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Special Article

Patient Blood Management for Neonates and Children Undergoing Cardiac Surgery: 2019 NATA Guidelines

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Pediatric cardiac surgery is associated with a substantial risk of bleeding, frequently requiring the administration of allogeneic blood products. Efforts to optimize preoperative hemoglobin, limit blood sampling, improve hemostasis, reduce bleeding, correct coagulopathy, and incorporate blood sparing techniques (including restrictive transfusion practices) are key elements of patient blood management (PBM) programs, and should be applied to the pediatric cardiac surgical population as across other disciplines. Many guidelines for implementation of PBM in adults undergoing cardiac surgery are available, but evidence regarding the implementation of PBM in children is limited to systematic reviews and specific guidelines for the pediatric cardiac population are missing. The objective of the task force from the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA, www.nataonline.com) is to provide evidence-based recommendations regarding anemia management and blood transfusion practices in the perioperative care of neonates and children undergoing cardiac surgery, and to highlight potential areas where additional research is urgently required.

Key Words: bleeding; transfusion; patient blood management; congenital heart surgery; pediatrics; guidelines

PEDIATRIC CARDIAC SURGERY is associated with a substantial risk of bleeding, frequently requiring the administration of allogeneic blood products. The anemia and coagulopathy observed in neonates and children perioperatively is complex and multifactorial. The risk factors identified can be summarized as follows: (1) hemodilution because of cardiopulmonary bypass (CPB) prime, cardioplegia, and administration of fluids in the perioperative period, (2) activation of coagulation and fibrinolysis, (3) a consumptive coagulopathy, (4) anticoagulation using unfractionated heparin, and (5) other physiological disturbances (ie hypothermia, acidemia, hypocalcemia).[1,2] Although all these mechanisms affect both adults and children, the pediatric population presents major differences in their hemostatic system compared with adults, sustains greater hemodilution with CPB, some with a cyanotic heart disease, and often undergoes complex surgical procedures.[3] Efforts to optimize preoperative hemoglobin, limit blood sampling, improve hemostasis, reduce bleeding, correct coagulopathy, and incorporate blood sparing techniques are important pillars of patient blood management (PBM) programs,

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and should be applied to the pediatric cardiac surgical population as it is across other disciplines.[4,5] Guidelines for implementation of PBM in adults undergoing cardiac surgery were published recently,[6] but evidence regarding the implementation of PBM in children with congenital heart disease is limited to systematic reviews and specific guidelines are missing.[4,7]

The objective of the task force from the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA; www.nataonline.com) is to present the current literature regarding anemia management and blood transfusion practices in the perioperative care of neonates and children undergoing cardiac surgery, to provide evidence-based recommendations, and to highlight potential areas where more research urgently is required.

Methods

The NATA Board of Directors selected a task force of experts. The scope of the clinical guidelines was agreed upon by the task force members, the table of contents was established, and topics were allocated to the writing group. A systematic review of the published evidence in the field of blood conservation during pediatric cardiac surgery was performed. After study selection and quality assessment, recommendations and summary chapters were drafted and agreed based on the synthesis of the best medical evidence. Agreement was reached through conference calls and face-to-face meetings. The medical evidence was appraised critically for quality, including internal validity, external validity for the population of interest and publication bias using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines (Table 1).[8] According to it, the recommendations are assigned a number (relating to the strength of the recommendation) and a letter (relating to the quality of the supporting evidence). Statements are accompanied only by a letter. Although the adult literature is sometimes referred to, recommendations are made based only on the pediatric cardiac literature and extrapolation from adult recommendations were avoided. The Society of Thoracic Surgeons-European Association of Cardiothoracic Surgery (STS-EACTS) categories are used when referring to risk stratification, with STS-EACTS of 1 being considered as low-risk procedures (eg, atrial septal defect, ventricular septal defect, atrioventricular septal defect (AVSD), or aortic valve repair or replacement).[9,10]

Table 1
Grading of Recommendations Assessment, Development and Evaluation (GRADE) System

Grade of recommendation	Quality of Supporting Evidence	Implications
1A Strong recommendation. High-quality evidence.	Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change the authors' confidence in the estimate of benefit and risk.	Strong recommendation; can apply to most patients in most circumstances without reservation.
1B Strong recommendation. Moderate-quality evidence.	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect, or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on the authors' confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation; likely to apply to most patients.
1C Strong recommendation. Low-quality evidence.	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.	Relatively strong recommendation; might change when higher quality evidence becomes available.
2A Weak recommendation. High-quality evidence.	Consistent evidence from well-performed, randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change the authors' confidence in the estimate of benefit and risk.	Weak recommendation; best action may differ depending on circumstances or patients or societal values.
2B Weak recommendation. Moderate-quality evidence.	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on the authors'confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.
2C Weak recommendation. Low-quality evidence.	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation; other alternatives may be equally reasonable.

Preoperative Anemia and Optimization of Hemoglobin

One of the cornerstones of modern adult PBM programs is the identification and treatment of preoperative anemia. Pediatric cardiac surgery patients can range from newborns to adolescents suffering from cyanotic or noncyanotic cardiac defects, which result in varying baseline hemoglobin (Hb) concentrations and ferritin levels. The optimal preoperative Hb values for pediatric cardiac surgery is uncertain, especially for children below the age of 6 months or for those with chronic cyanosis.

The relationship between preoperative anemia and morbidity (eg, infection) or 30-day mortality has been studied in neonates

and children undergoing noncardiac surgery,[11,12] but data for the cardiac surgical population are weak. In a retrospective study, Mulaj et al.[13] showed that children undergoing noncomplex cardiac surgery (repair of ventricular or atrioventricular septal defects) are more likely to be transfused if their preoperative hematocrit was <34%. In a single-center retrospective cohort of 220 children undergoing cardiac surgery, preoperative anemia was associated with an increased risk of perioperative acute kidney injury.[14] Therefore, treatment of preoperative anemia appears to be important to decrease perioperative anemia-induced complications and blood transfusions.

The utility of preoperative iron in pediatric cardiac surgery has not been assessed. Indeed there are few studies that have assessed the effects of iron therapy in iron deficiency anemia in children.[15] In the largest retrospective cohort of 54 patients, Hassan et al.[16] demonstrated that intravenous iron (Ferumoxytol) was effective in treating iron deficiency anemia. The members of this group pointed out that a slow infusion rate and close monitoring will allow early detection of the infrequent adverse drug reactions. The use of erythropoietin also has been studied poorly. Shimpo et al.[17] demonstrated in a small retrospective study that up to 300 IU/kg erythropoietin was effective as an adjuvant therapy in children.In another study, Sonzogni et al.[18] reported that preoperative preparation with 100 IU erythropoietin enhanced the opportunity for autologous blood donation and reduced the risk for allogeneic blood transfusions.

Recommendations

- The authors recommend diagnosis and treatment of preoperative iron deficiency anemia with either oral or intravenous iron in pediatric cardiac surgery patients (Grade 1C).
- The authors suggest considering preoperative erythropoietin (EPO) only in specific needy situations (eg, Jehovah Witnesses) (Grade 2C).

Preoperative Coagulation Assessment and Risk Stratification

For decades, efforts have been made to predict bleeding in neonates and children undergoing cardiac surgery. In addition to patients' demographics, comorbidities, patients' physical status, and the severity of congenital heart disease, several studies have tried to identify preoperative coagulation parameters that could be correlated with intra- and postoperative bleeding.[19] In a prospective cohort study of 548 children undergoing open-heart surgery, Williams et al.[20] showed that preoperative standard coagulation testing and thromboelastography (TEG) parameters failed to predict bleeding in the studied population. In a study by Moganasundram et al.,[21] a 2-variable model including the activated partial thromboplastin time at induction of anesthesia and TEG mean amplitude postprotamine discriminated well for subsequent bleeding in 50 children undergoing cardiac surgery. Hayashi et al.[22] assessed the predictive value of thromboelastometry (ROTEM) and thrombin generation. While a weak correlation between preoperative endogenous thrombin potential and bleeding was reported, preoperative coagulation parameters failed to predict bleeding. Overall, because of the multifactorial etiology of bleeding and coagulopathy in pediatric cardiac surgery, coagulation parameters alone or in combination with a patient's characteristics failed to predict bleeding. In addition, there is no evidence to support a benefit of correcting abnormal laboratory values before surgery. Assessment of coagulation (eg, activated partial thromboplastin time (aPTT), partial thromboplastin time (PTT), or Clauss fibrinogen level) and platelet count could be considered on a case-by-case basis in neonates, patients on anticoagulation therapy, and patients on extracorporeal life support (eg, VAD or ECMO).

Recommendation

- The authors recommend against routine preoperative assessment of coagulation tests (eg, aPTT, PTT, or fibrinogen level) and platelet count in infants and children without a bleeding history before cardiac surgery (Grade 1C).

Antifibrinolytics

Antifibrinolytic agents include aprotinin, which is a serine protease with multiple effects that most notably works as a direct plasmin inhibitor, and the lysine analogs (epsilon-aminocaproic acid [EACA] and tranexamic acid [TXA]), which act as competitive inhibitors of plasminogen. TXA, when given within 3 hours of injury or 3 hours of birth, reduces bleeding deaths in adults after trauma and women with post-partum hemorrhage, respectively.[23,24]

The efficacy of prophylactic administration of lysine analogs in neonates and children undergoing cardiac surgery with CPB has been studied in small prospective studies.[25-34] In a systematic review and meta-analysis that compared TXA to placebo, prophylactic administration of TXA reduced the need for blood product transfusion and reduced postoperative blood loss in children with cyanotic heart disease who underwent complex surgical procedures.[35] Comparable results have been reported in studies that compared EACA to placebo.[36] The available literature presents some significant limitations. All the prospective studies published to date included small numbers of patients presenting with heterogeneous congenital heart diseases and undergoing procedures of different complexities. An important variability in TXA dosages also has been reported, with some centers using 3 boluses of 10 to 100 mg/kg, while others used a 10 to 100 mg/kg loading dose followed by a continuous infusion.[35] Simulation performed from the pediatric EACA pharmacokinetics (PK) study suggested a dosing regimen with a loading dose of 40 mg/kg and an infusion of 30 mg/kg/h, with a pump prime concentration of 100 mg/L to maintain plasma concentrations above 50 mg/L in 90% of neonates during CPB surgery.[37] In the TXA pharmacokinetic study published by Wesley et al.,[38] the authors suggested 9 doses based on the targeted plasma concentration and the patient's age. In order to maintain a plasma concentration of 60 μg/mL, a loading dose of 50 mg/kg followed by a continuous infusion of 7 mg/kg/h was suggested for neonates and infants <2 months of age, a loading dose of 26 mg/kg followed by a continuous infusion of 6 mg/kg/h for neonates and

infants aged from 2 to 12 months, and a loading dose of 13 mg/kg followed by a continuous infusion of 5.5 mg/kg/h for neonates and children >12 months and ≤20 kg. An additional bolus of 60 μg/mL of prime volume also was suggested. Unfortunately, the minimal concentration required to inhibit fibrinolytic activation in children has been assessed only ex vivo.[39-41] Therefore, further studies are needed to define the optimal plasmatic concentration required to effectively and safely inhibit fibrinolytic activation during pediatric CPB.

The neurologic safety of lysine analogs has not been studied adequately in children undergoing cardiac surgery. To date, only a few retrospective studies suggested an association between the administration of high dose TXA and the incidence of clinical seizures.[42,43] Kratzer et al.[44] suggested that high doses of TXA enhance neuronal excitation by antagonizing inhibitory gamma-aminobutyric acid neurotransmission by binding to lysine binding sites in the brain. Lecker et al.[45] showed that TXA inhibits neural glycine receptors, and reduced function of these receptors is an established cause of seizures. Interestingly, the TXA peak concentration observed in the cerebral spinal fluid was reached approximately 5 hours after the plasma peak concentration.

Prospective randomized studies that assessed the safety and efficacy of aprotinin in the pediatric cardiac population are rare and of poor quality. In a meta-analysis published in 2009,[46] among 18 studies of aprotinin in children undergoing cardiac surgery only 1 prospective study compared aprotinin with EACA.[27] In that study, Chauhan et al.[27] reported that EACA was as effective as low-dose aprotinin in reducing postoperative blood loss, red blood cell (RBC), and platelet requirements in children with cyanotic heart disease. In a retrospective analysis of antifibrinolytic drugs used in pediatric heart surgery, Pasquali et al.[47] reported reduced bleeding and mortality in children undergoing heart surgery who received aprotinin, with no increase in the incidence of postoperative renal failure requiring dialysis. However, comparative analyses suggest similar efficacy of EACA and improved outcomes associated with the administration of TXA when compared with aprotinin.

Based on the existing literature, a TXA loading dose of 30 mg/kg followed by a continuous infusion of 10 mg/kg/h can be used in children ≤1 year of age, while a loading dose of 10 mg/kg followed by a continuous infusion of 10 mg/kg/h can be used until the end of surgery in children >1 year of age.[48] For EACA, a 40 mg/kg loading dose followed by a 30 mg/kg/h infusion has been proposed.[48]

Recommendations

- The authors recommend prophylactic administration of lysine analogs (either TXA or EACA) for all neonates and children undergoing surgery with CPB in order to reduce perioperative bleeding and transfusion (Grade 1B).
- The authors recommend against the administration of high doses of lysine analogs (either TXA or EACA) because of the risk of clinical seizures (Grade 1C).
- Lysine analogs (either TXA or EACA) should be preferred over aprotinin in neonates and children undergoing cardiac surgery with CPB (Grade 2C).

Cardiopulmonary Bypass and Priming

Circuit Size

Several CPB management strategies (eg, type of priming, volume of priming, or use of ultrafiltration) have been developed to decrease the coagulopathy and the bleeding risk related to CPB. One potential target, unique to neonates and small infants when compared with adults is the disproportionately large CPB surface area with respect to patient size. Circuit miniaturization allows this ratio to be more in line with that of older children and adults but is fraught with technical and practical difficulties; however, experimental and clinical models suggest that these efforts could reduce fragmentation of blood cells and large proteins.[49-51] Investigations also suggest that avoiding the use of allogeneic blood in the pump prime (which can be achieved if the circuit size is restricted adequately) significantly may reduce CPB-induced inflammation and coagulopathy.[52] In a retrospective analysis of 259 consecutive patients weighing <15 kg, Durandy[53] downsized the CPB circuit and eliminated noncritical components to obtain a prime volume (after cardioplegia) of 140 mL for patients up to 6 kg, and of 170 mL for those weighing 6 to 15 kg. For intra- and postoperative care, transfusions were limited to 1 unit of RBCs and 1 unit of fresh frozen plasma (FFP) in 129 of the 134 patients weighing <6 kg. Seventy-six of 125 (61%) patients who were between 6 kg and 15 kg had bloodless surgery, and none of the 259 patients required platelet transfusion. No adverse effects were encountered with this procedure, and miniaturized prime volume was considered efficient and safe in decreasing blood use in the studied population. Using a modified CPB setup in 13 consecutive neonates ≤28 days old, Koster et al.[54] were able to reduce the total CPB priming volume from 200 mL to 110 mL. Seventy percent of the studied patients required no transfusions, although all patients with a cyanotic malformation who underwent palliative procedures received transfusions. In an analysis by Bojan et al.,[55] the use of a miniaturized circuit allowed for a significant reduction in CPB prime volumes from a mean of 432 to 265 mL, resulting in a decreased need for RBC and platelet transfusions. In an analysis of 23 consecutive neonates, the impact of very low-volume (95-110 mL) CPB circuit during arterial switch operations for transposition of the great arteries was assessed.[56] Intraoperative blood transfusion was only necessary in 6 of the 23 neonates. Eleven neonates received postoperative blood transfusions in the intensive care unit, leaving 6 infants who were transfusion free. Preoperative hemoglobin concentration was the only predictor for intraoperative transfusion requirement. In a study by Boettcher et al.,[57] CPB circuit was minimized to a priming volume of 73 mL for the smallest patients with body weight up to 2.5 kg and 85 to 95 mL for those with body weight of more than 2.5 kg. From 2013 to 2015, 149 consecutive neonates underwent 150 open-heart procedures without blood in priming volume. Transfusion-free operation was achieved in 44 procedures. Most (42/44) involved biventricular repair and included 50% (27/54) of arterial switch operations. In summary, despite the absence of

prospective randomized controlled trials, there is evidence that minimizing CPB prime volume can reduce the need for blood product transfusion in neonates and infants undergoing cardiac surgery.

Recommendation

- The authors recommend the implementation of miniaturized CPB for neonates and infants in order to reduce the effects of hemodilution and likelihood of transfusion (Grade 1C).

Target Hematocrit During CPB

The hematocrit to be maintained during CPB remains highly debated. Two randomized trials evaluated the impact of hematocrit during hypothermic CPB in infants undergoing biventricular repair not involving the aortic arch. The first study suggested that children with an on-CPB hematocrit of 20% had a worse outcome than those with an on-CPB hematocrit of 28%.[58] The second study concluded that there was little clinical benefit to increasing the on-CPB hematocrit above 25%.[59] The results of these two studies were combined to assess the effect of hematocrit as a continuous variable at the onset of low-flow CPB on psychomotor development index score at age 1 year.[60] The authors concluded that a hematocrit $\geq$24% at the onset of low-flow CPB was associated with higher psychomotor development index scores and reduced lactate levels. However they also emphasized that, because the effects of hemodilution will vary according to age at operation, diagnosis, CPB approach (eg, flow rate, temperature, or pH strategy), and possibly other intraoperative factors, the threshold of 24% cannot be considered a universally safe hemodilution level.[60]

Recommendation

- The authors suggest the addition of RBCs to maintain a hematocrit >24% during CPB based on the estimation of the degree of hemodilution related to CPB prime and cardioplegia (Grade 2C).

Priming Fluid

Only a few small studies have compared the effect of clear prime versus blood products (RBC and FFP) prime in neonates and infants undergoing cardiac surgery.[61-63] In 2004, McCall et al.[64] randomized 20 infants weighing less than 8 kg to receive either 1 unit of FFP (10 patients) or no FFP (10 patients) in the CPB prime. Patients in the FFP group received significantly fewer units of cryoprecipitate ($p < 0.001$) with no difference in mean total donor exposure and mean chest tube output over the first 24 hours. In the APPEAR study, Bianchi et al.[65] randomized 73 infants weighing <10 kg to receive FFP to supplement RBCs in the CPB priming solution or immediately after CPB. The authors concluded that FFP in the priming solution appears slightly superior to late administration in terms of postoperative bleeding.

The effect of fresh whole blood versus reconstituted blood for pump priming in infants undergoing cardiac surgery also was assessed in a prospective randomized study by Mou et al.,[66] where the use of fresh whole blood (96 patients) or a combination of packed red cells and FFP (104 patients) showed no difference in outcome. In another small prospective study,[67] patients less than 1 month of age were randomized to receive either reconstituted fresh whole blood (n = 31) or standard blood component therapy (n = 33) to prime the CPB circuit and for transfusion during the 24 hours after CPB. Reconstituted fresh whole blood resulted in reduced chest tube volume loss and improved clinical outcomes (eg, inotropic score, ventilation duration, and hospital length of stay) compared with standard blood component therapy. Although fresh whole blood seems to be an interesting alternative to banked reconstituted blood, fresh whole blood is not widely available.

When a clear prime is preferred, different crystalloid (eg, normal saline, lactated ringer, or plasmalyte-A) or colloid (eg, albumin, gelatin, or hydroxyethyl starches) solutions are available. In 2002, Riegger et al.[68] randomized pediatric patients of <14 kg undergoing cardiac surgery requiring CPB to receive either a 5% albumin prime or a crystalloid prime. Patients in the albumin group had a net negative fluid balance at the end of CPB compared with a net positive fluid balance in the crystalloid group. Unsurprisingly patients in the albumin group had significantly higher serum albumins and colloid osmotic pressures and gained less weight postoperatively. However, the major limitation to the use of albumin in most countries is its cost. In a prospective randomized study, Hanart et al.[69] randomized 119 children to receive up to 50 mL/kg of either 4% albumin (n = 59) or 6% hydroxyethyl starch (HES) 130/0.4 (n = 60) for intraoperative fluid volume replacement including the CPB priming fluid. In that study, measured and calculated blood loss were not different between groups, but a higher number of children in the albumin group required allogeneic blood transfusion (78% *v* 57%, p = 0.0188). Intraoperative fluid balance was significantly lower in the HES 130/0.4 group (p = 0.005). Postoperative outcome was not different between groups. In another 2-center, randomized, controlled, parallel-group, double-blind trial performed in children aged 2 to 12 years undergoing elective surgery for congenital heart disease with CPB, Van der Linden et al.[70] compared the effect of HES 130/0.4 to 5% albumin with regard to the total volume of colloid infusion for intraoperative volume replacement including priming of the extracorporeal circuit. Intraoperative fluid balance was less positive in the HES 130/0.4 group (p = 0.047) but there was no difference regarding hemodynamics, the use of vasoactive and inotropic drugs, blood loss, erythrocytes transfusion, and renal function. The results reported in that prospective study were confirmed in a subsequent propensity matched analysis of 1,495 children exposed to either human albumin or 6% HES 130/0.4.[71] In that study, intraoperative use of HES 130/0.4 was associated with a less positive fluid balance. Perioperative blood loss, volume of RBCs and FFP administered, as well as the number of children who received transfusions, were also significantly lower in the HES group. No difference was observed regarding the incidence of postoperative mortality and morbidity. The authors concluded

that 6% HES 130/0.4 could be an alternative to albumin in children undergoing cardiac surgery under CPB. These conclusions also were supported by Miao et al.[72] in a prospective randomized study of 60 children. In a small retrospective study, Patel et al.[73] compared albumin, HES, and Lactated Ringer solution. They concluded that albumin is expensive but is a better prime to maintain hemostasis, colloid oncotic pressure, and reduced blood product requirement. Safety of HES 130/0.4 has been questioned in critically ill patients, specifically regarding its effects on renal function and hemostasis.[74,75] Because of the concerns raised in critically ill adults, the European Medicine Agency's safety committee recommended suspending the marketing authorizations of these medicines because they continued to be used in critically ill patients and patients with sepsis despite restrictions introduced in 2013 owing to the risk of kidney injury and death in these patients (EMA/498908/2018, 17 July 2018. www.ema.europa.eu/en/medicines/human/referrals/hydroxyethyl-starch-hes-containing-medicinal-products). Although no harm has been observed in children undergoing cardiac surgery, until a final recommendation by the EMA or other agencies is provided, HES should only be used carefully after balancing benefits and risks.

Recommendations

- The authors suggest the addition of FFP to the CPB prime in neonates (<30 days) undergoing cardiac surgery with cardiopulmonary bypass (Grade 2C). Because of the absence of evidence, the authors cannot make a recommendation regarding the addition of FFP in infants and children (C).
- The authors recommend that colloids (eg, albumin) should be preferred over crystalloids for clear priming in children undergoing cardiac surgery (Grade 1C).

Ultrafiltration

Ultrafiltration is a hemofiltration technique that passes blood through a semipermeable membrane filter and, according to a transmembrane pressure gradient, removes water, electrolytes, and other substances of small molecular size. This technique has been designed to minimize fluid overload, decrease the need for blood product transfusion, and reduce the plasmatic concentration of inflammatory molecules.[76] Conventional ultrafiltration (performed during CPB) in children is associated with a statistically significant, but clinically modest, increase in the concentrations of fibrinogen and other coagulation factors at the end of the procedure.[77] Modified ultrafiltration (MUF), which is performed after weaning from CPB, has been demonstrated to increase plasma protein concentrations and decrease postoperative bleeding and transfusion requirements.[78,79] The efficacy of the 2 techniques has been discussed in several articles.[80-83] In 2006, Williams et al.[84] in a comparison of techniques showed that a combination of modified ultrafiltration and conventional ultrafiltration afforded no additional benefit in terms of patient outcome relative to either technique alone. In 2011, a meta-analysis of the available randomized controlled trials indicated that modified ultrafiltration had limited clinical benefits over conventional ultrafiltration, with no impact on postoperative blood loss, ventilator time, and intensive care unit length of stay.[85] These findings suggested that both modified ultrafiltration and conventional ultrafiltration can improve clinical conditions in the immediate post-CPB period. In a more recent prospective randomized study, modified ultrafiltration applied to all patients after the termination of CPB during either 10, 15, or 20 minutes acutely improved pulmonary compliance and gas exchange and, when lasting longer than 10 minutes, acutely increased hematocrit levels and blood pressure measurements.[86]

Recommendation

- The authors recommend conventional ultrafiltration or ≥10 minutes of modified ultrafiltration for neonates and infants undergoing cardiac surgery with CPB (Grade 1B).

Cell Salvage and Normovolemic Hemodilution

Though several meta-analyses have proved the effectiveness of cell salvage in reducing perioperative transfusion needs in adult cardiac surgery,[87-89] the level of evidence is sparse in the pediatric population. Because of the low blood volumes harvested during pediatric cardiac surgery, many cell salvage devices failed to process the amount of blood adequately. Recent technical advances have made cell salvage feasible in neonates and infants, and therefore the use of cell salvage devices in pediatric cardiac surgery is now more common, but only 2 randomized clinical trials demonstrate the benefit in pediatric cardiac surgery.[90,91] While for years some centers advocated that residual circuit blood can be administered without additional treatment because the quality of this blood seems to be exactly the same as the quality of the patient's blood at the time of CPB discontinuation,[92] washing RBCs may reduce inflammatory biomarkers and the number of transfusions.[93]

Acute normovolemic hemodilution (ANH) involves the removal of blood, mostly shortly after the induction of anesthesia, and its simultaneous replacement by an adequate volume of colloids or crystalloids to maintain "normovolemic" (ie, isovolemic) status.[94] As a result of the hemodilution process, blood volume subsequently lost during surgery will contain fewer RBCs, thereby reducing the net RBC mass lost and possibly the need for allogeneic blood transfusion. The efficacy of ANH depends on several factors: the volume of surgical blood loss, patient's initial hematocrit, target post-ANH hematocrit, and the hematocrit used as the transfusion trigger. Several equations have been developed to predict the efficacy of ANH, but their clinical usefulness remained limited as several factors were not always taken into account.[95] In a prospective controlled trial, Friesen et al.[96] randomized 32 infants (5-12 kg) undergoing noncomplex open cardiac surgery to either 15 mL/kg ANH or standard of care. Reinfusion of the fresh ANH blood improved platelet count, prothrombin time, and fibrinogen levels compared with the control group. However, the study was not powered to detect a difference in postoperative blood loss and in the need for allogeneic blood products transfusion. In addition, most patients received

allogeneic RBCs in the CPB prime as a result of hemodilution, which represents a major limitation to ANH in small infants. As part of a quality improvement initiative that includes ANH, Naguib et al.[97] retrospectively reviewed all children who underwent cardiac surgery with CPB for biventricular procedures at their hospital in 2013. The authors reported that the ANH could be applied in 96% of their children weighing more than 18 kg, 79% of those weighing between 6 and 18 kg, but only 36% in those weighing less than 6 kg. Size of the patient, but also starting hematocrit, cardiac anatomy, and whether the lesion is cyanotic or noncyanotic will impact not only the safety of the procedure, but also its successful completion. In summary, the studies published to date are of low-level evidence, and include a small number of patients.[96,98,99] Some studies combined different approaches, so the direct effect of ANH could not be estimated.[97,100] Overall, there is no clear suggestion that ANH is effective in children undergoing cardiac surgery with CPB.

Recommendations

- The authors recommend the use of cell salvage in pediatric cardiac surgery in order to reduce perioperative transfusion (Grade 1C).
- The authors suggest active salvaging of CPB circuit residual blood as it may decrease the number of transfusions (Grade 2C).
- The authors recommend against the use of routine ANH in patients undergoing cardiac surgery with CPB (Grade 1C).

Anticoagulation and Monitoring

By potentiating the action of antithrombin 10,000 fold, unfractionated heparin inhibits thrombin and factor Xa and also activated intrinsic coagulation factors.[101] Unfractionated heparin is usually administered in an initial bolus of 300 to 400 U/kg. The administration of 400 U/kg of heparin has been shown to produce adequately prolonged activated clotting time (ACT) >480 seconds in infants and children.[101] However, because of the low levels of antithrombin in neonates the standard weight-based doses have been shown to inadequately suppress thrombin generation. Indeed, the differences in heparin sensitivity in the pediatric population is likely to be related to antithrombin levels, and as antithrombin is produced by the liver, it is influenced by age, heart failure, liver dysfunction, and inflammation.[102,103] Manlhiot et al.[104] have shown that, as predicted, low circulating antithrombin activity was associated with lower heparin efficacy, leading ultimately to a lower ability to suppress thrombin generation during CPB.

Several centers have adopted patient-specific heparin concentration-based protocols in infants <6 to 12 months of age.[105-108] Although in a recent large cohort study, Nakamura et al.[109] found that heparin responsiveness before CPB was not reliably predicted by either in vitro heparin dose-response slopes estimated by the HMS Plus System (Medtronic, Minneapolis, MN) or regression models using commonly available preoperative clinical and laboratory data. Different techniques have been used to monitor anticoagulation intraoperatively. While standard whole blood ACT is routinely used, others have recommended monitoring heparin concentration along with the ACT as a more accurate guide for heparin administration to infants.[110] However, this technique is not ideal because it does not measure the amount of antithrombin in the patient. Overall, anticoagulation using unfractionated heparin remains challenging in neonate and infants. Differences between different commercialized heparin also have been reported, which supports the need for appropriate monitoring of anticoagulation.[111,112]

Antithrombin replacement therapy with FFP, antithrombin concentrates or recombinant human, may improve anticoagulation management, but no studies have assessed the efficacy and safety of antithrombin supplementation in neonates and children undergoing cardiac surgery.[113]

After the patient is weaned from CPB, protamine is administered to neutralize heparin's effects. The protamine dose is usually based on the total amount of heparin administered during CPB. Most centers use a protamine-to-heparin ratio of 1:1. Based on the pharmacokinetics of heparin, a 1:1 ratio could lead to protamine overdose and bleeding. Protamine dose also can be estimated based on heparin concentration monitoring.[106,108]

When unfractionated heparin is contraindicated or needs to be avoided, parenteral direct thrombin inhibitors such as argatroban and bivalirudin are first-line alternatives.[114] Bivalirudin has been studied in only 1 prospective randomized study.[115] Bivalirudin's unique PK/pharmacodynamics (PD) profile necessitates procedural modifications that impact all members of the care team, requiring the development of standardized institutional protocols.[116] The dose required to maintain an ACT of more than 480 seconds was 1 to 2 mg/kg followed by 2 to 3 mg/kg/h infusion.

Recommendations

- The authors recommend the use of whole blood ACT or heparin concentration to assess heparin response in neonates and children (Grade 1B).
- The authors recommend targeting an ACT > 480 seconds before and throughout CPB (Grade 1B).
- The authors recommend an initial dose of 400 U/kg of unfractionated heparin before CPB initiation (Grade 1C). In the presence of heparin resistance and in absence of antithrombin deficiency, the authors suggest the administration of an additional 100 U/kg (Grade 2C). The authors recommend FFP (10 mL/kg) or antithrombin supplementation in the presence of heparin resistance secondary to antithrombin deficiency (Grade 1C).
- The authors recommend the dose of protamine should be calculated based on heparin concentration (Grade 1C).
- The authors suggest against the use of a protamine-to-heparin ratio of 1:1 or higher as protamine in excess could increase the risk of bleeding (Grade 2C).
- The authors recommend the use of direct thrombin inhibitors when heparin is contraindicated (Grade 1C).

Intraoperative Monitoring of Hemostasis

Standard coagulation assays (eg, aPTT, PTT, or international normalized ratio (INR)) were developed originally for the diagnosis of congenital factor deficiencies, and later the INR was formatted to guide the administration of vitamin K antagonists in both adults and children.[117] Because of the quantity of unfractionated heparin used during CPB, these tests are of no utility at this time as they are uncoagulable. Although considered the "gold standard" of coagulation tests, these tests were not designed to monitor perioperative coagulopathy or to guide the administration of hemostatic agents in bleeding situations. As it usually takes 30 to 45 minutes of turnaround time for testing to be performed in the local hemostasis laboratory, limited information is obtained from these tests in the context of acute bleeding. In addition, standard laboratory tests are performed on platelet poor plasma and do not allow for a global assessment of coagulation (ie, do not assess platelet number and function and fibrinolysis). Over the past decade, viscoelastic tests (eg, ROTEM or TEG) have been used increasingly and have shown utility in the management of adult patients with perioperative bleeding associated or with or without CPB.[6,118,119] The use of TEG/ROTEM early parameters (as soon as 5 minutes after clotting time) has predicted the quality of clot formation in children.[120] A good correlation between viscoelastic tests and standard coagulation assays has been demonstrated in children undergoing cardiac surgery.[121-123]

However, similar to conventional coagulation screens, viscoelastic tests are of no utility in predicting bleeding in children undergoing cardiac surgery.[19,124-128] However the use of viscoelastic tests integrated into an algorithm to guide the use of blood products has been shown to significantly reduce blood product transfusion in 2 pediatric retrospective case-control studies[129,130] and 1 randomized controlled trial.[131] In this latter study, Nakayama et al. randomized 100 children to be managed using a conventional transfusion protocol based on routine practice (n = 50) or a ROTEM-based algorithm specifically designed in that center (n = 50). Application of the ROTEM-based algorithm was associated with a significant reduction in the total amount of chest tube drainage measured at 12 hours ($p < 0.001$) and 24 hours ($p = 0.002$) after intensive care admission, and a significant reduction of the intraoperative amount of FFP and platelet concentrate administered. The authors concluded that hemostatic therapy for pediatric patients based on post-CPB thromboelastometric measurements reduced postoperative blood loss and blood product transfusion.

Recommendations

- In the presence of excessive bleeding, the authors recommend the use of intraoperative monitoring of hemostasis to guide the administration of blood products (Grade 1B).
- The authors suggest that intraoperative monitoring of hemostasis should be integrated into institution-specific transfusion algorithms (Grade 2C).
- The authors suggest viscoelastic tests as an alternative to standard coagulation assays for intraoperative bleeding management (Grade 2C).

Postoperative RBC Transfusion and Thresholds

In a prospective multicenter 6-month cohort study, Mazine et al.[132] reported that most cardiac surgery patients (79%) received at least 1 RBC transfusion during their pediatric intensive care unit (PICU) stay. In 2014, a meta-analysis (11 trials, 862 subjects) concluded that there was insufficient evidence to assess accurately the effect of RBC transfusions on mortality and morbidity in pediatric patients with congenital heart disease undergoing cardiac surgery.[133] The authors hypothesized that the presence or absence of cyanosis could have an impact on trial outcomes, which would require different clinical management of the 2 groups. In a retrospective study, Willems et al.[134] compared children receiving prophylactic transfusion (RBC transfusion in the CPB prime to maintain calculated hematocrit above 20% after administration of cardioplegia) with children receiving therapeutic transfusion (RBC transfusion in the postoperative period to compensate for blood loss or signs of inadequate tissue oxygen delivery). Using multivariate analysis for other risk factors, the authors found that children exposed to a therapeutic transfusion had a higher risk for postoperative severe morbidity and mortality than those exposed to a prophylactic transfusion to avoid excessive hemodilution on CPB. Children exposed to such a prophylactic transfusion did not seem to have a higher incidence of severe postoperative morbidity and mortality when compared with children avoiding any transfusion during or after their surgical procedure.[135] Age below 1 year, low weight, illness severity, CPB, cyanotic heart condition, and lower admission Hb have all been reported to be independently associated with increased RBC transfusions.[136,137]

In view of the current debate on the risk-benefit balance of RBC transfusion, most authors recommend applying the "primum non nocere" principle and therefore to adopt a more restrictive approach to transfusion in cardiac children. Four trials have compared restrictive and liberal transfusion strategies in postoperative pediatric cardiac patients. In the Transfusion Requirements in Pediatric Intensive Care Unit (TRIPICU) study, 637 hemodynamically stable, critically ill children were randomized to receive RBC transfusion if their Hb dropped below 70 or 95 g/L for up to 28 days post-randomization.[138] In this multicenter noninferiority prospective randomized trial, there was no difference between the 2 groups regarding the primary outcome, which was the proportion of children who developed or had progression of multiple organ dysfunction syndrome. The authors concluded that in the studied population, a transfusion strategy using an Hb threshold of 70 g/L decreases the need for RBC transfusion without increasing the incidence of adverse outcome. In a subgroup analysis of cardiac surgery patients, a restrictive red-cell transfusion strategy, as compared with a liberal one, was not associated with any significant difference in new or progressive multiple organ dysfunction syndrome.[139] The second, single-center prospective randomized trial compared noncyanotic (arterial oxygen saturation >95%), cardiac surgery children (N = 107 participants) randomized before surgery to receive RBC transfusion if their Hb dropped below 80 or 108 g/L from the beginning of the procedure and up to PICU discharge.[140] Hospital length of stay (primary

outcome) was significantly lower in the restrictive group, whereas all other outcome measures and incidence of adverse events were not different between both transfusion groups.

The third, single-center prospective randomized trial compared infants and children with cyanosis and single ventricle physiology undergoing cavopulmonary connection (N = 60).[141] The study protocol was initiated at the time of PICU admission and maintained for 48 hours. Patients were randomized to a liberal transfusion group: 10 mL/kg of RBC transfused for any Hb < 140 g/L regardless of whether there was a clinical indication for transfusion, and a restrictive transfusion group: 10 mL/kg of RBC transfused for any Hb < 90 g/L accompanied by clinical signs suggestive of symptomatic anemia (ie, tachycardia or hypotension unresponsive to fluid infusion, poor perfusion, or worsening oxygenation). Mean and peak arterial lactate level (primary objective), and arterio-venous and arterio-cerebral content differences were not different between the 2 groups, whereas the number of RBC transfusion and donor exposure was lower in the restrictive group. All other outcome measures were not different between groups, but the study was not powered to demonstrate statistically significant difference.

The fourth, single-center prospective trial compared infants weighing 10 kg or less randomly assigned to either a postoperative restrictive or liberal transfusion strategy (N = 162 participants).[142] The restrictive transfusion strategy for biventricular repairs was 10 mL/kg when Hb dropped below 70 g/L and clinical indication, and for palliative procedure was 10 mL/kg RBC when Hb dropped below 90 g/L and clinical indication. The liberal transfusion strategy for biventricular repairs was 10 mL/kg RBC when Hb dropped below 90 g/L, regardless of clinical indication, and for the palliative procedure was 10 mL/kg RBC when Hb dropped below 120 g/L regardless of clinical indication. The transfusion strategy was initiated at admission to the PICU and maintained until transfer from the PICU service postoperative day 28, decision to cannulate for ECMO, or death. Transfusion compliance within the restrictive group was 93% (100% in the biventricular repair group and 79% in the palliative group). Daily Hb concentrations were significantly lower in the restrictive groups by postoperative day 1 and remained lower for more than 10 days. The percentage of patients receiving RBC transfusion, the number, and the volume of transfusion were lower in the restrictive groups. Mean and peak and clearance of lactate, arterio-venous oxygen difference, and clinical outcomes were not different between the restrictive and the liberal transfusion groups for both biventricular repairs and palliative procedures. The authors concluded that both populations can tolerate a restrictive transfusion strategy, although the small number of Norwood procedures (n = 12; 6 in each group) limits their conclusion for this very high-risk population.

Goal-directed RBC transfusion strategy targeting a physiological goal may be a more appropriate approach than specific Hb levels.[143] However, there are currently no solid data on goal-directed transfusion strategies in pediatric cardiac patients. Different physiologic parameters like blood lactate,[144] mixed venous oxygen saturation or its surrogate central venous oxygen saturation,[145] oxygen extraction ratio,[146] or, at the regional level, cerebral oxygen saturation measured by near infrared spectroscopy[144] might be considered. According to Barr and Bailie,[147] the decision to transfuse should be guided by an assessment of individual patient on the basis of a combination of symptoms, clinical and physiologic signs, laboratory measurements, and not by a single Hb level.

Recommendations

- The authors recommend a postoperative hemoglobin threshold for transfusion in stable, acyanotic cardiac children of Hb 70 g/L, or 80 g/L in the presence of clinical signs suggestive of symptomatic anemia (Grade 1B).
- The authors recommend a postoperative hemoglobin threshold for transfusion in stable, cyanotic cardiac children with clinical signs suggestive of symptomatic anemia as of 90 g/L (Grade 1C).

Platelet Transfusion

Thrombocytopenia and platelet dysfunction are a consequence of the use of CPB and significantly increase the risk of bleeding complications and transfusion requirements in cardiac surgery with CPB. However, there is little evidence on optimal use of platelet transfusions for cardiac surgery even in adults, and few guidelines, adult or pediatric, make specific recommendations regarding platelet transfusion thresholds for cardiac surgery. The platelet count and function in infants and children undergoing cardiac surgery is affected by the duration of CPB and the degree of hemodilution, whereas hypothermia correlated with platelet dysfunction alone.[148-151] Small studies suggest that the effect of CPB on platelet number and function is age related, with greater platelet dysfunction (either activation or hyporeactivity) after CPB in neonates and younger infants compared with older children.

No studies have assessed the effect of platelet transfusion on postoperative bleeding in children undergoing cardiac surgery or compared different volumes and types of platelet transfusion (eg, concentrated platelets). Thus the recommendations for platelet transfusion are mainly consensus, taking into account adult cardiac[6] and pediatric transfusion guidelines.[5]

Recommendation

- In the presence of excessive bleeding post CPB despite adequate heparin reversal, the authors suggest platelet transfusion (Grade 2C).

Fibrinogen Supplementation

Decreased plasma fibrinogen has been associated with early postoperative blood loss in infants and children undergoing cardiac surgery.[122] Fibrinogen can be supplemented by the administration of cryoprecipitate, or fibrinogen concentrate. FFP also contains fibrinogen but in inadequate amounts to increment a low fibrinogen in a child. Cryoprecipitate contains fibrinogen (range: 150-700 mg per unit) and is the preferred option for raising fibrinogen in the United States and United Kingdom.

Fibrinogen concentrate is not licensed for treating acquired hypofibrinogenemia outside of mainland Europe and is often used off-label. The efficacy of fibrinogen concentrate for the management of acute acquired hypofibrinogenemia during pediatric heart surgery has been assessed in 1 prospective randomized study,[152] where children were randomized to receive either 60 mg/kg of fibrinogen concentrate (n = 30) or 10 mL/kg of cryoprecipitate if bleeding was associated with fibrinogen levels <1 g/dL after CPB. The median 48-hour blood loss was not significantly different between the 2 groups (320 mL [157-750] *v* 410 mL [215-510], p = 0.672). After treatment, plasma fibrinogen concentration increased similarly after administration of both products. There were no differences in allogeneic blood transfusion after intervention treatment. Considering that fibrinogen concentrate is a plasma-derived product submitted to pasteurization that minimizes the risk of transfusion-transmitted disease, the results suggest that fibrinogen concentrate is a safe alternative to cryoprecipitate.

Recommendations

- In bleeding neonates and children, the authors recommend hypofibrinogenemia diagnosed either by Clauss method (<1.5 g/L) or viscoelastic tests (based on institution-specific algorithm) should be treated (Grade 1C) either with cryoprecipitate or fibrinogen concentrate (Grade 2C).
- The authors suggest FFP should be considered for treating hypofibrinogenemia in bleeding neonates and children ONLY when cryoprecipitate or fibrinogen concentrates are not available (Grade 2C).

Prothrombin Complex Concentrates

These are available in 4-factor (4F) (FII, FVII, FIX, and FX) and 3-factor (3F) (FII, FIX, FX, and very low FVII) preparations. The 4F prothrombin complex concentrates (PCCs) are widely approved and recommended for the reversal of vitamin K antagonists, while 3F PCCs were originally approved for factor IX repletion in hemophilia B and should not be used for reversal of vitamin K antagonists unless 4F PCC is not available. Factor VIII inhibitor bypassing activity (FEIBA) is an additional PCC containing FII, FIX, FX, and activated VIIa. These agents are considered to have a prothrombotic effect and this has led to concerns about safety. All those preparations are approved for the management of congenital coagulation factor deficiency but also have been used anecdotally for bleeding management in the context of acquired coagulopathy. The ex vivo effect of PCCs on optimization of thrombin generation in neonatal plasma has been assessed in 2 studies.[153,154] Despite a low content of FVII, Guzzetta et al.[153] reported that 3F PCC exerts potent procoagulant activity compared with rFVIIa ex vivo. In another ex vivo study, thrombin generation in neonatal plasma was augmented by the addition of 4F PCCs or FEIBA. The peak amount and rate of thrombin generation were enhanced with both preparations, whereas the lag time was shortened more with FEIBA.[154] In neonates and children, little is known regarding the efficacy and there is concern for safety of PCCs in regard to thrombotic risk. In 2014, Giorni et al.,[155] in an observational prospective study, assessed the effect of PCC administered in 14 infants younger than 1 year after weaning from CPB and in the presence of nonsurgical bleeding,who were matched to 11 comparable patients who did not receive PCC. The use of PCC reduced postoperative bleeding and allowed fewer units of packed RBCs to be transfused in the postoperative period without major side effects. In another case series published by Jooste et al.,[156] 3F PCCs were administered to 6 infants with ongoing hemorrhage post CPB after standard-of-care transfusions of allogeneic blood products. The administration of PCCs was felt to reduce clinically evident bleeding, but there remains a significant concern for the risk of thrombosis. Considering the risk of thrombosis seen in other groups receiving PCC and the absence of clinical data supporting the efficacy and safety of PCCs in managing bleeding post CPB in neonates and children, further studies are urgently needed before PCCs can be used in this high-risk population.

Recommendation

- The authors recommend against the use of PCC in pediatric cardiac surgery unless it is part of a clinical trial (Grade 1C).

Other Products: Recombinant Activated Factor VII and Desmopressin

Recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Copenhagen, Denmark) is widely approved for the treatment and prevention of bleeding in the hemophilia community with inhibitors and those with acquired hemophilia. Evidence from its extensive use in this population and in vitro work demonstrates that pharmacologic doses of rFVIIa restore hemostasis by enhancing thrombin generation on the activated platelet surface, thus enhancing hemostasis at the site of injury.[157] Only 1 prospective study evaluated the safety and hemostatic potential of prophylactically administered rFVIIa in children undergoing cardiac surgery.[158] In this study, 76 children under 1 year old with congenital heart disease were randomized to receive either rFVIIa (40 μg/kg) or a placebo in addition to standard hemostatic replacement therapy. No benefit was reported in term of blood loss or the use of blood products. The efficacy and the safety of rFVIIa as part of the bleeding management strategy in neonates and children undergoing cardiac surgery were evaluated in a large number of retrospective studies.[159-163] In the most recent study by Downey et al.,[163] pediatric patients with post-CPB bleeding who received rFVIIa were an estimated 3.9 times (95% confidence interval [CI], 2.6-5.9) more likely to develop thrombotic complications when compared with propensity-matched controls. However, results from retrospective studies are limited by the absence of randomization, and one could argue that patients treated with rFVIIa experienced more severe bleeding during more complex surgical procedures.

Desmopressin (DDAVP) is a vasopressin analogue that increases circulating levels of coagulation factor VIII and von Willebrand factor by stimulating the release of stored von Willebrand factor from the Weibel Palade bodies in the endothelium. DDAVP is used mainly to improve hemostasis in patients with von Willebrands' disease, hemophilia A, and certain inherited disorders of platelet function. The efficacy of DDAVP in reducing bleeding and transfusion in children undergoing cardiac surgery has been assessed in only 3 studies.[164-166] The administration of DDAVP was not associated with significant reduction in blood loss or blood product transfusion. Further well-designed studies are needed to assess the effect of DDAVP on platelet function and blood loss in children undergoing cardiac surgery.

Recommendations

- The authors recommend against the administration of rFVIIa to treat acquired coagulopathy in neonates and children undergoing cardiac surgery (Grade 1C).
- The authors recommend against the use of DDAVP for bleeding management in children undergoing cardiac surgery (Grade 1B).

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Conflicts of Interests

The authors have no conflicts of interest to disclose.

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