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REVIEW

Minimizing the need for transfusion in pediatric congenital heart surgery

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Abstract: Blood conservation has become an essential institutional initiative in cardiac surgery patients secondary to published reports associating transfusion with increased morbidity and mortality. Cardiopulmonary bypass (CPB) for children with congenital heart disease presents unique challenges in regard to transfusion practice. The circuit size relative to the pediatric patient's circulating blood volume results in more hemodilution forcing clinicians to adopt several strategies to counteract this. It is generally agreed that the effects of hemodilution in this population are less well understood. That being said, there is evidence that neurologic outcomes are impacted by significant anemia in neonates and infants undergoing CPB. This adds to the level of concern clinicians should have when managing congenital heart surgery patients. Optimized surgical outcomes are dependent on neurologic outcomes. Specific transfusion guidelines for pediatric cardiac surgery still vary widely across institutions, and a safe minimum hematocrit on bypass has not been established. Evidence-based guidelines are more prevalent in adult cardiac surgery patients, but there are a growing number of reports for pediatrics. Clearly, well-defined operative strategies and a team approach will decrease blood product transfusions and minimize the associated risks in pediatric patients, especially in regard to neurologic outcomes. The ongoing development of evidence-based guidelines for pediatric perfusion will serve clinicians, and most importantly, their patients, well. The purpose of this review is to present current practice to limit blood transfusions in pediatric cardiac surgery exclusively inside the operating room and related to CPB as well as minimizing the side effects of the coagulation disturbances caused by the level of hemodilution these patients may encounter.

Keywords: cardiopulmonary bypass, congenital heart disease, cardiac surgery, blood conservation strategies, blood transfusion

Introduction

Blood conservation has become an essential institutional initiative to improve the quality of care, optimize resource usage, lower costs, and achieve better outcomes in cardiac surgery patients. More than 500,000 patients yearly undergo coronary artery bypass graft surgery with the support of cardiopulmonary bypass (CPB), and there are considerable and surprising variations in transfusion practices among heart centers.[1] Clinicians have been revamping their transfusion practices in adults due to published reports associating transfusion with increased morbidity and mortality.[2] In children with congenital heart disease (CHD), however, the complex relationship among anemia, oxygen delivery, transfusions and patient outcomes is less well understood. While the avoidance of unnecessary blood transfusions is certainly a high priority, universally accepted transfusion thresholds in pediatrics have yet to be

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determined. Traditionally, pediatric cardiac surgery has been associated with higher transfusion requirements due to the CPB circuit volume relative to the patient's blood volume, altered hemostasis, bleeding and hemodynamic instability.[3] Furthermore, congenital heart surgery patients may be at increased risk with anemia if their ability to increase cardiac output to maintain tissue oxygen delivery is compromised. Despite these challenges, it is increasingly recognized that many children with CHD, however vulnerable, can be safely managed with conservative blood management practices.[4]

Anemia in pediatric cardiac surgery is primarily related to hemodilution from CPB priming solutions, intravenous fluids, coagulation status changes and operative bleeding. Anemia tolerance, bleeding risk and transfusion therapy are influenced by various factors including patient age and weight, surgical complexity, operative duration, degree of cyanosis and coagulopathies induced by CPB.[3,5] Increased risks for morbidity and mortality exist with anemia and so if an elective transfusion-free operation is planned, it should not move forward until preoperative hematocrit levels can support that goal.[5–7]

The rational use of blood products is a multimodal and multidisciplinary approach where transfusion should be guided by evidence-based practices. Evidenced-based guidelines for the multidisciplinary operative team have been published worldwide.[8,9] It is important to notice the recent patient blood management (PBM) publication in the field of adult cardiac surgery by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA).[10] This specific PBM publication in cardiac surgery provides practical recommendations for all clinicians working in the field of cardiac surgery, emphasizing on preoperative patient optimization and intraoperative maintenance of hemostasis, which minimizes the impact of CPB and postoperative treatment for bleeding complications. Specific guidelines for pediatric cardiac surgery still vary widely across institutions, and a safe minimum hematocrit on bypass has not been established.[6] Well-defined operative strategies and a team approach intuitively will decrease blood product transfusions and minimize the associated risks in pediatric patients and are therefore warranted. The purpose of this review is to present current practice managing blood transfusions in pediatric cardiac surgery exclusively inside the operating room and related to CPB.

Target hematocrit

The role of hematocrit relative to patient outcomes was well studied in the Boston Hematocrit Trials where two-ventricle congenital heart surgery patients were studied.[11,12] These trials first looked at CPB hematocrit levels at the onset of low-flow perfusion of 20% as compared to 30% and then 25% versus 35%. A follow-up analysis of these trials was later published where neurologic outcomes were highlighted.[6] The take-home conclusion from these efforts was that 1-year psychomotor development index scores improved up to a hematocrit of 23.5% at the onset of low-flow perfusion but showed no significant improvement thereafter. This has led some to conclude that an on-bypass hematocrit of ≥23.5% is advantageous, while others believe there should be some latitude for acute changes on bypass and therefore recommend 28–30% to ensure the nadir hematocrit exceeds 23.5% at all times.[13] It is important to note that the Boston Hematocrit Trials did not explicitly define a safe minimum on-bypass hematocrit level for congenital heart surgery cases.

The on-bypass hematocrit is important since it helps define the oxygen delivery capacity to tissues. Hemoglobin is a critical component. Lower hemoglobin levels should be inversely compensated for with higher blood flow rates to ensure adequate oxygen delivery. Optimizing the CPB prime and the target pump flow rate must account for these considerations. The use of near-infrared spectroscopy (NIRS) has allowed clinicians to tailor blood transfusion intraoperatively based on real-time data during the various stages of an operation.[13] Menke and Moller studied the relationship between NIRS measurements and vital perioperative parameters (such as rectal temperature, mean arterial pressure [MAP], central venous pressure, arterial oxygen saturation and arterial blood gas measurements) in 10 pediatric CPB patients.[14] Their model showed that changes in perfusion pressure, temperature, arterial oxygen saturation and central venous pressure explained 85% of changes in rSO_2 NIRS measurements and 91% of changes in tissue hemoglobin content. They concluded that NIRS might be useful in optimizing patient management to improve cerebral protection during CPB. Moreover, a study of 15 pediatric patients <10 kg undergoing CPB surgery found that central venous oxygen saturation ($ScVO_2$) was well approximated by both cerebral and somatic/renal NIRS, with the NIRS appropriately reflecting at-risk changes in cardiac output.[15] NIRS monitoring has also been useful in patient management to prevent acute kidney injury (AKI). The duration of time at a critically low renal NIRS is associated with an increased risk of AKI.[16–18] Hematocrit along with pump flow rate primarily determine oxygen delivery to the tissues and so the two must be considered dependently during CPB.[19]

Although several groups have reported transfusion-free pediatric cardiac surgery pushing the limits of CPB components and nadir hematocrit, long-term outcome comparisons have not been published.[13,20–23] Whereas goal-directed perfusion has been discussed more so in the adult literature, it is still an emerging model in the field of surgery for pediatric congenital heart surgery patients and has the potential to address the lack of universal guidelines.[24] Certainly, the target hematocrit is an important consideration for outcomes in pediatric cardiac surgery and will impact transfusion requirements.

CPB equipment

All pediatric cardiac surgery recipients are exposed to the hemodilutional effect of CPB circuit prime volume, with neonates experiencing the greatest effects as the CPB prime is often 200–300% of their blood volume.[25] Reducing the total circuit prime volume includes the use of a low prime oxygenator, often with an integrated arterial line filter, short tubing lengths and the smallest inner diameter (ID) tubing which can safely support the anticipated flow rates for a case. One method to reduce hemodilution from circuit prime volume is miniaturization of CPB components.[22] Ando et al reported that in their miniaturized system, patients <5 kg undergoing ventricular septal defect repair with CPB could be done without a blood prime in >70% of cases.[26] They also reported that 95% of their patients were not transfused during the perioperative period. In 2007, Miyaji et al reported on complex transfusion-free procedures in patients weighing >4 kg by using a low priming volume circuit.[20] More recently, a miniaturized circuit with an arterial head roller pump considerably reduced the priming volume and formed the basis for a comprehensive blood conservation program at a pediatric center.[27] While equipment and disposables for CPB have evolved with lower prime volumes and this has significantly decreased the need for transfusions overall in pediatric patients, it has yet to eliminate transfusions for most pediatric cardiac surgery patients at most heart centers.

Retrograde autologous priming

It has been demonstrated that the application of retrograde autologous priming (RAP) in adult cardiac surgery patients can improve intraoperative hematocrit and reduce the need for transfusions.[28–30] The application of RAP in small adults can also reduce priming volume and thus hemodilution, but its applicability for pediatric patients is less clear.[31] The effect of RAP on hemodynamics is higher in pediatric patients than adults due to the relative loss of intravascular volume during the process. One group showed that RAP could effectively reduce the hemodilution in children <20 kg.[32] They demonstrated the use of RAP with stable hemodynamics and used less, or no, banked blood. Still, the use of RAP in pediatrics, particularly neonates and infants, appears to have limited practical use and impact on overall transfusion requirements and so the technique has not been universally adopted.

Venous drainage techniques

Another CPB technique helpful in mitigating the need for transfusions during CPB is pushing the limits of tubing size for arterial and venous limbs of the circuit. Though, one must keep in mind that smaller ID tubing affects performance, especially in neonates and infants.[33] Adequate venous drainage, in particular, is essential for the optimal conduct of perfusion. Inadequate venous drainage can result in edema and organ dysfunction, and a venous line which is too small may contribute to this.[34,35] Even the method of venous drainage is of consideration when trying to minimize circuit prime. A recent study compared the technique of using two smaller ID venous lines (popular in some countries) versus a single larger ID venous line. Here, the authors showed that improved drainage could be achieved with less prime volume for neonatal and infant patients when using the more common single venous line technique.[36] This result certainly appears to be a win–win outcome promoting the more common use of a single venous line in the CPB circuit.

One technique which most centers utilize is vacuum-assisted venous drainage (VAVD). Although VAVD allows the use of smaller venous tubing in the CPB circuit, it does not come without risk. Studies have shown increased gaseous microemboli (GME) with VAVD when higher negative pressures are utilized.[37,38] The effect of these GME on pediatric patient outcomes is unclear.[39] Nevertheless, most clinicians agree that GME should be limited (and therefore VAVD levels) since the adult literature correlates outcomes negatively with increased GME numbers.[36,40,41]

Ultrafiltration

Ultrafiltration is another technique aimed at limiting hemodilution and transfusion requirements. Ultrafiltration is nearly universally utilized during pediatric CPB, and many centers use the technique after CPB as well. Conventional ultrafiltration (CUF) during bypass removes excess “free water” (water, electrolytes and substances with a molecular size smaller than the membrane pore size) which may exist due to cardioplegia administration, preoperative volume overload, valve testing solution or circuit prime.[13] CUF use is constrained by the need to maintain a minimum venous reservoir volume for circuit function and safety. Ultrafiltration can also be performed after bypass with a CPB circuit modified for such. Modified ultrafiltration (MUF) essentially creates a circuit smaller than what was required during the surgery. Parts of the original larger CPB circuit then donate volume to the MUF circuit whereby ultrafiltrate taken off is replaced with patient whole blood from the circuit thereby improving the hematocrit.[42,43] The use of MUF has additional potential benefits aside from improvement in the hematocrit, although a 2011 meta-analysis failed to show a difference in clinical outcomes.[44] A later 2016 study showed the use of all forms of ultrafiltration together improved the hemodynamic status of patients and significantly decreased the duration of mechanical ventilation and inotrope requirement within 48 hrs after surgery.[45] More recently, the significance of MUF has been questioned in one paper where the authors concluded that if the MUF circuit requires additional circuit prime volume, it may be better not to perform the technique.[46] It is important to note that there are numerous methods of performing MUF, and therefore its influence on a practice will vary. At the very least, most MUF circuits improve the patient's hematocrit after bypass with patient whole blood and not just red blood cells (RBCs) as is the case with cell saver blood or RBC transfusions.[13] Clinicians must evaluate methods of performing MUF in addition to just selecting the technique in order to successfully incorporate it into their practice.

Cell salvage devices

Intraoperative cell salvage reinfusion is another strategy utilized to reduce the need for allogeneic RBC transfusion. These devices wash both shed blood from the surgical field as well as residual CPB circuit blood after the CPB period.[47] Cell savage essentially creates a product of washed RBCs suspended in saline, or a balanced electrolyte solution, which can be transfused to the patient as needed for immediate and efficient volume and RBC replacement.[48] There is growing literature to support the use of cell savage in pediatric cardiac surgery as a component of blood conservation programs.[47,49–52] Cell salvage was traditionally excluded from pediatric cardiac surgery patients with the thought being that the recovered volume did not warrant the expense. That mode of thinking has changed with evidence of decreased transfusion requirements and blood bank costs for pediatric cardiac surgery patients when cell savers are used.[47] Regardless of institutional techniques, it appears that the use of cell savage is warranted as part of a blood conservation strategy since all bypass circuits have residual autologous volume which can be recovered and transfused as needed to the patient without the risks associated with allogeneic blood transfusions.

The composition of CPB prime

Blood primes may include fresh whole blood (FWB), reconstituted whole blood (RWB) made up of RBCs mixed with FFP or just RBCs. FWB may be defined as blood that has been stored for less than 48 hrs, although some centers are more liberal with the definition and define fresh as including blood stored for up to 7 days.[53–55] FWB is also thought to provide improved preservation of coagulation factors including platelets.[56] A prospective randomized controlled trial of 64 neonates compared chest tube drainage and clinical outcomes between those receiving either FWB or RBCs for pump prime and transfusions in the first 24 hrs after surgery.-[57] The authors reported significantly less chest tube drainage and shorter lengths of mechanical ventilation and intensive care unit (ICU) stay in the FWB arm. A study not in favor of FWB compared CPB blood primes using FWB versus RWB in children <1 year.[54] Here, the authors found patients managed with FWB had increased ICU length of stay and more fluid overload compared to the group receiving RWB in the CPB prime. Finally, a retrospective analysis of 100 patients up to 4 years old who received either an FWB or RBC-only prime found that the FWB group had significantly fewer total exposures but no difference in clinical outcomes.[58] The use of the more commonly available products of non-fresh or RWB as components of the CPB prime for CHD surgery is not without disadvantages. This includes clinically significant reductions in platelet counts for reconstituted units consisting only of packed RBCs and plasma. Transfusion of platelets and cryoprecipitate is more likely to be needed to deal with ongoing bleeding, while surgical hemostasis is achieved. One group has shown that these components are necessary to obtain a normalized hemostatic profile prior to leaving the operating room.[59] So, the ideal blood product for the CPB may not be easy to identify but a blood prime, in general, has additional benefits aside from its role in oxygen delivery. It is also important for colloid osmotic pressure. Chores et al showed statistically significant increases in fluid balance, postoperative blood loss and blood product usage when the colloid osmotic pressure dropped below 15 mmHg.[60] Colloid osmotic pressure is impacted by the blood type and albumin content in the CPB circuit prime. Thawed plasma is commonly used to prevent CPB-associated coagulation abnormalities and while there are small series published on the topic, there is little high-grade evidence to support its use.[61] A prospective randomized controlled trial of infants and children from 1 to 16 years with either 20% albumin (50–100 mL) or FFP (1–2 units) in the pump prime compared hematologic assays and clinical outcomes.[62] While there were improved point-of-care results in the operating room in the FFP group, no clinical differences were noted ≥24 hrs after surgery. Some centers reserve FFP in their pump prime for children <1 month of age to increase fibrinogen levels and reduce blood loss.[63] Whether or not RWB is advantageous is yet to be proven. When blood products are used in the bypass prime, an additional consideration is the electrolyte composition and presence of mediators of inflammation in the final prime. Prebypass ultrafiltration (PBUF) of the prime before bypass is used by many centers to provide a more physiologic blood prime, particularly in pediatric patients.[13,64,65] Additional pediatric specific research is needed to determine the optimal CPB prime composition for pediatric cardiac surgery patients.

Avoiding bleeding: surgical technique and topical hemostasis

Perioperative coagulopathy is common in children undergoing cardiac surgery with CPB, and this requires coagulant product transfusions.[66] Certainly, exceptional care must be afforded with operative techniques to minimize surgical bleeding. When conventional methods including cautery and suturing are not enough, topical hemostatic agents are commonly used to help limit blood loss even though prospective randomized trials proving their efficacy are lacking.[67] The Society of Thoracic Surgeons recently published the Blood Conservation Guideline Task Force Guidelines and gave the class IIb recommendation to topical hemostatic agents as part of a multimodality blood management program.[68] In pediatric cardiac surgery, using fibrin sealants at bleeding sites may be effective, particularly in the presence of coagulopathy or when postoperative coagulopathy is a risk.[69,70] Further, blood product transfusions should be tailored to treat specific coagulopathies since transfusions can be associated with negative outcomes. Blood transfusions have been associated with increased incidence of postoperative pulmonary complications, prolonged duration of mechanical ventilation, infections and prolonged hospital and ICU stays.[71–73]

Specific point-of-care tests for guidance with product transfusions would be ideal in pediatrics to help tailor transfusions in real time. The activated partial thromboplastin time and prothrombin time/international normalized ratio and fibrinogen remain widely used to assess coagulation status. Unfortunately, these tests are not ideal to guide administration of hemostatic agents during active bleeding due to the analysis time required. Results from these standard coagulation assays require 30–45 mins, limiting their utility in the context of acute bleeding.[74] Thromboelastography and ROTEM are useful to assess hemostasis, providing the information of clot firmness or clot lysis, and guide the administration of blood products in bleeding patients. These assays assess the intrinsic (INTEM) and extrinsic pathway (EXTEM) and fibrinogen function (FIBTEM). More recently, point-of-care platelet function assays allow near real-time assessment of platelet aggregation responses. A recent study suggested that early values of clot amplitudes could be used to predict maximum clot firmness.[75] Transfusion algorithms now make use of viscoelastic assays, and published guidelines support their use.[76]

In children undergoing cardiac operations, viscoelastic tests can assess coagulopathy and guide the administration of blood products.[77–80] In a recent study in pediatric cardiac surgical patients after CPB, Nakayama et al found reduced blood loss, decreased red cell transfusion requirements and reduced critical care duration associated with ROTEM-guided early hemostatic intervention.[81] Of the different non-red cell blood products used to manage bleeding, platelets, fresh frozen plasma (FFP) and cryoprecipitate remain common.[82,83] One small prospective study in children suggested that fibrinogen concentrate, as an alternative to plasma and cryoprecipitate, provided equivalent efficacy to cryoprecipitate in children undergoing cardiac operations.[84] In opposition to the concern for making clot is the concern for thrombotic complications. Recombinant activated factor VII (rFVIIa) is used in pediatric cardiac operations even though the Congenital Cardiac Anesthesia Society Task Force acknowledged a paucity of quality data to make evidence-based recommendations for its administration.[85] Further, a 2017 study in neonates and children undergoing cardiac operations found an increased rate of thrombotic complications when rFVIIa was used.[86] With this in mind, it is generally agreed that rFVIIa should be restricted to extreme clinical situations and used cautiously when there is uncontrolled bleeding despite the use of standard blood products.[87]

Anticoagulation on CPB and UFH reversal

Systemic anticoagulation is required during CPB to prevent circuit thrombosis as well as control contact activation of the coagulation system. Unfractionated heparin (UFH) is most often used since it has proven to provide a rapid and reliable onset with predictable reversal using protamine.[88]

Adjustment of UFH dosing is most often done with the activated clotting time (ACT) though other tests including heparin levels in the blood have been used.[89,90] While heparin levels are promoted by some to guide anticoagulation management, these values do not correlate well with the ACT, particularly in the setting of hemodilution and hypothermia.[91] Furthermore, age-related differences with heparin sensitivity and heparin–protamine interactions make heparin and protamine dosing challenging in the heterogeneous group of pediatric patients presenting for cardiac surgery.[92] Adequate anticoagulation during CPB is essential as is proper reversal after CPB. Protamine sulfate reverses heparin's effect, but one must use caution since excess protamine can promote coagulopathy and increase bleeding through platelet and serine protease inhibition.[93] Protamine dosing is generally determined either by a weight-based formula or heparin concentration in conjunction with estimates of patient blood volume.[94] Minimizing transfusion in pediatric cardiac surgery patients, therefore, includes titrated anticoagulation and reversal to limit bleeding in the perioperative period.

Conclusion

A multidisciplinary approach is essential to improving operative protocols and procedures aimed at minimizing transfusion requirements in pediatric congenital heart surgery patients. Many institutions performing CPB have adopted blood conservation programs that include the use of low-prime volume circuits with and without VAVD, ultrafiltration (PBUF, CUF and MUF) and cell savage for all pediatric patients. With these techniques, many centers report not only decreased blood transfusions and costs but also improved clinical outcomes compared to their previous strategies.

Disclosure

The authors report no conflicts of interest in this work.

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