Review Article

Strategies for blood conservation in pediatric cardiac surgery

Sarvesh Pal Singh

Department of CTVS, Cardiac Surgical Intensive Care Unit, Cardiothoracic Sciences Centre, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Cardiac surgery accounts for the majority of blood transfusions in a hospital. Blood transfusion has been associated with complications and major adverse events after cardiac surgery. Compared to adults it is more difficult to avoid blood transfusion in children after cardiac surgery. This article takes into account the challenges and emphasizes on the various strategies that could be implemented, to conserve blood during pediatric cardiac surgery.

Received: 25-11-15
Accepted: 25-05-16

Key words: Blood; Cardiac; Conservation; Pediatric; Surgery

INTRODUCTION

The number of children undergoing complex surgeries for congenital heart diseases is increasing day by day. In comparison to adults, children are at an increased risk of postoperative bleeding. The amount of blood loss and transfusion in children undergoing cardiac surgery is up to 15–110 and 155 ml/kg, respectively.[1,2] A study by Chambers *et al.* in 1996 documented that 98% of children who underwent cardiac surgery (with the aid of cardiopulmonary bypass [CPB]) received packed red blood cells (RBCs).[3] A recent review reported that 38–74% of children who underwent cardiac surgery received a blood transfusion.[4]

RISKS AND CLINICAL IMPACT OF BLOOD TRANSFUSION

The most common complications of blood transfusion are leukocyte-related target organ damage (2–5%), febrile nonhemolytic transfusion reaction (1%), transfusion-related lung injury (0.05%), and bacterial infection (0.05%).[5] Blood transfusion leads to increased incidence of infections (sepsis), respiratory complications (acute lung injury), cardiac complications (low cardiac output syndrome, increased inotropic usage), renal complications (acute kidney injury), duration of mechanical ventilation, Intensive Care Unit (ICU) and hospital length of stay, and cost of treatment and mortality.[6-12] In pediatric patients undergoing heart transplant increasing amount of RBC transfusions are associated with increase length of ICU stay, inotropic scores, and major adverse events. Following modified Blalock–Taussig shunt procedures, blood transfusion >6 ml/kg is an independent risk factor for mortality.[13] Larger volume blood transfusion correlates with longer intubation durations, ICU and hospital stays, higher peak C-reactive protein levels, and an increased blood urea nitrogen/creatinine ratio.[14] Increased volume of packed blood cells when used in CPB prime and during CPB lead to excessive postoperative bleeding in pediatric cardiac surgery.[15]

Access this article online
Website: www.annals.in
DOI: 10.4103/0971-9784.191562
Quick Response Code:

Address for correspondence: Dr. Sarvesh Pal Singh, Department of CTVS, Cardiac Surgical Intensive Care Unit, Cardiothoracic Sciences Centre, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: sarveshpal.singh@gmail.com

Cite this article as: Singh SP. Strategies for blood conservation in pediatric cardiac surgery. Ann Card Anaesth 2016;19:705-16.

CHALLENGES FOR BLOOD CONSERVATION IN PEDIATRIC AGE GROUP

Children pose a unique set of challenges pertaining to blood conservation due to their small blood volume; large priming volume of CPB circuits, requirements of higher hematocrit during CPB, presence of cyanosis in some children, immature coagulation system and hypothermia during CPB. Congenital deficiency of coagulation factor VII, VIII or von Willebrand factor further increases the risk of bleeding and therefore, blood transfusion.[16-18] Furthemore, children with cardiac lesions involving systolic flow abnormalities are at increased risk of developing qualitative platelet dysfunction than those with diastolic flow abnormalities.[19] The exposure to extracorporeal circuit also leads to the development of qualitative and quantitative platelet abnormalities, coagulation factor deficiencies, and hypofibrinogenemia.[20]

STRATEGIES

The strategies for conserving blood in children undergoing cardiac surgery are listed in Table 1.

Table 1: Strategies for blood conservation in pediatric cardiac surgery

Preoperative
Autologous blood donation
Erythropoietin therapy
Intraoperative
Monitoring lines and sampling volume
Acute normovolemic hemodilution
Anti-fibrinolytics
Retrograde autologous priming
Miniature circuits
Microplegia
Ultrafiltration
Vacuum assisted venous drainage
Surface modified bypass circuits
Cell saving devices
Special coagulators
Topical hemostatic agents
Postoperative
Point of care tests and transfusion algorithms
Anti-fibrinolytics and aprotinin
Recombinant activated factor VII
Reducing blood sampling in the postoperative period

Preoperative

Autologous blood donation

Autologous blood donation (ABD) is usually done in children more than 3 years of age or weight more than 15 kg. A femoral vein or an external jugular vein may be used for withdrawing blood under mild anesthesia. Repeated withdrawals are required, and a volume of 10 ml/kg may be collected per phlebotomy while replacing the volume and electrolyte deficit with 0.9% saline or colloid. Autologous blood may be stored for 3 weeks with a citrate phosphate dextrose adenine (CPDA) solution in liquid form and up to 6 weeks with cryopreservation. In smaller children, once maximum permissible blood is withdrawn a 3–4 week interval is required before another donation. The last donation may be as late as 1 week before surgery. The volume to be drawn to successfully avoid homologous blood transfusion can only be learned by experience.[21] The demerits of ABD are that every autologous donation is succeeded by erythropoietin (EPO) therapy, practically cumbersome, difficult with poor venous access, increased the load on blood bank services, repeated visits are required, requires convincing the child, increased the cost of treatment, and complications of EPO therapy.

Komai *et al*. developed a protocol in which they withdrew 8 ml/kg of autologous blood twice before surgery and administered human EPO 100–300 units/kg subcutaneously at each donation. The blood was replaced with 16 ml/kg of the electrolyte solution, and the iron supplement was given after each EPO injection. For intraoperative blood conservation, they used aprotinin, ultrafiltration (conventional and modified), and infusion of residual CPB blood, after washing with an autotransfusion device.[22]

Erythropoietin therapy

EPO therapy in the preoperative period may be used in children with low preoperative hemoglobin or as a part of ABD. Recombinant human EPO (rHuEPO) is administered in a dose of 300 μ/kg 1 week before autologous donation or surgery. The same dose may be repeated at subsequent autologous donations. Supplemental iron, Vitamins (A, C, K), folic acid and B_{12} are also given at the time of rHuEPO. Hypertension and flu-like syndrome are common side effects of EPO therapy.[23] Pretreatment with rHuEPO, 1 week before surgery, increases the hematocrit significantly in a dose-dependent manner. Anemic patients may benefit more than nonanemic ones. The decrease in the incidence of packed RBC (pRBC) transfusion in the postoperative period may not be significantly less.[24]

Intraoperative

Monitoring lines and sampling volume; closed blood conservation device

While acquiring invasive lines for monitoring certain

precautions may help in avoiding excessive blood loss, especially in small neonates. Repeated attempts at same site should be avoided and in the case of failed puncture prompt compression of puncture sites should be done. Whenever feasible a change in the site for vascular access and possibly a change of hands are advisable. Limiting frequent flushing of invasive lines prevents hemodilution and whenever desirable the sampling volumes should be restricted to minimum (≤1 ml). Recent clinical analyzers may provide an arterial blood gas analysis with as little as three drops of blood. The use of "double stopcock technique" decreases hemodilution and conserves blood [Figure 1].[25]

The use of a closed blood conservation device, the venous arterial blood management protection system, decreases the incidence of catheter-related contamination of the intraluminal fluid.[26]

Acute normovolemic hemodilution

There are no general guidelines for acute normovolemic hemodilution (ANH) before going on CPB. Before initiating ANH, it is prudent to have a hematocrit >30% at baseline. The blood may be withdrawn using an arterial or a central venous line. Sufficient volume of blood that can be withdrawn without causing hemodynamic unstability cannot be predicted; however, a safe assumption may be to withdraw not more than 10–15% of blood volume while replacing the fluid deficit with either crystalloid or colloid. Furthermore, it is important to monitor perfusion and oxygenation of vital organs. Near infrared spectroscopy may be used to measure the cerebral oxygenation in addition to the routine American Society of Anesthesiologists monitoring.[27] The withdrawn autologous blood is anti-coagulated with appropriate amount of CPDA solution or blood may also be withdrawn after heparin administration. It is not uncommon to transfuse the autologous blood during CPB to maintain the target hematocrit. While reinfusing the withdrawn blood calcium chloride (10 mg/kg) or gluconate is administered to counter the chelation of calcium ions by CPDA solution.[28] The advantage of ANH is that diluted blood is lost during surgery and postoperatively fresh whole blood is transfused (which reduces postoperative bleeding the best).

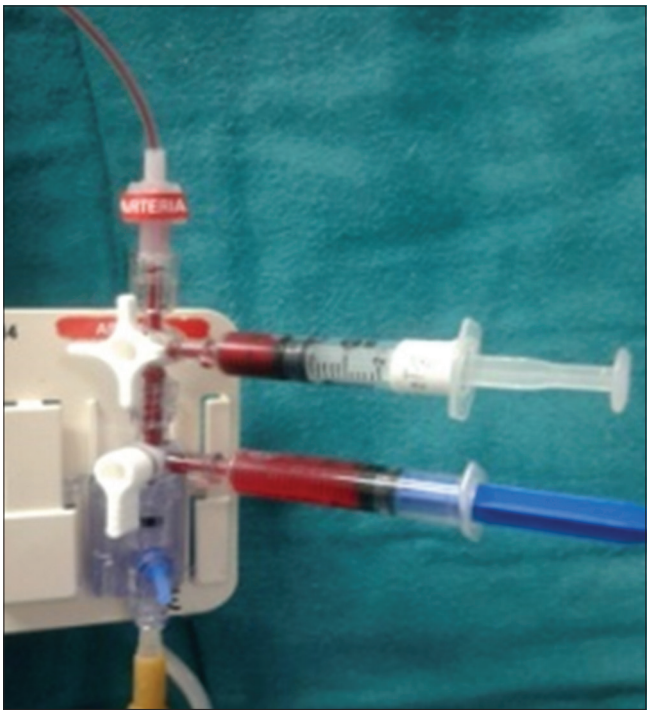

Figure 1: Double stopcock technique

Anti-fibrinolytics

In the normal coagulation pathway, the formation of fibrin is followed by fibrinolysis mediated by plasmin. Alpha2 anti-plasmin inhibitor is a naturally occurring anti-fibrinolytic protein which regulates the fibrinolysis. It is a potent inhibitor of free plasmin but has only a mild effect on plasmin bound to fibrin. Aprotinin acts in a similar fashion and improves hemostasis. However, tranexamic acid and epsilon aminocaproic acid (EACA) prevent excessive plasmin formation by inhibiting binding of plasminogen with fibrin. They acquire the lysine binding site of plasminogen and prevent its interaction with fibrin.

Aprotinin

Aprotinin inhibits trypsin, chymotrypsin, plasmin, kallikrein, elastase, and thrombin. It decreases activation of the contact system, prevents fibrinolysis, and preserves platelet function. Aprotinin prevents proteolysis of the major thrombin receptor on platelets (PAR 1), thereby preventing platelet activation. Due to its anti-inflammatory effect, there is a decrease in the level of cytokines interleukin (IL)-6, IL-8, tumor necrosis factor-α, and expression of macrophage 1 antigen.

Aprotinin when introduced in clinical practice was accepted universally as a prophylactic and therapeutic hemostatic agent in the perioperative period.[29,30] The safety of aprotinin came into question when two studies – Blood Conservation using Anti-fibrinolytics in a Randomized Trial and a study by Mangano *et al*. suggested that aprotinin increased the incidence of major adverse events and mortality. These observations were followed by withdrawal of aprotinin from the

market. Later, the Food and Drug Administration (FDA) re-analyzed the data of all studies that concluded against aprotinin and found there were many confounding factors influencing the conclusion.[31-34] Thereafter, Health Canada licensed the use of aprotinin in revascularization surgeries. Aprotinin has been shown to reduce perioperative bleeding and blood transfusion during reoperations and congenital heart surgery.[35]

Tranexamic acid

A 100 mg/kg bolus before skin incision and an intraoperative infusion of 10 mg/kg/h was effective in conserving blood and improved clinical outcomes after pediatric cardiac surgery.[36] The optimal dose that can be recommended for prophylaxis against postoperative bleeding is not yet determined. However, it has been postulated that the adverse events after tranexamic acid administration may be dose-dependent.[37]

Prospective studies to evaluate the safety profile and potential adverse effects in the pediatric cardiac population are also lacking. Therefore, the association of tranexamic acid with seizures is based on underpowered studies.

Epsilon aminocaproic acid

Following the withdrawal of aprotinin from the market, clinicians resorted to alternate anti-fibrinolytics, tranexamic acid, and EACA. The use of EACA in pediatric cardiac surgery was not recommended till now because of the lack of studies documenting its safety profile in children. Compared to placebo, EACA was associated with decreased postoperative blood loss, reduction in blood transfusion, reduction in re-exploration rate, higher platelet counts, lower activated clotting time (ACT), and higher fibrinogen levels in children undergoing cardiac surgery.[38-42] A metaanalysis compared five studies and concluded "EACA should be recommended for the prevention of postoperative blood transfusion in pediatric cardiac surgery." The authors of the above-stated meta-analysis have cited several limitations of their study, but an additional limitation of their study was that four out of five studies they selected for analysis were from a single institute.[43] Furthermore, these studies were not designed to study the safety profile of EACA administration in children; therefore, additional prospective studies specifically designed to study adverse effects of EACA are required before a recommendation may be made for its routine use in pediatric cardiac surgery.

Before recommending the alternative anti-fibrinolytics for routine prophylaxis, the safety profile needs to be adjudged so that they do not meet the fate of aprotinin.

Retrograde autologous priming

Retrograde autologous priming (RAP) is done to either completely or partially replace the prime volume of the CPB pump. It takes about 4–5 min before commencing CPB. By displacing 50% of prime volume with RAP hematocrit is reduced by 50% only (vs. 75% without RAP). To counteract the transient fall in mean arterial pressure (MAP <35 mm Hg infants) small boluses of phenylephrine (10 μg) may be used.

Miniature circuits

Miniature circuits are modified and dwarfed versions of conventional CPB circuits (CCPBs). With different permutation – combinations of the diameter and size of tubing, of the CPB circuit, prime volume can be varied between 110 and 170 ml for children <5 kg. The internal diameter of the arterial line can be decreased to 1/8". The arterial filter has been eliminated from certain oxygenators which use "Self-venting technology" to get rid of air bubbles. Oxygenators such as Kids D100 (Sorin) and Baby FX (Terumo) decrease prime volume and prevent hemodilution. To decrease the length of venous tubing, the venous reservoir is elevated to the level of the right atrium and venous return is maintained using vacuum-assisted venous drainage (VVAD). Because of the decrease in prime volume, hemodilution is much less and there is no requirement of hemofilter. Examples of different combinations of microcircuits are - 1/8" A line + 3/16" V line + Baby RX 5/Lilliput 1 = 175 ml prime (No arterial filter) and 1/8" A line + 3/16" V line + Kids D 100 + Sorin arterial filter D 130 = 110 ml.

Kotani *et al*. combined different sizes of arterial (5/16"; 1/4"; 3/14") and venous (5/16"; 1/4") lines and compared different arterio-venous combinations with respect to amount of prime volume, blood transfusion, sodium bicarbonate use (to maintain pH), and hemodynamics. They concluded that downsizing the lines decreased prime volume, blood transfusion, and sodium bicarbonate use but had no effect on hemodynamics.[44]

Miniature extracorporeal circuits (MECC) are half as long as CCPBs.[45] MECC decrease the interactions between blood and artificial surface, therefore, preventing an exaggerated systemic inflammatory response during CPB.[45] Mini-CPB requires one-third of blood transfusion compared to CCPB with lesser postoperative bleeding and blood transfusion-related complications.[46-48]

MICROPLEGIA

To deliver microplegia blood is diverted from the arterial line of the CPB circuit or a special port from oxygenator through a roller pump. The cardioplegia with high potassium content (40 or 100 mEq/l) is delivered in this blood by a syringe pump. A ratio of 1 part cardioplegia and sixty parts blood is achieved by maintaining the infusion rate of a roller pump in ml/min and that of the syringe pump in ml/h, while keeping the numeric value constant (e.g., 10 ml/min of roller pump = 10 ml/h of syringe pump). Microplegia prevents hemodilution, especially on repeated delivery, decreases the tendency for tissue edema, and provides better myocardial protection, higher oxygen delivery (higher hemoglobin), and negligible fluid balance of cardioplegia.[49-51] The advantages of microplegia have not been studied exclusively in pediatric patients undergoing cardiac surgery.

A North American survey of 122 congenital heart surgeons revealed that 5% of them use microplegia, consisting of oxygenated blood with potassium concentration of 40 or 100 mEq/l during pediatric cardiac surgery.[52] In this survey, the temperature at which Microplegia was used varied between <5 and 20°C, induction dose between 10 and 30 ml/kg and maintenance dose between 5 and 10 ml/kg. The redosing interval has been debated and may vary from 15 to 35 min.[53]

ULTRAFILTRATION

Conventional ultrafiltration increases hematocrit and postoperative blood loss after pediatric cardiac surgery. It helps in eliminating inflammatory mediators generated during CPB. Children who are operated under profound hypothermia are the most benefited. In comparison with cell saving devices (CSDs) plasma proteins and platelets are preserved during ultrafiltration. In children undergoing cardiac surgery modified ultrafiltration (MUF) increases hematocrit, improves hemostasis, decreases blood loss and transfusion, and increases levels of prothrombin, factor VII and fibrinogen.[5,54-57] A systematic review by Kuratani *et al*. highlighted that, compared to CUF, MUF increases post-CPB hematocrit significantly, but the decrease in chest tube drainage is not significant when compared with controls.[58] Longer duration of MUF is associated with better hematocrit and blood pressure in infants undergoing arterial switch operation.[59] A demerit of ultrafiltration is that cannot be used with miniaturized circuits.

VACUUM-ASSISTED VENOUS DRAINAGE

Earlier used as a troubleshooting therapy in patients with compromised venous drainage during CPB, VAVD is now an essential component of microcircuitry used in pediatric CPB. As discussed above, with microcircuits the hard shell reservoir is nearly at the level of the right atrium. Therefore, there is a loss of the siphoning effect of the gravity dependent drainage. VAVD compensates for this loss of gravity dependent drainage and allows the reservoir and rotor pump to be raise to the patient level.[60] With VAVD the venous return may be increased by as much as 40% in 3/16 inch tubing. For example, 20 cm reservoir age/reservoir drainage height + 40 mm Hg vacuum to the reservoir is equivalent to a 72 cm drainage height.

Since the venous drainage is essentially dependent on vacuum suction, a backup should be available at all times to circumvent any failure of the vacuum device. It has been reported that there is an increased formation of gaseous microemboli with an increase in the vacuum level. A vacuum suction pressure of <40 mm Hg is associated with the same embolic load as gravity dependent siphon drainage.[61] Therefore, it is recommended not to increase the vacuum level more than 40 mm Hg. Hemolysis may also occur which can be prevented by decreasing hematocrit on CPB (25%) and avoiding high suction pressures. A safety feature in form a pressure relief valve is present on VAVD device which opens at + 5 mm Hg or −80 mm Hg.[62]

SURFACE MODIFIED BYPASS CIRCUITS

The use of an artificial circuit triggers an inflammatory response during CPB. To prevent this inflammatory response, various agents have been used to coat the surface of the CPB circuit. Heparin, trillium, poly-2-methoxyehylacrylate, phosphorylcholine, and senko e-ternal coating has been used till date.[63-70] The purpose of modifying the surface of extracorporeal circuit is to prevent the inflammatory response that occurs during CPB. Therefore, the majority of studies done on surface modified circuits have evaluated the rise and fall in the serum levels of inflammatory cytokines and molecules.[63-69] These studies were not designed to study the effects of surface modifying agents on bleeding and blood transfusion after cardiac surgery. Hence, with the currently available literature, it cannot be established that surface modified CPB circuits decrease bleeding and postoperative blood transfusion.

CELL SAVING DEVICES

CSDs were assumed to be of benefit in adult surgeries with huge amounts of blood loss because the volumes required to process in the earlier CSDs were large. With the development of newer continuous centrifugation CSD, which can process as little as 30 ml blood continuously, without delay, their role in pediatric cardiac surgery is increasing. A CSD not only conserves blood but also removes debris and therefore decreases the risk of embolism. The processing of blood in a cell saver removes coagulation factors, platelets, and plasma proteins and may cause bleeding due to residual anti-coagulant. Therefore, it is essential to reverse the residual heparin by protamine. Any residual blood post-CPB should be collected in a bag and transfused as and when required rather than subjecting it to a cell saver because it is safe, efficient, simple, and less expensive than CSD.

Cell saver blood can be safely stored at the bedside for 24 h after collection from neonates and infants undergoing cardiac surgery. The transfusion of this blood decreases the amount of RBC and blood products transfusion in the immediate postoperative period (48 h) significantly. However, within 7 days after surgery, the difference was not found to be statistically significant.[71] From an economic point of view, cell salvage and allogenic blood transfusion are least expensive, followed by cell salvage and autologous blood transfusion, allogenic blood transfusion alone and autologous blood transfusion alone.[72]

SPECIAL COAGULATORS

Ultraincision harmonic scalpel cuts and coagulates at the same time. The vibration (55,500 Hz) of the scalpel cuts through tissue, and the protein denaturation seals it. Initially developed with the intention of improving surgical dissection and reducing tissue trauma, it was found to improve hemostasis during operations. A study of 150 adult patients undergoing redo surgeries found that the use of harmonic scalpel decreased mediastinal chest tube drainage, allogenic blood transfusion and the transfusion of fresh frozen plasma in the postoperative period. The use of harmonic scalpel was associated with better postoperative outcomes.[73] However, similar studies in the pediatric age group are lacking. One case of the surgical division of a double aortic arch in a 2.0 kg child using harmonic scalpel has been reported.[74]

TOPICAL HEMOSTATIC AGENTS

There are different types of topical hemostatic agents available for use in patients undergoing cardiac surgery:[75]

- Fibrin sealant - TISSEEL, Beriplast P, Vivostat
- Absorbable gelatin sponge - Spongostan
- Oxidized regenerated cellulose - Surgical
- Gelatin and thrombin - Floseal
- Microporous polysaccharide - HemoStase
- Chitin and chitosan based agents - HemCon; Chitoseal.

The literature regarding the use of topical hemostatic agents in pediatric cardiac surgery and their effect on postoperative bleeding and blood transfusion is very less. The only randomized controlled trial in pediatric cardiac surgery evaluating the use of a fibrin sealant was published by Codispoti and Mankad in 2002. The authors of this study concluded that the use of a fibrin sealant, intraoperatively, decreased bleeding, blood transfusion, and the time for surgical hemostasis.[76] Huth *et al*. studied fibrin sealant in children with tetralogy of Fallot and transposition of the great arteries, retrospectively, and concluded that use of tisseel decreased immediate postoperative blood loss.[77]

Other studies had enrolled mixed population or only adults in comparing different hemostatic agents either among themselves or controls. The results of all these trials and a systematic review by Rousou *et al*. have established the efficacy of topical agents as effective modalities to conserve blood.[78-83]

Postoperative

- Point of care (POC) tests and transfusion algorithms (transfusion trigger)
- Anti-fibrinolytics and aprotinin
- Recombinant activated factor VII (rFVIIa)
- Reducing blood sampling in the postoperative period.

Point of care tests and transfusion algorithms

In pediatric cardiac surgery, there is a significant dilution of coagulation factors when the half of the total blood volume is replaced by fluids, which are deficient in coagulation factors (pRBCs, crystalloids, or colloids).[84] In small children, there is a more than 50% decrease in coagulation factors at the initiation of CPB.[85] The fibrinogen level may fall below 1 g/dl in neonates after CPB.[86] The incidence of various abnormalities post-CPB are – thrombocytopenia (<100,000/mm^3) - 60%,

qualitative platelet defects 10–33%, coagulation factor deficiency (<20% activity) - 30% and hypofibrinogenemia (<100mg/dl) - 9%.[20] The following POC tests may help to identify the above defects in the ICU.

- ACT
- Platelet count
- Fibrinogen levels
- Prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio
- Viscoelastic tests: Thromboelastography (TEG), Sonoclot, rotational thromboelastometry (ROTEM)
- Qualitative platelet function tests.

Viscoelastic tests

Thromboelastography can predict postoperative bleeding, after heparin neutralization, in both cyanotic and acyanotic children undergoing cardiac surgery.[87,88] It has been shown that the transfusion requirements based on TEG are different in comparison to standard coagulation tests and when treated, on the basis of TEG, postoperative bleeding decreases.[87] ROTEM in the post-CPB period predicts bleeding in children undergoing corrective biventricular or palliative univentricular repairs.[88] One study of 107 children, however, concluded that TEG is not superior to conventional coagulation tests in predicting postoperative bleeding in children undergoing cardiac surgery and should not be used as a predictor of blood loss.[89] Sonoclot as a predictor for postoperative bleeding has not been evaluated in children. The baseline parameters in cyanotic and acyanotic children have been studied, but they have not been correlated with bleeding.[90] In adults, Sonoclot has been shown to predict abnormal postoperative bleeding with or without heparin neutralization.[91,92]

Qualitative platelet function tests (platelet function analyzer)

The platelet function analyzer measures the closure time when blood is passed through a small hole in a collagen membrane. A prolonged closure time indicates platelet dysfunction. A prolonged closure time in the preoperative period is associated with increased transfusion of pRBCs and fresh frozen plasma in the intraoperative period, in children undergoing cardiac surgery.[93]

Transfusion algorithm

Indication	**Product and dose**
PT >1.5 times control	Fresh frozen plasma (FFP) 10–15 ml/kg
APTT >2.0 times control	FFP 10–15 ml/kg
Platelet count <50 × 10^9–100 × 10^9 Platelet	concentrate 10 ml/kg
Fibrinogen <0.8–1.0 g/l	Cryoprecipitate 1 unit/10 kg

To prevent dilutional coagulopathy, it is recommended to transfuse pRBC with plasma in a ratio of 1:1. Prophylactic platelet transfusion after pediatric cardiac surgery is of questionable benefit.

Transfusion trigger

Wypij *et al*. in 2008 published the combined results of two National Institute of Health supported trials a goal hematocrit of 30 or 35% could be achieved during CPB without greater need for transfusion.[94] The authors also concluded that a hematocrit of more than 24 during CPB correlated with better psychomotor development at 1 year age. Willems *et al*. studied 125 postcardiac surgery children by allocating them into two groups on the basis of transfusion thresholds – a restrictive group with a transfusion trigger of <7.0 g/dl and a liberal group with a trigger of <9.5 g/dl.[95] There was no difference in the onset or progression of the multiple organ-dysfunction syndrome (MODS) in the two groups. A recent study by de Gast-Bakker *et al*. found no difference in outcomes between groups with restrictive (<8 g/dl) and liberal (<10.8 g/dl) thresholds. The length of hospital stay and cost of treatment was less in the restricted group.[12] Children with congenital heart disease and single ventricle physiology who undergo cavopulmonary anastomosis also do not benefit from a liberal (>13 g/dl vs. 9 g/dl) transfusion strategy.[96] A North American Multicenter study of 175 children who underwent cardiac surgery revealed that 79% of patients received at least one RBC transfusion in the ICU and that only in 17% of patients the primary indication for transfusion was low hemoglobin level.[97] The authors concluded that there is great variability in the transfusion practices across postcardiac surgery pediatric ICUs of North America and clear guidelines are required in this respect.

In view of many publications that have addressed the issue of blood transfusion in children following points may be considered:

- There is no uniform cutoff value to define restrictive (7–9 g/dl) and liberal (9.5–13) transfusion practices
- It seems logical to have higher hematocrits in children with cyanosis and/or single ventricle physiology, in comparison to acyanotic children, but the benefits remain to be proven

- Restrictive transfusion strategy is safe under strict monitoring of end organ oxygenation parameters
- Liberal transfusion strategy is not associated with an increase in MODS or life-threatening complications
- A goal hematocrit of 30–35% should be achieved by blood conservation rather than transfusion, wherever possible
- In children with hemodynamic instability restrictive strategy is of questionable value.

Recombinant factor VIIa

Postaprotinin era saw the emergence of rFVIIa as a rescue hemostatic agent in the postoperative patients when the bleeding appeared life threatening. Although not approved by FDA for control of postsurgery bleeding it has been used after obstetric and cardiac surgery to control refractory hemorrhage.[98-103] In addition to its, therapeutic role rFVIIa has also been used as a prophylactic agent to prevent excessive blood loss.[104] Before administering rFVIIa, the platelet count should be fair (50,000/μl) and any consumption coagulopathy should be ruled out. Recombinant factor VIIa is contraindicated in disseminated intravascular coagulation (DIC). In DIC, there is a widespread expression of tissue factor (TF) and rFVIIa by activating this TF may cause widespread coagulation leading to death. Two major deterrents to use rFVIIa are cost and thrombosis. Due to the risk of thrombosis, the routine use of rFVIIa cannot be recommended to control postoperative bleeding after pediatric cardiac surgery. In children, a dose of 72–87 μg/kg reduces chest tube drainage and transfusion of blood and blood products. It may be beneficial to administer a second dose if there is no or suboptimal effect after the first dose.[102]

Reducing blood sampling and flushing in the postoperative period

Infants and neonates, in comparison to older children and adults, have small circulating blood volume and therefore repeated blood sampling for investigations causes loss of significant amount of blood volume. Flushing of the monitoring lines with heparinized saline also causes hemodilution. A reduction in a total number of tests done per patient not only decreases the incidence of transfusion in the postoperative period but also decreases the cost of treatment.[105]

CONCLUSION

Blood conservation is possible in children undergoing cardiac surgery with better outcomes. Various modalities available should be used in conjunction with one another to achieve maximum benefit. However, the risk-benefit of blood conservation should be weighed on an individual basis before practicing routinely.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Manno CS, Hedberg KW, Kim HC, Bunin GR, Nicolson S, Jobes D, *et al.* Comparison of the hemostatic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children. Blood 1991;77:930-6.
2. Boldt J, Knothe C, Zickmann B, Wege N, Dapper F, Hempelmann G. Aprotinin in pediatric cardiac operations: Platelet function, blood loss, and use of homologous blood. Ann Thorac Surg 1993;55:1460-6.
3. Chambers LA, Cohen DM, Davis JT. Transfusion patterns in pediatric open heart surgery. Transfusion 1996;36:150-4.
4. Du Pont-Thibodeau G, Harrington K, Lacroix J. Anemia and red blood cell transfusion in critically ill cardiac patients. Ann Intensive Care 2014;4:16.
5. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, *et al.* Perioperative blood transfusion and blood conservation in cardiac surgery: The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists clinical practice guideline. Ann Thorac Surg 2007;83 5 Suppl: S27-86.
6. Straney L, Clements A, Alexander J, Slater A; ANZICS Paediatric Study Group. Variation in duration of respiratory support among Australian and New Zealand pediatric intensive care units. Pediatr Crit Care Med 2011;12:9-13.
7. Kneyber MC, Grotenhuis F, Berger RF, Ebels TW, Burgerhof JG, Albers MJ. Transfusion of leukocyte-depleted RBCs is independently associated with increased morbidity after pediatric cardiac surgery. Pediatr Crit Care Med 2013;14:298-305.
8. Willems A, Van Lerberghe C, Gonsette K, De Villé A, Melot C, Hardy JF, *et al.* The indication for perioperative red blood cell transfusions is a predictive risk factor for severe postoperative morbidity and mortality in children undergoing cardiac surgery. Eur J Cardiothorac Surg 2014;45:1050-7.
9. Salvin JW, Scheurer MA, Laussen PC, Wypij D, Polito A, Bacha EA, *et al.* Blood transfusion after pediatric cardiac surgery is associated with prolonged hospital stay. Ann Thorac Surg 2011;91:204-10.
10. Howard-Quijano K, Schwarzenberger JC, Scovotti JC, Alejos A, Ngo J, Gornbein J, *et al.* Increased red blood cell transfusions are associated with worsening outcomes in pediatric heart transplant patients. Anesth Analg 2013;116:1295-308.
11. Guzzetta NA, Allen NN, Wilson EC, Foster GS, Ehrlich AC,

Miller BE. Excessive postoperative bleeding and outcomes in neonates undergoing cardiopulmonary bypass. Anesth Analg 2015;120:405-10.
12. de Gast-Bakker DH, de Wilde RB, Hazekamp MG, Sojak V, Zwaginga JJ, Wolterbeek R, *et al.* Safety and effects of two red blood cell transfusion strategies in pediatric cardiac surgery patients: A randomized controlled trial. Intensive Care Med 2013;39:2011-9.
13. Singh SP, Chauhan S, Choudhury M, Malik V, Talwar S, Hote MP, *et al.* Modified Blalock Taussig shunt: Comparison between neonates, infants and older children. Ann Card Anaesth 2014;17:191-7.
14. Kwak JG, Park M, Lee J, Lee CH. Multiple approaches to minimize transfusions for pediatric patients in open-heart surgery. Pediatr Cardiol 2016;37:44-9.
15. Agarwal HS, Barrett SS, Barry K, Xu M, Saville BR, Donahue BS, *et al.* Association of blood products administration during cardiopulmonary bypass and excessive post-operative bleeding in pediatric cardiac surgery. Pediatr Cardiol 2015;36:459-67.
16. Pérez-Ferrer A, Gredilla E, de Vicente J, Laporta Y. Cardiac surgery without blood products in a Jehovah's Witness child with factor VII deficiency. J Cardiothorac Vasc Anesth 2012;26:651-3.
17. Arslan MT, Ozyurek R, Kavakli K, Levent E, Ulger Z, Gurses D, *et al.* Frequency of acquired von Willebrand's disease in children with congenital heart disease. Acta Cardiol 2007;62:403-8.
18. Murugan SJ, Viswanathan S, Thomson J, Parsons JM, Richards M. Heart surgery in infants with hemophilia. Ann Thorac Surg 2006;81:336-9.
19. Bailly DK, Boshkov LK, Zubair MM, Rogers VJ, Lantz G, Armsby L, *et al.* Congenital cardiac lesions involving systolic flow abnormalities are associated with platelet dysfunction in children. Ann Thorac Surg 2014;98:1419-24.
20. Despotis G, Avidan M, Eby C. Prediction and management of bleeding in cardiac surgery. J Thromb Haemost 2009;7 Suppl 1:111-7.
21. Masuda M, Kawachi Y, Inaba S, Matsuzaki K, Fukumura F, Morita S, *et al.* Preoperative autologous blood donations in pediatric cardiac surgery. Ann Thorac Surg 1995;60:1694-7.
22. Komai H, Naito Y, Okamura Y, Fujiwara K, Suzuki H, Uemura S. Preliminary study of autologous blood predonation in pediatric open-heart surgery impact of advance infusion of recombinant human erythropoietin. Pediatr Cardiol 2005;26:50-5.
23. Giannakopoulou C, Bolonaki I, Stiakaki E, Dimitriou H, Galanaki H, Hatzidaki E, *et al.* Erythropoietin (rHuEPO) administration to premature infants for the treatment of their anemia. Pediatr Hematol Oncol 1998;15:37-43.
24. Ootaki Y, Yamaguchi M, Yoshimura N, Oka S, Yoshida M, Hasegawa T. The efficacy of preoperative administration of a single dose of recombinant human erythropoietin in pediatric cardiac surgery. Heart Surg Forum 2007;10:E115-9.
25. Hanover CK, Spillers CR, Francom SF, Locker PK, Hughes GS Jr. A double stopcock technique for repeated sampling of venous blood. Methods Find Exp Clin Pharmacol 1992;14:537-43.
26. Tang M, Feng M, Chen L, Zhang J, Ji P, Luo S. Closed blood conservation device for reducing catheter-related infections in children after cardiac surgery. Crit Care Nurse 2014;34:53-60.
27. Dewhirst E, Winch P, Naguib A, Galantowicz M, Tobias JD. Cerebral oximetry monitoring during preoperative phlebotomy to limit allogeneic blood use in patients undergoing cardiac surgery. Pediatr Cardiol 2013;34:75-80.
28. Winch PD, Naguib AN, Bradshaw JR, Galantowicz M, Tobias JD. Decreasing the need for transfusion: Infant cardiac surgery using hemodilution and recombinant factor VIIa. Pediatr Cardiol 2013;34:119-24.
29. Lindvall G, Sartipy U, van der Linden J. Aprotinin reduces bleeding and blood product use in patients treated with clopidogrel before coronary artery bypass grafting. Ann Thorac Surg 2005;80:922-7.
30. van der Linden J, Lindvall G, Sartipy U. Aprotinin decreases postoperative bleeding and number of transfusions in patients on clopidogrel undergoing coronary artery bypass graft surgery: A double-blind, placebo-controlled, randomized clinical trial. Circulation 2005;112 9 Suppl: I276-80.
31. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, *et al.* A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319-31.
32. Mangano DT, Tudor IC, Dietzel C; Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006;354:353-65.
33. Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary-artery bypass grafting and risk of death. N Engl J Med 2008;358:771-83.
34. Shaw AD, Stafford-Smith M, White WD, Phillips-Bute B, Swaminathan M, Milano C, *et al.* The effect of aprotinin on outcome after coronary-artery bypass grafting. N Engl J Med 2008;358:784-93.
35. Arnold DM, Fergusson DA, Chan AK, Cook RJ, Fraser GA, Lim W, *et al.* Avoiding transfusions in children undergoing cardiac surgery: A meta-analysis of randomized trials of aprotinin. Anesth Analg 2006;102:731-7.
36. Hasegawa T, Oshima Y, Maruo A, Matsuhisa H, Tanaka A, Noda R, *et al.* Intraoperative tranexamic acid in pediatric bloodless cardiac surgery. Asian Cardiovasc Thorac Ann 2014;22:1039-45.
37. Faraoni D. Safety of tranexamic acid in pediatric cardiac surgery: What we do not know. Eur J Cardiothorac Surg 2011;40:1550-1.
38. Chauhan S, Das SN, Bisoi A, Kale S, Kiran U. Comparison of epsilon aminocaproic acid and tranexamic acid in pediatric cardiac surgery. J Cardiothorac Vasc Anesth 2004;18:141-3.
39. Chauhan S, Kumar BA, Rao BH, Rao MS, Dubey B, Saxena N, *et al.* Efficacy of aprotinin, epsilon aminocaproic acid, or combination in cyanotic heart disease. Ann Thorac Surg 2000;70:1308-12.
40. Rao BH, Saxena N, Chauhan S, Bisoi AK, Venugopal P. Epsilon aminocaproic acid in paediatric cardiac surgery to reduce postoperative blood loss. Indian J Med Res 2000;111:57-61.
41. Yang XW, Guo LJ, Li DQ, Zhang Y, Li ZY, Fu Y. Comparison of the effects of epsilon-aminocaproic acid and aprotinin on fibrinolytic system in children

undergoing cardiopulmonary bypass. Chin Remedies Clin 2003;3:32-5.
42. Sarupria A, Makhija N, Lakshmy R, Kiran U. Comparison of different doses of e-aminocaproic acid in children for tetralogy of Fallot surgery: Clinical efficacy and safety. J Cardiothorac Vasc Anesth 2013;27:23-9.
43. Lu J, Meng H, Meng Z, Sun Y, Pribis JP, Zhu C, *et al.* Epsilon aminocaproic acid reduces blood transfusion and improves the coagulation test after pediatric open-heart surgery: A meta-analysis of 5 clinical trials. Int J Clin Exp Pathol 2015;8:7978-87.
44. Kotani Y, Honjo O, Nakakura M, Ugaki S, Kawabata T, Kuroko Y, *et al.* Impact of miniaturization of cardiopulmonary bypass circuit on blood transfusion requirement in neonatal open-heart surgery. ASAIO J 2007;53:662-5.
45. Remadi JP, Marticho P, Butoi I, Rakotoarivelo Z, Trojette F, Benamar A, *et al.* Clinical experience with the mini-extracorporeal circulation system: An evolution or a revolution? Ann Thorac Surg 2004;77:2172-5.
46. Curtis N, Vohra HA, Ohri SK. Mini extracorporeal circuit cardiopulmonary bypass system: A review. Perfusion 2010;25:115-24.
47. Abdel Aal M, ElNahal N, Bakir BM, Fouda M. Mini-cardiopulmonary bypass impact on blood conservation strategy in coronary artery bypass grafting. Interact Cardiovasc Thorac Surg 2011;12:600-4.
48. Gerritsen WB, van Boven WJ, Wesselink RM, Smelt M, Morshuis WJ, van Dongen HP, *et al.* Significant reduction in blood loss in patients undergoing minimal extracorporeal circulation. Transfus Med 2006;16:329-34.
49. Calafiore AM, Teodori G, Mezzetti A, Bosco G, Verna AM, Di Giammarco G, *et al.* Intermittent antegrade warm blood cardioplegia. Ann Thorac Surg 1995;59:398-402.
50. Menasché P. Blood cardioplegia: Do we still need to dilute? Ann Thorac Surg 1996;62:957-60.
51. Menasché P, Touchot B, Pradier F, Bloch G, Piwnica A. Simplified method for delivering normothermic blood cardioplegia. Ann Thorac Surg 1993;55:177-8.
52. Kotani Y, Tweddell J, Gruber P, Pizarro C, Austin EH 3rd, Woods RK, *et al.* Current cardioplegia practice in pediatric cardiac surgery: A North American multiinstitutional survey. Ann Thorac Surg 2013;96:923-9.
53. Durandy Y, Rubatti M. Warm blood microplegia redosing interval in pediatric surgery. Ann Thorac Surg 2013;96:2285-6.
54. Bando K, Vijay P, Turrentine MW, Sharp TG, Means LJ, Ensing GJ, *et al.* Dilutional and modified ultrafiltration reduces pulmonary hypertension after operations for congenital heart disease: A prospective randomized study. J Thorac Cardiovasc Surg 1998;115:517-25.
55. Friesen RH, Campbell DN, Clarke DR, Tornabene MA. Modified ultrafiltration attenuates dilutional coagulopathy in pediatric open heart operations. Ann Thorac Surg 1997;64:1787-9.
56. Buchholz BJ, Bert AA, Price DR, Hopkins RA, Stearns GT. Veno-arterial modified ultrafiltration in children after cardiopulmonary bypass. J Extra Corpor Technol 1999;31:47-9.
57. Ootaki Y, Yamaguchi M, Oshima Y, Yoshimura N, Oka S. Effects of modified ultrafiltration on coagulation factors in pediatric cardiac surgery. Surg Today 2002;32:203-6.
58. Kuratani N, Bunsangjaroen P, Srimueang T, Masaki E, Suzuki T, Katogi T. Modified versus conventional ultrafiltration in pediatric cardiac surgery: A meta-analysis of randomized controlled trials comparing clinical outcome parameters. J Thorac Cardiovasc Surg 2011;142:861-7.
59. Türköz A, Tunçay E, Balci ST, Can MG, Altun D, Türköz R, *et al.* The effect of modified ultrafiltration duration on pulmonary functions and hemodynamics in newborns and infants following arterial switch operation. Pediatr Crit Care Med 2014;15:600-7.
60. Durandy Y. The impact of vacuum-assisted venous drainage and miniaturized bypass circuits on blood transfusion in pediatric cardiac surgery. ASAIO J 2009;55:117-20.
61. Jones TJ, Deal DD, Vernon JC, Blackburn N, Stump DA. Does vacuum-assisted venous drainage increase gaseous microemboli during cardiopulmonary bypass? Ann Thorac Surg 2002;74:2132-7.
62. Hill SL, Holt DW. Can vacuum assisted venous drainage be achieved using a roller pump in an emergency? A pilot study using neonatal circuitry. J Extra Corpor Technol 2007;39:254-6.
63. Miyaji K, Hannan RL, Ojito J, Jacobs JP, White JA, Burke RP. Heparin-coated cardiopulmonary bypass circuit: Clinical effects in pediatric cardiac surgery. J Card Surg 2000;15:194-8.
64. Ozawa T, Yoshihara K, Koyama N, Watanabe Y, Shiono N, Takanashi Y. Clinical efficacy of heparin-bonded bypass circuits related to cytokine responses in children. Ann Thorac Surg 2000;69:584-90.
65. Itoh H, Ichiba S, Ujike Y, Douguchi T, Kasahara S, Arai S, *et al.* A prospective randomized trial comparing the clinical effectiveness and biocompatibility of heparin-coated circuits and PMEA-coated circuits in pediatric cardiopulmonary bypass. Perfusion 2016;31:247-54.
66. Cazzaniga A, Ranucci M, Isgrò G, Soro G, De Benedetti D, Corradi R, *et al.* Trillium biopassive surface: A new biocompatible treatment for extracorporeal circulation circuits. Int J Artif Organs 2000;23:319-24.
67. Suzuki Y, Daitoku K, Minakawa M, Fukui K, Fukuda I. Poly-2-methoxyethylacrylate-coated bypass circuits reduce activation of coagulation system and inflammatory response in congenital cardiac surgery. J Artif Organs 2008;11:111-6.
68. Deptula J, Glogowski K, Merrigan K, Hanson K, Felix D, Hammel J, *et al.* Evaluation of biocompatible cardiopulmonary bypass circuit use during pediatric open heart surgery. J Extra Corpor Technol 2006;38:22-6.
69. Kirshbom PM, Miller BE, Spitzer K, Easley KA, Spainhour CE, Kogon BE, *et al.* Failure of surface-modified bypass circuits to improve platelet function during pediatric cardiac surgery. J Thorac Cardiovasc Surg 2006;132:675-80.
70. Fukui T, Nishida H, Takanashi S. Biocompatibility of cardiopulmonary bypass circuit with new polymer Senko E-Ternal Coating™. Perfusion 2015;30:572-9.
71. Cholette JM, Powers KS, Alfieris GM, Angona R, Henrichs KF, Masel D, *et al.* Transfusion of cell saver

salvaged blood in neonates and infants undergoing open heart surgery significantly reduces RBC and coagulant product transfusions and donor exposures: Results of a prospective, randomized, clinical trial. Pediatr Crit Care Med 2013;14:137-47.
72. Samnaliev M, Tran CM, Sloan SR, Gasior I, Lightdale JR, Brustowicz RM. Economic evaluation of cell salvage in pediatric surgery. Paediatr Anaesth 2013;23:1027-34.
73. Luciani N, Anselmi A, Gaudino M, Nasso G, Glieca F, Martinelli L, *et al.* Harmonic scalpel reduces bleeding and postoperative complications in redo cardiac surgery. Ann Thorac Surg 2005;80:934-8.
74. Laje P, Martínez-Ferro M. Thoracoscopic double aortic arch division with Harmonic scalpel: A case report. J Thorac Cardiovasc Surg 2007;133:819-20.
75. Barnard J, Millner R. A review of topical hemostatic agents for use in cardiac surgery. Ann Thorac Surg 2009;88:1377-83.
76. Codispoti M, Mankad PS. Significant merits of a fibrin sealant in the presence of coagulopathy following paediatric cardiac surgery: Randomised controlled trial. Eur J Cardiothorac Surg 2002;22:200-5.
77. Huth C, Seybold-Epting W, Hoffmeister HE. Local hemostasis with fibrin glue after intracardiac repair of tetralogy of Fallot and transposition of the great arteries. Thorac Cardiovasc Surg 1983;31:142-6.
78. Rousou J, Levitsky S, Gonzalez-Lavin L, Cosgrove D, Magilligan D, Weldon C, *et al.* Randomized clinical trial of fibrin sealant in patients undergoing resternotomy or reoperation after cardiac operations. A multicenter study. J Thorac Cardiovasc Surg 1989;97:194-203.
79. Lowe J, Luber J, Levitsky S, Hantak E, Montgomery J, Schiestl N, *et al.* Evaluation of the topical hemostatic efficacy and safety of TISSEEL VH S/D fibrin sealant compared with currently licensed TISSEEL VH in patients undergoing cardiac surgery: A phase 3, randomized, double-blind clinical study. J Cardiovasc Surg (Torino) 2007;48:323-31.
80. Hanks JB, Kjaergard HK, Hollingsbee DA. A comparison of the haemostatic effect of Vivostat patient-derived fibrin sealant with oxidised cellulose (Surgicel) in multiple surgical procedures. Eur Surg Res 2003;35:439-44.
81. von Segesser LK, Fasnacht MS, Vogt PR, Genoni M, Arbenz U, Turina MI. Prevention of residual ventricular septal defects with fibrin sealant. Ann Thorac Surg 1995;60:511-5.
82. Leca F, Karam J, Vouhe PR, Khoury W, Tamisier D, Bical O, *et al.* Surgical treatment of multiple ventricular septal defects using a biologic glue. J Thorac Cardiovasc Surg 1994;107:96-102.
83. Rousou JA. Use of fibrin sealants in cardiovascular surgery: A systematic review. J Card Surg 2013;28:238-47.
84. Durandy Y. Use of blood products in pediatric cardiac surgery. Artif Organs 2015;39:21-7.
85. Chan AK, Leaker M, Burrows FA, Williams WG, Gruenwald CE, Whyte L, *et al.* Coagulation and fibrinolytic profile of paediatric patients undergoing cardiopulmonary bypass. Thromb Haemost 1997;77:270-7.
86. Kern FH, Morana NJ, Sears JJ, Hickey PR. Coagulation defects in neonates during cardiopulmonary bypass. Ann Thorac Surg 1992;54:541-6.
87. Niebler RA, Gill JC, Brabant CP, Mitchell ME, Nugent M, Simpson P, *et al.* Thromboelastography in the assessment of bleeding following surgery for congenital heart disease. World J Pediatr Congenit Heart Surg 2012;3:433-8.
88. Tirosh-Wagner T, Strauss T, Rubinshtein M, Tamarin I, Mishaly D, Paret G, *et al.* Point of care testing in children undergoing cardiopulmonary bypass. Pediatr Blood Cancer 2011;56:794-8.
89. Pekelharing J, Furck A, Banya W, Macrae D, Davidson SJ. Comparison between thromboelastography and conventional coagulation tests after cardiopulmonary bypass surgery in the paediatric intensive care unit. Int J Lab Hematol 2014;36:465-71.
90. Chaudhary V, Chauhan S, Choudhury M, Kiran U, Talwar S, Kapoor PM. Sonoclot analysis in children with congenital heart disease. Asian Cardiovasc Thorac Ann 2012;20:544-7.
91. Yamada T, Katori N, Tanaka KA, Takeda J. Impact of Sonoclot hemostasis analysis after cardiopulmonary bypass on postoperative hemorrhage in cardiac surgery. J Anesth 2007;21:148-52.
92. Bischof DB, Ganter MT, Shore-Lesserson L, Hartnack S, Klaghofer R, Graves K, *et al.* Viscoelastic blood coagulation measurement with Sonoclot predicts postoperative bleeding in cardiac surgery after heparin reversal. J Cardiothorac Vasc Anesth 2015;29:715-22.
93. Zubair MM, Bailly DK, Lantz G, Sunstrom RE, Saharan S, Boshkov LK, *et al.* Preoperative platelet dysfunction predicts blood product transfusion in children undergoing cardiac surgery. Interact Cardiovasc Thorac Surg 2015;20:24-30.
94. Wypij D, Jonas RA, Bellinger DC, Del Nido PJ, Mayer JE Jr., Bacha EA, *et al.* The effect of hematocrit during hypothermic cardiopulmonary bypass in infant heart surgery: Results from the combined Boston hematocrit trials. J Thorac Cardiovasc Surg 2008;135:355-60.
95. Willems A, Harrington K, Lacroix J, Biarent D, Joffe AR, Wensley D, *et al.* Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: A subgroup analysis. Crit Care Med 2010;38:649-56.
96. Cholette JM, Rubenstein JS, Alfieris GM, Powers KS, Eaton M, Lerner NB. Children with single-ventricle physiology do not benefit from higher hemoglobin levels post cavopulmonary connection: Results of a prospective, randomized, controlled trial of a restrictive versus liberal red-cell transfusion strategy. Pediatr Crit Care Med 2011;12:39-45.
97. Mazine A, Rached-D'Astous S, Ducruet T, Lacroix J, Poirier N; Pediatric Acute Lung Injury and Sepsis Investigators Network. Blood transfusions after pediatric cardiac operations: A North American Multicenter Prospective Study. Ann Thorac Surg 2015;100:671-7.
98. Karkouti K, Arellano R, Aye T, Dupuis JY, Kent B, Lee TW, *et al.* Off-label use of recombinant activated factor VII in surgical and non-surgical patients at 16 Canadian hospitals from 2007 to 2010 (Canadian Registry Report). Can J Anaesth 2014;61:727-35.
99. Singh SP, Chauhan S, Choudhury M, Malik V, Choudhary SK. Recombinant activated factor VII in cardiac surgery: Single-center experience. Asian

Cardiovasc Thorac Ann 2014;22:148-54.
100. Magon N, Babu K. Recombinant factor VIIa in post-partum hemorrhage: A new weapon in obstetrician's armamentarium. N Am J Med Sci 2012;4:157-62.
101. Phillips LE, McLintock C, Pollock W, Gatt S, Popham P, Jankelowitz G, *et al.* Recombinant activated factor VII in obstetric hemorrhage: Experiences from the Australian and New Zealand Haemostasis Registry. Anesth Analg 2009;109:1908-15.
102. Singh SP, Chauhan S, Choudhary M, Vasdev S, Talwar S. Recombinant activated factor VII for hemorrhage after pediatric cardiac surgery. Asian Cardiovasc Thorac Ann 2012;20:19-23.
103. McLintock C, James AH. Obstetric hemorrhage. J Thromb Haemost 2011;9:1441-51.
104. Scott JP, Costigan DJ, Hoffman GM, Simpson PM, Dasgupta M, Punzalan R, *et al.* Increased recombinant activated factor VII use and need for surgical reexploration following a switch from aprotinin to epsilon-aminocaproic acid in infant cardiac surgery. J Clin Anesth 2014;26:204-11.
105. Delgado-Corcoran C, Bodily S, Frank DU, Witte MK, Castillo R, Bratton SL. Reducing blood testing in pediatric patients after heart surgery: A quality improvement project. Pediatr Crit Care Med 2014;15:756-61.