Perioperative bleeding management in pediatric patients

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Purpose of review
Managing the bleeding pediatric patient perioperatively can be extremely challenging. The primary goals include avoiding hypotension, maintaining adequate tissue perfusion and oxygenation, and maintaining hemostasis. Traditional bleeding management has consisted of transfusion of autologous blood products, however, there is strong evidence that transfusion-related side-effects are associated with increased morbidity and mortality in children. Especially concerning is the increased reported incidence of noninfectious adverse events such as transfusion-related acute lung injury, transfusion-related circulatory overload and transfusion-related immunomodulation. The current approach in perioperative bleeding management of the pediatric patient should focus on the diagnosis and treatment of anemia and coagulopathy with the transfusion of blood products only when clinically indicated and guided by goal-directed strategies.

Recent findings
Current guidelines recommend that a comprehensive multimodal patient blood management strategy is critical in optimizing patient care, avoiding unnecessary transfusion of blood and blood product and limiting transfusion-related side-effects.

Summary
This article will highlight current guidelines in perioperative bleeding management for our most vulnerable pediatric patients with emphasis on individualized targeted intervention using point-of-care testing and specific coagulation products.

Keywords
blood conservation techniques, blood product transfusion, pediatric bleeding management, thromboelastometry

INTRODUCTION

Major pediatric surgery and trauma may be associated with significant blood loss. Risk factors for major bleeding can be divided into patient factors (such as underlying inherited or acquired bleeding/clotting disorders) and surgical/traumatic factors. As much as 60–90% of infants and children undergoing liver transplant, cardiac or cranial surgery receive blood products [1].

Massive hemorrhage is defined as blood loss exceeding one circulating blood volume within a 24-h period or blood loss of 50% of circulating blood volume within a 3-h period or transfusion rate equal to 10% of circulating blood volume every 10 min. A transfusion threshold of 40 ml/kg of all blood products given in the first 24 h was identified as putting critically injured children at high risk for early and in-hospital death [2].

BLEEDING AND BLOOD TRANSFUSION: MORBIDITY AND MORTALITY

In pediatric major surgery, meticulous attention must be given to maintaining normovolemia as hypovolemia due to blood loss is the most common identifiable cause of anesthesia-related cardiac arrest, and is responsible for at least 12% of all cardiac arrests in children [3]. Although traditional bleeding management, consisting of transfusion of

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KEY POINTS

- A comprehensive multimodal patient blood management strategy is critical in optimizing pediatric patient care.
- Transfusion of allogeneic blood products should be performed only when clinically indicated and guided by goal-directed strategies.
- The use of ROTEM or thrombelastography has been demonstrated to be extremely useful in detecting coagulopathies and guiding bleeding management.

autologous blood products, offers a fairly acceptable safety profile, there is strong evidence that transfusion-related side-effects are associated with increased morbidity and mortality in children [4,5]. The rate of death corresponds to two per 100 000 blood products transfused. The three main causes of mortality are transfusion-related acute lung injury, transfusion-related acute circulatory overload and hemolytic transfusion reactions with mortality rates as high as 15–30% [5]. Other risks include transfusion-transmitted infection and transfusion-related immunomodulation. Furthermore, bleeding and resuscitation can be associated with electrolyte abnormalities (such as hypocalcemia, hypomagnesemia, hypokalemia, hyperkalemia and/or citrate toxicity) and a lethal triad of acidosis, hypothermia and coagulopathy [6]. Massive blood transfusion in pediatric trauma, surgery and critical care has been identified as an independent predictor of multiple organ failure, systemic inflammatory response syndrome, increased infection and increased mortality [7]. Massive pediatric transfusion is independently associated with an increased 24-h mortality (odds ratio 2.50) and in-hospital mortality (odds ratio 2.58) [2]. Early recognition, appropriate and timely treatment of major blood loss and its consequences are vital to reducing morbidity and mortality.

PREVENTION OF PREOPERATIVE BLEEDING: BLOOD CONSERVATION TECHNIQUES

Judicious perioperative care should involve the use of multimodal blood conservation techniques to minimize bleeding and related complications of allogeneic blood product transfusion. The World Health Organization and the American Medical Association recommend that the implementation of comprehensive strategies for patient blood management be the focus in perioperative transfusion/coagulation management to improve safety [8]. Indeed, patient blood management programs, as recommended by organizations such as Society for the Advancement of Blood Management and the American Association of Blood Banks, have been shown to reduce in-hospital blood product transfusion, mortality and costs [9,10].

Preoperatively, diagnosis and treatment of anemia by delaying elective surgery, iron supplementation or administering recombinant human erythropoietin has been described [11,12]. The incidence of preoperative anemia in neonates is as high as 37% in US hospitals and is an independent risk factor for neonatal postoperative mortality, increasing the incidence by at least two-fold [13▪].

Preoperative autologous blood donation may be offered in an older child, but problems with this process include issues with incomplete donations, wastage, clerical error, blood storage issues and rendering the child anemic preoperatively.

Intraoperatively, there are a number of options that should be used in combination [14]. Careful fluid management to avoid hemodilution, optimizing tissue oxygenation and minimizing tissue oxygen consumption are imperative. Employing a restrictive transfusion practice (setting a transfusion target of a hemoglobin 7 g/dl instead of 9 g/dl) has been shown to be safe in the pediatric ICU setting and should be considered if the patient is hemodynamically stable [15,16], although evidence is lacking on the safest strategy for the neonatal population [17]. Hypothermia, in combination with acidosis, inevitably leads to an impaired coagulation process and may, therefore, worsen bleeding. Thus, forced-air warming should be rigorously performed and temperature, as well as pH values, measured.

Surgical techniques can help control bleeding and include pre-emptive tumor vessel or arteriovenous malformation embolization, minimally invasive surgery and using topical haemostatic agents. Intraoperative blood/cell salvage is another option that involves collecting autologous blood from the surgical site to be processed and given back to the patient during the surgery [18,19]. Contraindications include tumor surgery (potential dissemination of tumor cells) and the use of agents that would result in red blood cell lysis (sterile water, alcohol and hydrogen peroxide) and clotting agents (surgical and gelfoam), contaminants (urine, bone and infection) and irrigating solutions.

Postoperatively, the avoidance of hemodilution, careful hemodynamic control, minimizing blood draws and other causes of iatrogenic blood loss, utilizing restrictive transfusion guidelines and blood product transfusion protocols should be considered. Table 1 details these pediatric patient blood management strategies.

Table 1. Pediatric patient blood management strategies

Preoperative	Intraoperative	Postoperative
Schedule optimal timing for procedure	Maximize tissue oxygen delivery	Optimize ventilation, cardiac output and tissue oxygenation
Avoid unnecessary laboratory work-up	Minimize tissue oxygen consumption	Optimize fluid management; avoid hemodilution
Clear structured bleeding anamnesis	Careful blood pressure management	Education of medical professional in PBM goals
Early diagnosis and treatment of anemia	Optimize fluid management; avoid hemodilution	Tolerate anemia if possible
Stimulate erythropoiesis	Keep normothermia, avoid acidosis	Treat anemia with iron therapy
Education of medical professionals in PBM goals	Clear algorithm for bleeding management	Stimulate erythropoiesis
Implementation of PBM program	Optimize surgical technique and consider blood-sparing alternatives	Limit iatrogenic blood loss
	Usage of topical hemostatic agents	Reduce amount and volume of laboratory blood draws
	Antifibrinolytics	Clear algorithm for blood product transfusion
	POC assessment of hemostasis	Avoid treatment of impaired standard laboratory tests without clinical relevance
	Usage of cell salvage	Treat coagulopathy with vitamin K if indicated
	Usage of purified coagulation factors whenever possible and when available	Tolerate coagulopathy if possible
	Restrictive transfusion practice	Consider antifibrinolytic treatment
	Transfusion of appropriate type and volume blood products when necessary; avoid unnecessary and overtransfusion	

PBM, patient blood management; POC, point-of-care.

DIAGNOSIS OF PERIOPERATIVE BLEEDING: VISCOELASTIC TESTING VS. STANDARD LABORATORY WORK-UP

The cause of haemostatic changes during pediatric major surgery and trauma is multifactorial and may be related to dilutional coagulopathy, hyperfibrinolysis, surgical complexity with increased blood loss and the consecutive loss of coagulation factors [20]. Fibrinogen is the first coagulation factor that achieves a critical low value during massive blood loss, whereas all other factors seem to be less affected by blood loss and hemodilution [21]. In addition, tissue injury can produce tissue activators (tissue plasminogen activator, urokinase and kallikrein) and activate plasmin from plasminogen, which can cause a shift from physiological fibrinolysis to hyperfibrinolysis. This hyperfibrinolysis decreases clot stability and increases bleeding tendency, by increasing consumption of fibrinogen and coagulation factors. Plasmin induces many other responses that contribute to coagulopathy and bleeding, including activation of thrombin generation, cleavage of fibrinogen to fibrin and cleavage of receptors on platelets [22]. This in turn starts a vicious cycle of coagulopathy and inflammation in the bleeding child.

Thus, the presence of this multifactorial cause necessitates the use of a fast and reliable test to diagnose the cause and treat the bleeding properly. The most recently published guidelines recommend performance of standard plasmatic coagulation testing [23▪], however, there is actually no sound evidence from well-designed studies to confirm the usefulness of those test results for the diagnosis of coagulopathy or to guide haemostatic therapy. The unacceptable time delay seems to be the one reason why bleeding management may be performed empirically without a clear, targeted therapeutic focus. Notably, viscoelastic point-of-care such as thromboelastometry (ROTEM) or thrombelastography has been shown to be effective in guiding perioperative bleeding management [23▪,24–33]. Such tests have been shown to be effective at reducing the transfusion of any allogeneic blood products and they also offer a substantial cost saving [34,35▪]. However, the insensitivity to the effect of antiplatelet drugs and to the inhibition of nonthrombin-activated platelet pathways is the main limitation of viscoelastic tests and should be acknowledged.

Future decision-makers should consider the use of such point-of-care testing as a mandatory component of the routine work-up of hemostatic management during major pediatric surgery.

MANAGEMENT OF THE BLEEDING CHILD

Fluid management: crystalloids and colloids

The goal of intraoperative fluid management should be to maintain normovolemia while avoiding hypervolemia to minimize swelling, edema and hemodilution.

Ringers Lactate (273 mOsm) and Plasmalyte (294 mOsm) are preferred as they are associated with less severe acidosis than isotonic saline [36]. It seems prudent to replace blood loss initially by administration of crystalloids or colloids in a 2 : 1 ratio of estimated blood loss. However, if losses are rapid and at least 20% of estimated blood volume in an infant below 10 kg, administering colloids in a 1 : 1 ratio may be required to maintain hemodynamic stability. In a recent meta-analysis, it was concluded that colloids and crystalloids can be similarly used for fluid resuscitation [37].

Low cardiac output states and hypotension should be avoided as this leads to decreased tissue oxygen delivery and should be rapidly treated and temporized by instituting vasopressors along with aggressive fluid and blood product resuscitation as clinically indicated [38].

Transfusion of blood and platelets

Universal transfusion guidelines recommend against a single transfusion trigger [23▪,38], however, maintenance of a hemoglobin level at 8 g/dl is an accepted standard during massive intraoperative blood loss [4], while in stable critically ill children, a threshold of 7 g/dl might be sufficient [39]. This corresponds to hematocrits between 21 and 25% and should provide an impetus for blood transfusion taking into consideration clinical status of the child and the potential for ongoing blood loss. As a rule of thumb, the required transfusion volume of packed red blood cells in children can be calculated as follows: body weight (kg) × desired increment in hemoglobin (g/dl) × 5 [40]. Overtransfusion should be avoided.

Expert consensus recommends that a minimal platelet count of 50 000 cells/μl should be maintained for patients with ongoing bleeding [23▪,38,41]. Platelet count can be expected to rise by approximately 50 000–100 000 cells/μl after transfusion of 5–10 ml/kg of an apheresis platelet concentrate. The transfusion of platelet concentrate carries the highest risk of side-effects of all allogeneic blood products (bacterial contamination of platelet components is the second most common cause of transfusion-related deaths in the USA) and therefore should be performed cautiously [42].

Rapid transfusion of blood has been associated with fatal hyperkalemia [43]. The 'Wake Up Safe' initiative from Society of Pediatric Anesthesia recommends that RBC should be 'fresh', that is less than 1-week old or washed if the patient is below 1-year old or weights less than 10 kg to avoid hyperkalemia [44].

Transfusion of fresh frozen plasma, cryoprecipitate or fibrinogen concentrate

Current clinical guidelines suggest replacing coagulation factor deficiency with fresh frozen plasma (FFP) at a dose of 10–15 ml/kg when there is an ongoing clinical bleeding and the prothrombin time, partial thromboplastin time and International Normalized Ratio are 1.5 times normal. Notably, evidence-based data supporting this approach are lacking [45▪]. However, there appears to be an overuse of plasma for indications that have never proven to be beneficial [46,47]. Accumulating data suggest that acquired fibrinogen deficiency seems to be the leading determinant in the development of perioperative dilutional coagulopathy [20,21,38]. Current guidelines support the substitution of fibrinogen if below 150–200 mg/dl or maximum clot firmness in the ROTEM FIBTEM assay is less than 8 mm [38,48]. Treatment of acquired fibrinogen deficiency consists traditionally of transfusion of FFP or cryoprecipitate, or administration of purified fibrinogen concentrate. Although frequently used, the recommended dosages for FFP [49] may not be adequate to achieve a clinically meaningful improvement in fibrinogen deficiency and therefore cryoprecipitate of fibrinogen substitute is preferred [50]. Cryoprecipitate contains higher concentrations of fibrinogen as compared with FFP, but was withdrawn from European countries because of risk of immunologic reactions and potential transmission of infectious agents [51]. Alternatively, intraoperative substitution with fibrinogen concentrate can be safely and effectively used to treat fibrinogen deficiency [21,35▪,52–54].

Transfusion of specific coagulation factors

Prothrombin complex concentrate (PCC) can help correct dilutional coagulopathy by increasing thrombin generation [55–57], however, data about the effectiveness or optimal dosing of PCC for pediatric perioperative bleeding are scarce [58].

Acquired factor XIII deficiency appears prevalent even in major pediatric surgery, but no sound data exist on pediatric FXIII supplementation [25,35▪].

Recombinant factor VIIa (rFVIIa) has been described as useful for controlling severe bleeding in cardiac [59–61] and neurosurgical procedures in children [62–64], although a prospective, randomized trial in pediatric cardiac surgery failed to prove a significant difference in blood loss following administration of rFVIIa compared to placebo [65]. Thus, there are insufficient data to make any evidence-based recommendations concerning the efficacy of rFVIIa as prophylactic, routine or rescue therapy in pediatric perioperative bleeding management [66].

Massive transfusion protocol

The goal of a massive transfusion protocol (MTP) is to avoid coagulopathy as a consequence of platelet and clotting factor depletion secondary to transfusion restricted to packed red blood cells. For the treatment of massive hemorrhage in adult trauma patients, early and aggressive transfusion of FFP in a 1 : 1 ratio with packed red blood cells may improve survival [67–69]. Such MTPs, using fixed ratios of blood products (RBC:FFP:Platelets in a ratio of 1 : 1:1), may improve outcome in coagulopathic military and civilian adult trauma patients, but there is a paucity of data on the efficacy of MTP for pediatric trauma patients, whose mechanism of injury may differ from those in adults. Also, it is unclear how this strategy pertains to managing massive blood loss in the pediatric surgical patient.

Even if MTPs are feasible to perform in pediatrics, they are associated with increased blood product transfusion with no increased survival in children. The value of aggressive blood product transfusion using MTPs for the pediatric patient with massive hemorrhage requires further prospective validation [70–73].

ANTIFIBRINOLYTICS

There is strong evidence that the implementation of a patient blood management strategy involving intraoperative prophylactic administration of antifibrinolytics is efficacious (with a good safety profile) at decreasing bleeding in trauma, cardiac, craniofacial and scoliosis surgery [22,74–78]. Tranexamic acid (TXA) is the most common antifibrinolytic used worldwide as epsilon aminocaproic acid (EACA) is not available in many countries (such as Canada, New Zealand and most of Europe). Craniosynostosis patients who were not treated with TXA had an increased odds ratio of 2.6 for all adverse postoperative events not only related to decreased blood loss [79]. Similarly, EACA decreases blood loss and transfusion in observational and retrospective analysis [80,81]. There are a wide variety of dosage schemes for TXA and EACA reported in mostly single center trials, however, to maximize efficacy and minimize side-effects, guidelines should be based on pharmacokinetic data [82]. On the basis of pharmacokinetic data and modeling, a TXA loading dose of 10 mg/kg over 15 min followed by a 5 mg/kg/h maintenance infusion may be sufficient to maintain adequate TXA plasma concentrations during craniosynostosis surgery; based on a presumed minimal TXA plasma concentration of 20 μg/ml. For EACA, a loading dose of 100 mg/kg followed by an infusion of 40 mg/kg/h has been shown to maintain therapeutic plasma concentrations [22,83–85]. A recently completed pharmacokinetic/pharmacodynamic trial in scoliosis surgery will provide better guidelines of the efficacy and safety profile of TXA as well as the optimum therapeutic plasma concentration and the most effective dosage scheme [86].

There may also be a role of TXA in treating subarachnoid hemorrhage in the prevention of rebleeding and improvement in neurological outcome [87,88] and an ongoing trial may answer this question [89]. To date, there is an ongoing Clinical Randomization of an Antifibrinolytic in Significant Head Injury trial investigating the efficacy and safety of TXA in traumatic pediatric brain injury [90].

CONCLUSION

A comprehensive understanding of pathophysiology of hematologic derangements and a multimodal patient blood management strategy is crucial in quickly and safely managing anemia and coagulopathy associated with massive intraoperative blood loss during pediatric major surgery. The goals should be to maintain hemodynamic stability, oxygen carrying capacity and perfusion to vital organs. Overtransfusion and transfusion-related side-effects should be minimized. Future efforts should focus on furthering the education of pediatric anesthesiologists, surgeons and intensivists regarding pediatric patient blood management techniques with particular focus on goal-directed targeted diagnosis using point-of-care testing and targeted therapy utilizing currently unlicensed drugs (such as fibrinogen and PCCs).

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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