?

Both ROTEM (Rotational Thromboelastrogram) and TEG are useful in detecting hyperfibrinolysis. Some studies have found that goal directed transfusion via ROTEM has decreased cost to the patients as well, primarily by decreasing administration of FFP to patients. Additionally, clot firmness gives much more information to a clinical picture rather than the number of platelets. Very specific algorithms regarding the various factors within ROTEM have helped guide transfusion and as a result have been shown to decrease morbidity and mortality. In the setting of ongoing bleeding, ROTEM should be repeated 10–15 minutes after a specific intervention to reassess the hemostatic change.

Are PT and aPTT Interchangeable with ROTEM?

PT and PTT are not interchangeable with ROTEM according to newer studies as it appears that PT and aPTT may overestimate the need for transfusion. ROTEM also produces a faster result for treatment as opposed to the more traditional coagulation tests.

What Is a FibTEM?

FibTEM is a functional fibrinogen test that allows the examination of clot firmness based on the fibrinogen function and activity. Because fibrinogen and fibrin

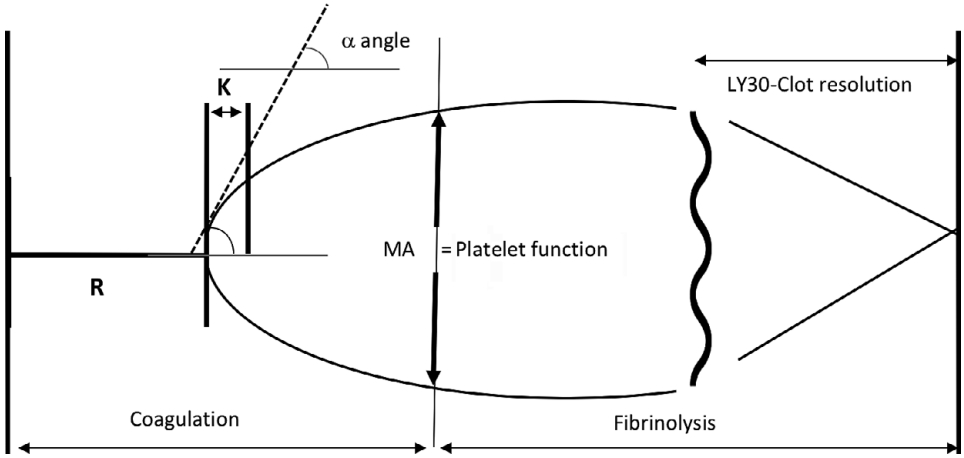

Figure 9.2 Schematic demonstrating the variables measured by thromboelastography and the corresponding portion of the cascade assessed. R=reaction time; MA=measures platelet function in mm; K=fibrin cross-linkage time; α angle=fibrinogen function. Illustration by Adam C. Adler, MD

https://doi.org/10.1017/9781108668736.010 Published online by Cambridge University Press

Table 9.2 Thromboelastography variables by function

Variable	Process evaluated	Definition	Low	High
			Treatment	**Treatment**
R time	Reaction time of clotting factors	Time to formation of Fibrin	Hyperstimulation of pathway	Factor deficiency or residual heparinization
			Anticoagulation	FFP or protamine
K time	Fibrinogen function, clotting factors	Fibrin cross-linkage time (Rate of thrombin formation)	Fibrinogen/factor 8 deficiency	Platelet hypercoagulation
			Cryoprecipitate or FFP	–
α angle	Clot kinetics Fibrinogen function	Rate of clot formation	Fibrinogen/factor 8 deficiency	Platelet hypercoagulation
			Cryoprecipitate or FFP	–
MA	Platelet function, strength, and stability	Fibrin and platelet interaction	Quantitative or qualitative platelets or fibrinogen issue	Platelet hypercoagulation
			Platelet transfusion	Anti-platelet agent
LY30 Lysis 30min	Clot stability	Amount (%) of clot lysis 30 minutes after MA achieved	–	Fibrinolysis or TPA use
			–	Antifibrinolytics

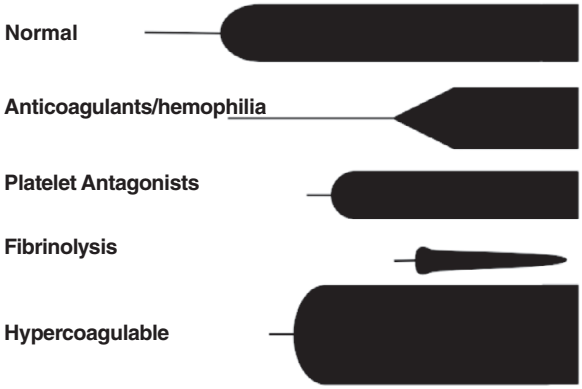

Figure 9.3 Appearance of thromboelastography maps by specific deficiencies. Illustration by Adam C. Adler, MD

are the first factors to be reduced during a significant perioperative hemorrhage, the FibTEM test allows faster examination of the fibrinogen function.

What Role Does Activated Protein C Play in Diagnosis of Coagulopathy?

A few recent studies have shown a correlation between activated protein C levels and aPTT, PT, tPA, as well as D-dimers. Activation of activated protein C signifies risk of MODS (multi-organ dysfunction syndrome), ALI (acute lung injury), as well as mortality.

How Is TRALI Diagnosed and How Significant Is It?

TRALI is diagnosed by noncardiac pulmonary edema and patchy infiltrates, and is typically indistinguishable from ARDS. It is seen in 1/5,000 transfusion and must be noted <6 hours after transfusion to be attributed to the transfusion. The highest risk of TRALI is seen in plasma rich products: FFP, platelets, whole blood. One theory is that neutrophil sequestration results in increased adhesion of molecules to pulmonary vasculature; these neutrophils are activated by donor anti-leukocyte antibodies. Acute transient leukopenia is often noted as well. For these reasons, TRALI is less likely in the neutropenic population.

Drugs

- **Meizothrombin** is inhibited by hirudin and other direct thrombin inhibitors, but is not inhibited by heparin. Specific assays may be utilized for

https://doi.org/10.1017/9781108668736.010 Published online by Cambridge University Press

patients with specific issues, for example, for those patients who are on extracorporeal membrane oxygenation (ECMO).

- **Tirofiban** is a nonpeptide reversible antagonist of fibrinogen binding to the GP IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation.

When Is Factor VIIa Appropriate to Administer?

Factor VIIa is approved for hemophiliacs with high titer inhibitors or for patients with a factor VII deficiency. There has been some debate over when it is appropriate to transfuse. It should be considered that there is a 1.4–10% risk of a major embolic event in adults after transfusion of Factor VII.

What Measures Can Minimize Perioperative Blood Loss?

Erythropoietin is a pharmacologic agent that stimulates the production of endogenous RBC production. It is particularly useful in preterm infants, and for patients undergoing chemotherapy, or for children of Jehovah's witnesses. In the perioperative setting, it is typically used for major surgeries where significant blood loss is anticipated.

Preoperative Autologous Blood Donation is an alternative to allogeneic RBC transfusion, which entails the patient to place banked blood up to 35–42 days prior to the anticipated use. It is not recommended for patients with significant cardiac disease or with ongoing infections, as this will be deleterious for the patient's overall condition. Caution should be exercised when family-donated blood is given to a patient as these patients have a higher risk of graft versus host disease, so the blood should be irradiated to minimize this.

Cell Saver/Blood Recovery and Reinfusion can be used to minimize exposure to allogeneic blood thereby reducing the potential for infections and reactions. The blood is collected directly from the operative site and is washed in a centrifuge so the hematocrit of blood being infused is between 50–60%. Enough blood has to be received from the operative site to be able to convert this into a usable cell saver unit, so it is unlikely to be of help in infants and younger children. Lastly, cell saver devices and operators can have a significant cost, so are typically only financially helpful if three or fewer units of allogeneic RBCs are transfused. Contraindications to use of this equipment would include contamination of blood from bacteria (bowel, abscesses), sickle cell disease (SCD), foreign materials such as methylmethacrylate, neomycin, as well as malignancy, which is a relative contraindication.

Controlled Hypotension: This is a method whereby the systemic perfusion pressure is reduced to attempt to minimize blood loss. Techniques include vasodilators, high concentrations of volatile anesthetic, and large-dose opioid infusions. Consideration should be given to the potential of rapid blood loss, in which case a rapid reversal agent would be more beneficial to mitigate the hemodynamic response and potential collapse. Caution should be exercised because although there are no pediatric studies to support this, adult studies have shown that brain ischemia has been evident at MAP of 55 mmHg in the presence of hypocarbia.

Normovolemic Hemodilution: This is a purposeful hemodilution to minimize the need for allogenic blood transfusions. Two alternate methods are utilized to achieve normovolemic hemodilution; the first is allowing the surgical blood loss to continue until the hematocrit is in the upper teens, and then transfusing packed red blood cells (PRBCs) at the end of the case, which is theorized to allow the bleeding to occur at a lower hematocrit, lessening the loss of RBCs. The second method is to remove blood from the child closer to the initial incision while administering crystalloid and reinfusing the blood at the end of the procedure after bleeding has stopped. Normovolemic hemodilution is contraindicated in patients with cyanotic heart disease, septicemia, and SCD, and any other disease that is strongly dependent upon perfusion. Overall this can minimize the allogenic RBC requirement, but if the hematocrit is less that 15%, subendocardial myocardial ischemia is possible.

Antifibrinolytics: Aminocaproic acid and tranexamic acid (TXA) inhibit fibrinolysis primarily used to minimize bleeding. Adverse effects include anaphylaxis and risk of deep vein thrombosis, and pulmonary embolism. Some studies have found that TXA as an antifibrinolytic agent has been useful in reducing perioperative blood loss. There is evidence-based medicine suggesting that initial bolus doses with an infusion are helpful in craniofacial surgeries as well as spine surgeries to minimize blood loss.

https://doi.org/10.1017/9781108668736.010 Published online by Cambridge University Press

Suggested Reading

Haas T, Goobie S, Spielmann N, et al. Improvements in patient blood management for pediatric craniosynostosis surgery using a ROTEM(®)-assisted strategy – feasibility and costs. *Paediatr Anaesth*. 2014;24(7):774–80, PMID: 24417649.

Haas T, Spielmann N, Mauch J, et al. Comparison of thromboelastometry (ROTEM®) with standard plasmatic coagulation testing in paediatric surgery. *Br J Anaesth*. 2012;108(1):36–41. PMID: 22086509.

Marques MB, Tuncer HH, Divers SG, et al. Acute transient leukopenia as a sign of TRALI. *Am J Hematol*. 2005;80(1):90–1. PMID: 16138350.

Mazzeffi MA, Stone ME. Perioperative management of von Willebrand disease: a review for the anesthesiologist. *J Clin Anesth*. 2011;23(5):418–26. PMID: 21741810.

Mehra T, Seifert B, Bravo-Reiter S, et al. Implementation of a patient blood management monitoring and feedback program significantly reduces transfusions and costs. *Transfusion*. 2015;55(12):2807–15. PMID: 26264557.

Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. *N Engl J Med*. 2017;376 (16):1561–73.

Toy P, Popovsky MA, Abraham E, et al. Transfusion-related acute lung injury: definition and review. *Crit Care Med*. 2005;33(4):721–6. PMID: 15818095.

Vogel AM, Radwan ZA, Cox CS Jr., et al. Admission rapid thrombelastography delivers real-time "actionable" data in pediatric trauma. *J Pediatr Surg*. 2013;48 (6):1371–6. PMID: 23845632.

https://doi.org/10.1017/9781108668736.010 Published online by Cambridge University Press