Pediatric Patient Blood Management Programs: Not Just Transfusing Little Adults

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A B S T R A C T
Red blood cell transfusions are a common life-saving intervention for neonates and children with anemia, but transfusion decisions, indications, and doses in neonates and children are different from those of adults. Patient blood management (PBM) programs are designed to assist clinicians with appropriately transfusing patients. Although PBM programs are well recognized and appreciated in the adult setting, they are quite far from standard of care in the pediatric patient population. Adult PBM standards cannot be uniformly applied to children, and there currently is significant variation in transfusion practices. Because transfusing unnecessarily can expose children to increased risk without benefit, it is important to design PBM programs to standardize transfusion decisions. This article assesses the key elements necessary for a successful pediatric PBM program, systematically explores various possible pediatric specific blood conservation strategies and the current available literature supporting them, and outlines the gaps in the evidence suggesting need for further/improved research. Pediatric PBM programs are critically important initiatives that not only involve a cooperative effort between pediatric surgery, anesthesia, perfusion, critical care, and transfusion medicine services but also need operational support from administration, clinical leadership, finance, and the hospital information technology personnel. These programs also expand the scope for high-quality collaborative research. A key component of pediatric PBM programs is monitoring pediatric blood utilization and assessing adherence to transfusion guidelines. Data suggest that restrictive transfusion strategies should be used for neonates and children similar to adults, but further research is needed to assess the best oxygenation requirements, hemoglobin threshold, and transfusion strategy for patients with active bleeding, hemodynamic instability, unstable cardiac disease, and cyanotic cardiac disease. Perioperative blood management strategies include minimizing blood draws, restricting transfusions, intraoperative cell salvage, acute normovolemic hemodilution, antifibrinolytic agents, and using point-of-care tests to guide transfusion decisions. However, further research is needed for the use of intravenous iron, erythropoiesis-stimulating agents, and possible use of whole blood and pathogen inactivation. There are numerous areas where newly formed collaborations could be used to investigate pediatric transfusion, and these studies would provide critical data to support vital pediatric PBM programs to optimize neonatal and pediatric care.

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Red blood cell (RBC) transfusions are a common life-saving intervention for neonates and children with anemia. Data from a pediatric intensive care unit (PICU) show that 17%–49% of children receive at least 1 RBC transfusion for an ICU stay lasting at least 2 days [1]. However, there is significant variation in the indications and quantity provided (administration/dosing) for these transfusions, especially prior to the restrictive transfusion trials, with clinicians transfusing RBCs for their stable patients with hemoglobin levels varying from 7 to 12 g/dL [2-4]. Despite substantial benefits for those with anemia, transfusion is associated with both noninfectious risks (transfusion-related acute lung injury, transfusion-associated circulatory overload, and allergic transfusion reactions) and infectious risks (HIV, hepatitis B virus, hepatitis C virus, and emerging infectious diseases) [5-11]. Children are also likely at higher risk for noninfectious adverse events associated with transfusion than adults [12,13]. Because transfusing RBCs may unnecessarily expose children to increased risk without benefit, it is important to design blood management programs specific for children to optimize transfusions in this age group.

Structure of Patient Blood Management Programs and Pediatric Specific Challenges

Patient blood management (PBM) programs strive to optimize the care of patients who need transfusion support. As an adaptation of the “five rights” of medication administration, the transfusion medicine community has appropriately summarized PBM as “transfusing the right product, in the right dose, to the right patient, at the right time, for the right reason” [14,15]. A hospitalwide comprehensive, multidisciplinary, and interdepartmental PBM program has the opportunity to optimize patient care, avoid unnecessary transfusions of blood products, and limit adverse effects [16]. Successful adult PBM programs are rooted in evidence-based medicine and enhance patient safety and outcomes through measurable improvements [17].

Patient blood management programs should not be located solely within transfusion medicine. Active input, commitment, and leadership from medical, surgical, anesthesia, intensive care, hospitalist services, and nursing with significant variation in the indications and quantity provided (administration/dosing) for these transfusions, especially prior to the restrictive transfusion trials, with clinicians transfusing RBCs for their stable patients with hemoglobin levels varying from 7 to 12 g/dL [2-4]. Despite substantial benefits for those with anemia, transfusion is associated with both noninfectious risks (transfusion-related acute lung injury, transfusion-associated circulatory overload, and allergic transfusion reactions) and infectious risks (HIV, hepatitis B virus, hepatitis C virus, and emerging infectious diseases) [5-11]. Children are also likely at higher risk for noninfectious adverse events associated with transfusion than adults [12,13]. Because transfusing RBCs may unnecessarily expose children to increased risk without benefit, it is important to design blood management programs specific for children to optimize transfusions in this age group.

Blood Conservation

Although blood conservation is important for all patients, it is especially critical for neonates and children. It is good clinical practice to limit blood draws. When blood is required for laboratory tests, however, it is important to prevent the patient’s blood from being wasted. This can be performed by using minimum volumes in small tubes or microtainers, reducing the blood requirements for cultures (eg, using pediatric blood culture bottles), batching laboratory tests, using shorter blood draw lines, and returning blood waste in the lines.
Indications and Thresholds for Transfusion in Children

Red blood cells are transfused to increase the oxygen delivery in patients. Among healthy individuals, oxygen delivery by RBCs exceeds resting requirements by 2- to 4-fold [21]. Tissue hypoxia occurs once oxygen delivery becomes lower than the metabolic demands of the tissue; severe anemia leads to lactic acidosis [21,22]. Transfusion indications should be determined not just on the basis of the hemoglobin concentration and/or hematocrit value but must take into account cardiopulmonary risk factors, cause of the anemia, extent of symptoms, and the expected course of the anemia. Although integer-based transfusion thresholds have been a start in the process of transfusion limitation, it is important to note that transfusions should be physiology-based to ensure sufficient oxygen delivery to tissues.

Recent evidence increasingly supports restrictive transfusion practices. More than 30 randomized trials with >12 000 adult patients have consistently shown among almost all subgroups that a restrictive transfusion strategy of 7-8 g/dL does not adversely impact clinical outcome [23]. The Transfusion Requirements in Pediatric Intensive Care Units trial provides the best evidence supporting a restrictive transfusion strategy of 7-8 g/dL (hemoglobin concentrations <9.5 g/dL) or conservative (hemoglobin concentrations <7 g/dL) RBC transfusion strategy and found no benefits to the liberal strategy [24,25]. In a follow-up subgroup analysis of patients with sepsis or septic shock, there were no clinically significant differences found for the occurrence of new or progressive multisystem organ dysfunction syndrome (P = .97), pediatric critical care unit length of stay (P = .74), or mortality (P = .44) in the restrictive vs liberal groups [26]. Other subgroup analyses of this trial with more or less severe illness, noncardiac surgery, and noncyanotic cardiac surgery showed the same trends favoring a restrictive transfusion strategy [27,28]. Although restrictive transfusion strategies are generally embraced by pediatric PBM programs, further research is needed. The Transfusion Requirements in Pediatric Intensive Care Units trial is the only robust trial in children, and it has not been replicated. The results of this pediatric trial also cannot be easily applied to patients with active bleeding (including trauma), hemodynamic instability, brain injury, and cancer (including hematopoietic stem cell transplantation) [29]. In addition, patients with unstable cardiac disease or cyanotic cardiac disease may benefit from a more liberal transfusion strategy, but the data are extremely sparse [28]. Further research is also needed to determine the best hemoglobin threshold for the restrictive transfusion strategy. Several prospective studies in Africa found no benefit for RBC transfusion in children with hemoglobin levels greater than 5 g/dL [30-32]. and it has been suggested that a randomized trial is needed to evaluate the optimal threshold in children [33].

Review and Monitoring of Blood Utilization

There is wide variability in intraoperative and postoperative RBC transfusions in pediatric surgery. Using the American College of Surgeons’ National Surgical Quality Improvement Program pediatric data set consisting of 50 participating pediatric hospitals across North America, Stey et al found that 5 preoperative variables were associated with greater than 3-fold increased odds of receiving an intraoperative or postoperative RBC transfusion. These included young age (29 days to 1 year), American Society of Anesthesiologists Class IV (highest adverse risk anesthesia category), procedure risk (calculated a priori), preoperative septic shock, and preoperative cardiopulmonary resuscitation [34]. In addition, the lack of uniformity in transfusion practices and thresholds was notable. These findings underscore the fact that different pediatric hospitals across the United States have dramatically different transfusion practices even despite uniform patient and procedural characteristics. Thus, there is a strong need for data and clinical practice guidelines to be developed to better support pediatric PBM programs. A key component of a PBM program is monitoring blood utilization and assessing adherence to transfusion guidelines, but few studies have assessed the actual current practices in pediatric hospitals or pediatric services [20]. A retrospective cohort study compared the transfusion practices in hospitalized children by service at a large tertiary care academic institution. They found that RBC transfusion therapy varied significantly in hospitalized children with mean hemoglobin triggers above a restrictive threshold of 7 g/dL for 8 of 12 pediatric subspecialty services evaluated. In addition, among all of the services, there were significant differences between the mean hemoglobin thresholds (>2.5 g/dL) and between the posttransfusion hemoglobin levels (>3 g/dL). They concluded that transfusions may be overused in hospitalized pediatric patients and that implementing a restrictive transfusion strategy could decrease the use of RBC
transfusions [43,55]. However, many pediatric populations have not been studied, as noted above, and the desired compliance measure may be the physiologic target, not an absolute integer value.

**Perioperative Issues in Pediatric PBM**

There are multiple strategies to reduce transfusions perioperatively that are occasionally used by pediatric PBM programs (Table 1).

**Preoperative Strategies to Optimizing Hemoglobin Levels**

Iron deficiency is the most common cause of asymptomatic anemia in the adult surgical settings and is a known predictor of intraoperative and postoperative blood transfusion [36]. Thus, strategies to augment hemoglobin levels prior to surgery may play a key role in avoiding perioperative transfusions. Although oral iron supplementation can be helpful, it will likely not achieve rapid correction of anemia before surgery [37,38]. Parenteral iron has been shown to be safe and effective as an adjunct/alternative to blood transfusions in the adult population [39,40]. The consensus statement from the Network for Alternatives to Transfusion combined evidence from randomized controlled trials and observational studies in orthopedic and cardiac surgical procedures and concluded that quality of evidence for use was moderate to low. The Network for Alternatives to Transfusion recommended preoperative intravenous iron administration for adult patients undergoing major orthopedic surgery with serum ferritin <100 ng/mL, transferrin saturation <20%, or expected blood loss >1500 mL (weak recommendation based on moderate-/low-quality evidence). For all other types of surgery for adults, they had no evidence-based recommendations [41].

Multiple adult studies have assessed the pros and cons of erythropoiesis-stimulating agents like erythropoietin with or without concomitant iron and folate [42]. Data specific to the pediatric population are limited on the benefit of erythropoiesis-stimulating agents [43,44]. However, one study of 82 children reported the effective use of a single dose of recombinant human erythropoietin 7 days prior to surgery to avoid allogeneic transfusion in surgery [45]. Erythropoiesis-stimulating agents have also been used for children of Jehovah’s Witness children [46,47]. The kidney disease improving global outcomes guidelines recommends erythropoiesis-stimulating agents for children with chronic kidney disease [48].

**Preoperative Autologous Blood Donation**

Preoperative autologous blood donation has been used for years in pediatrics, especially in the late 1980s and 1990s, as public and professional awareness of the risk of infectious disease transmissions from blood products heightened. Studies found conflicting results regarding the efficacy of autologous donation in preventing allogeneic transfusions [49]. Although a few found that preoperative donation increased patients’ risk of being transfused [50], one study in children and teenagers found that erythropoietin administration at the time of autologous donation avoided allogeneic transfusion during spinal deformity surgery [51]. One center reported 19 years of experience with preoperative autologous donation in children and found a higher incidence of donation-related problems in children (17.3%) than adults (6.0%). Donation complications included hypotension, restlessness, postponement of surgery (mainly due to respiratory infection), and venous access issues [52]. In addition, preoperative autologous donation is not usually cost saving because many units are never transfused [53]. Thus, the evidence supporting the benefits of preoperative autologous blood donation remains conflicting.

**Intraoperative PBM Strategies**

Intraoperative PBM techniques include acute normovolemic hemodilution (ANH), intraoperative blood recovery (cell salvage), prophylactic use of antifibrinolytic agents, prophylactic coagulation factor replacement, restrictive transfusion thresholds, and point-of-care-based goal-directed transfusion algorithms. These techniques have a range of applicability or evidence supporting their efficacy as blood management tools in the pediatric patient population.

**Acute Normovolemic Hemodilution**

Acute normovolemic hemodilution refers to the collection of 1 or more whole blood units with concurrent volume replacement using a crystalloid or colloid solution at the onset of surgery and reinfusion of the whole blood at the end of the surgery. As a result, the intraoperative blood that is lost has a lower hematocrit and thus conserves overall RBC mass. In addition, the reinfused autologous blood (stored at room temperature) is a source of platelets and coagulation factors leading to better hemostasis. Among adults, ANH has been shown to not cause myocardial ischemia or lack of tissue oxygenation [54], but severe hemodilution impairs cognitive function and may lead to electrocardiographic ST-segment changes [55,56]. The use of ANH in the pediatric surgical population is limited. In major pediatric surgery, however, close attention must be given to maintaining normovolemia because hypovolemia due to blood loss is the most recognized cause of anesthesia-related cardiac arrest, as high as 12% of all cardiac arrests in children [57,58]. Observational data suggest that ANH is clinically acceptable for children [59]. The efficacy of ANH in avoiding allogeneic transfusion in children is unclear because of conflicting results in the small number of pediatric studies that have been published [60,61].

**Cell Salvage**

Intraoperative cell salvage and reinfusion have been evaluated as a PBM strategy in few studies in children. A prospective, randomized, clinical trial using transfusion of cell saver blood in 100 neonates and infants undergoing open heart surgery showed significantly reduced RBC and coagulation product transfusion and donor exposures [62]. However, the strategy of collecting and storing cell saver collected blood pretransfusion for up to 24 hours, as assessed in this trial, is not standard. Another study using intraoperative cell salvage and reinfusion in children undergoing posterior spinal fusion surgery confirmed decreased allogeneic transfusion rates in the cell saver group.
particularly in surgical procedures >6 hours [63]. Similarly, blood recycling with cell saver during major craniosynostosis repair was shown to be safe, with only 30% of children undergoing surgery requiring allogenic transfusions using cell saver. In addition to being effective in reducing exposure to allogenic transfusion, cell salvage can also be cost saving [64], especially when compared with preoperative autologous blood donation [65]. However, another study found that intraoperative cell salvage in infants demonstrated no economic benefit [66]. One study suggested that red cell mass rather than salvaged blood volume should be used as a predictor of when to attempt recovery of salvaged blood to improve efficiency and avoid wastage from process-related costs when insufficient blood has been salvaged [67].

The minimum volume of blood necessary for the washing process in cell salvage has historically limited its use in infants and small children, with the lower age limit for cell salvage feasibility estimated at 6 months of age [68]. New cell salvage devices with small volume centrifugal bowls have come to market that allow blood salvage even in very small children. One nonrandomized prospective trial in infants undergoing cardiopulmonary bypass (CPB) surgery with a body weight of less than 10 kg reported that use of cell saver significantly reduced postoperative allogeneic blood transfusion [66].

**Antifibrinolytic Agents**

Antifibrinolytic agents have been shown to be useful for reducing pediatric perioperative blood transfusions in a variety of clinical settings, although the current evidence is not as extensive for adults. Goobie et al. documented the efficacy of tranexamic acid (TXA), an antifibrinolytic agent, in reducing perioperative blood loss as well as subsequent blood transfusions through a randomized, double-blinded, placebo-controlled trial in pediatric craniosynostosis surgery [69]. Likewise, there is evidence showing the effectiveness of TXA to reduce blood loss and transfusions in pediatric cardiac, orthopedic, and other cranial remodeling surgical procedures without significant adverse events [70,71]. A recent analysis of the Pediatric Health Information System database revealed that the majority (64%) of the use of TXA in children was for children undergoing CPB, with only 0.31% of the total use in children with trauma, whereas in adults with traumatic hemorrhage, use of TXA is considered the standard of care and is the only drug shown to improve mortality [72]. Because trauma is the leading cause of death in pediatrics and a recent clinical trial has shown that the use of TXA was independently associated with decreased mortality and no adverse events, pediatric trauma experts have encouraged the increased use of this inexpensive, cost-effective medication [73,74].

**Factor Concentrates**

Intraoperative hypofibrinogenemia is a major cause of coagulopathy. Preoperative fibrinogen concentration has been shown to predict total perioperative blood loss in adolescents [75]. Thus, repletion of fibrinogen intraoperatively could be a useful strategy to maintain effective hemostasis. Prophylactic maintenance of higher fibrinogen concentrations through administration of fibrinogen concentrate has been shown to significantly decrease bleeding as well as transfusion requirements in some adult populations; however, the data are very limited in the pediatric population. In a prospective, randomized controlled trial of children aged 6 months to 17 years undergoing craniosynostosis surgery, Haas et al. demonstrated that using a more liberal threshold for replacement of fibrinogen concentrate based on FIBTEM (maximum clot firmness, a rotational thromboelastometry [ROTEM] parameter) and replacing for <13 mm compared with a conventional threshold of 8 mm significantly reduced RBC transfusions and decreased blood loss. However, they did not document significant reduction in transfusions or bleeding in the scoliosis population which had less bleeding [76]. Further studies are needed to evaluate the efficacy, safety, and best transfusion threshold for fibrinogen concentrate in the pediatric perioperative setting.

**Whole Blood**

Another possible pediatric PBM approach is use of reconstituted whole blood (donor-matched plasma and RBC and platelets) [77]. At a large tertiary care pediatric center, in children undergoing craniofacial reconstruction surgery, donor-matched FFP and RBC units were combined and administered intraoperatively as reconstituted blood to prevent coagulopathy. In comparing a prospective registry with retrospective historical cohort, the authors report decreased overall donor exposure as well as decreased incidence of abnormal postoperative coagulation testing (prothrombin time, partial thromboplastin time, and fibrinogen); however, they did not report any differences in the postoperative surgical drain output [78]. Other groups have advocated for the use of fresh whole blood (FWB). A study from a large academic children's hospital used directed donor FWB <6 hours old and demonstrated in patients 2 years or younger undergoing complex cardiac repair involving CPB a decrease in blood loss and transfusion requirements as compared with those receiving individual components [79]. A report from the same children's hospital recently reported that despite logistical challenges, it was feasible to implement a protocol of electively using FWB collected within 24–48 hours of surgery. In addition, they demonstrated that with the use of FWB, there was consistent reduction in overall donor exposure and potential risks of transfusion [80]. However, FWB is not standard and not available at most centers. More data are needed for pediatric patients to define which patient populations would benefit.

**Postoperative Transfusion Thresholds**

Decision points driving practitioners to transfuse RBCs after pediatric surgery are not well understood. Specifically, the optimal hemoglobin level or physiological goal after surgical procedures in children is unknown. Investigators of the Pediatric Acute Lung Injury & Sepsis Investigators network recently reported results from a prospective, multicenter, 6-month cohort study on the management of anemia in critically ill pediatric patients conducted in 30 PICUs in the United States and Canada. They reported that 79% of the postcardiac surgical patients received at least 1 RBC transfusion in the PICU and that a low hemoglobin level was the primary indication for transfusion in only 17% of cases. They demonstrated great variability in transfusion practices across North American PICUs, highlighting the need for improved epidemiologic data on transfusion indications to guide subsequent studies in this specific population [81].

A large percentage of patients undergoing open-heart surgery require postoperative blood transfusion. Prophylactic use of antifibrinolytic therapeutic agents is gradually emerging as an approach to reduce postoperative blood loss. Aprotinin reduces blood loss in cardiac surgery patients but is strongly correlated with serious adverse events, including renal dysfunction and cardiocerebrovascular events [70]. TXA and epsilon aminocaproic acid (EACA) are as effective as aprotinin in reducing postoperative blood loss and blood transfusion rates in pediatric open-heart surgery [82]. Lu et al. showed via a meta-analysis that use of prophylactic EACA minimizes postoperative blood transfusion and helps maintain hemostasis in pediatric patients undergoing open-heart surgery [83]. Patients treated with EACA received fewer postoperative blood transfusions, including RBCs (P = 0.001), fresh frozen plasma (P = 0.001), and platelets (P = 0.007), and had a lower reexploration rate (P = 0.03). Prophylactic EACA also improved coagulation tests 6 hours after open-heart surgery. Therefore, the authors recommended adjunctive EACA for the prevention of postoperative blood transfusion following pediatric cardiac surgery [83]. These results are similar to 2 previous meta-analyses of EACA effectiveness in adult cardiac surgery patients [84,85].

**Other Strategies to Minimize Perioperative Transfusions in Pediatric Surgical Procedures**

Pediatric investigators have also used other strategies to reduce the overall transfusion volume including (1) shortening the length of CPB...
Jehovah’s Witness faith extended the application of its bloodless surgery and (4) restricting RBC transfusions during postoperative period to hematology of the use of TEG and ROTEM in clinical decision making for mates of the amplification of thrombus formation (EXTEM) have been shown to provide a good estimate. This study proposed TEG as a cost-effective method to direct ventilator requirements, and postoperative bleeding events were equivalent. This study reported that irrespective of TEG results, RBC and plasma transfusion remained similar. However, there was a substantial reduction in the transfusion of platelets (P<.001) and cryoprecipitate (P<.001) in patients with intraoperative TEG results without an increase in postoperative complications. Overall, the TEG group had a greater than 50% reduction in hospital costs of platelet and cryoprecipitate transfusions. Mortality, length of stay, ventilator requirements, and postoperative bleeding events were equivalent. This study proposed TEG as a cost-effective method to direct blood product replacement in pediatric heart surgery [88]. However, these tools are not universally used or accepted; in addition, these questions should be evaluated using randomized controlled trial designs.

In other retrospective studies, dynamic ROTEM parameters of total thrombus formation (EXTEM) have been shown to provide a good estimate of the amplification and the propagation phases of coagulation in children and good specificity for the prediction of postoperative fresh frozen plasma transfusion [89]. Another retrospective study showed that ROTEM analysis before weaning from CPB and hemoconcentration have reliable predictive value of coagulopathy in pediatric cardiac surgery patients post-CPB [90]. There are increasing support and recognition of the use of TEG and ROTEM in clinical decision making for transfusion in pediatric patients with perioperative bleeding [91]. TEG and ROTEM parameters may accurately predict the need for hemostatic products in children undergoing cardiac and other surgery and consequently lead to more optimal blood management, but further research is needed involving well-designed prospective studies.

Other Patient Populations

In addition to surgical patients, pediatric patients undergoing extracorporeal membrane oxygenation (ECMO) and those with primary hematologic malignancies often require substantial transfusion support. Bleeding and coagulopathy are the 2 most common complications associated with ECMO for both adult and pediatric patients [92]. However, nonrandomized observational studies of adults have demonstrated that a restrictive transfusion approach for these patients with anticoagulation targeting is likely the best strategy [93-95]. For nonsurgical patients that require substantial transfusion support, such as those on ECMO and requiring hematopoietic stem cell transplants, it is important to establish standard operating procedures and include them in the pediatric PBM planning. The effects of these PBM initiatives will also impact the population subgroups which are chronically transfused like sickle cell patients and thalassemic patients.

Future Challenges and Opportunities

Although children are often transfused and may be at higher risk of adverse events [12,13], little epidemiologic data on the prevalence and incidence of transfusion-related adverse events as well as guidance for indication, dosing, transfusion triggers, and methods to reduce transfusion-related risks are available. Pediatric PBM programs are critically important initiatives that necessitate a collaborative effort between multiple clinical services and have the prospect of expanding high-quality multidisciplinary research. There are numerous areas where these newly formed collaborations between the laboratory and clinical services that are requesting transfusion support could be used to promote evidence-based practices, such as optimal strategies to define transfusion thresholds/physiologic requirements, evaluate pediatric blood utilization, assess perioperative strategies, determine adjunct interventions to minimize unnecessary transfusions, and identify an expanded role for point-of-care tests in pediatric PBM. These studies would provide critical data to support vital pediatric PBM programs to optimize neonatal and pediatric care while avoiding unnecessary transfusions.

Conflict of Interest

The authors declare no conflicts.

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