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Bleeding following deep hypothermia and circulatory arrest in children

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THE BURDEN OF CARDIAC SURGERY ON BLOOD BANKS

The total blood supply, and blood bank resources in the Unites States remains a significant issue, despite improvements in methods of blood collection, processing and use of transfusion algorithms[1]. In a review of US blood bank resources, the total annual US blood supply was over 13 million units of packed red blood cells (PRBC), and seven million units of platelets. Despite this large supply, daily reports from multiple sentinel sites monitoring the capacity to meet demands showed a median of the days' supply for PRBC of 7.2 days, and only a 1-day supply of platelets[2].

The largest demand for blood resources remains to be from cardiac surgical procedures in adults and children. In fact, 65% of all patients undergoing surgery on cardiopulmonary bypass (CPB) require a transfusion, using 15% of all PRBC and 50% of platelets transfused[1,3].

Supply of fresh whole blood for pediatric cardiac surgery is difficult to maintain by blood banks. The demand for fresh whole blood (less than 48 hours old) for transfusion in children undergoing cardiac surgery is due to studies showing less blood loss compared to patients receiving reconstituted products (51.7 ± 7.4 *versus* 96.2 ± mL/kg, $p < 0.001$) especially in children age < 2 years old undergoing complex cardiac operations[4]. However, recent randomized, controlled trials comparing bypass-circuit priming in infants, showed a prolonged intensive care unit length of stay, increased cumulative fluid balance, and no improvement in bleeding, transfusion or inflammatory markers with fresh whole blood priming[5]. The discrepancy in these study findings may be due to the difference in the preservatives used, and the timing of whole blood use (circuit priming *versus* postoperative transfusion).

THE IMPACT OF AGE AND TYPE OF CARDIAC SURGERY ON TRANSFUSION REQUIREMENTS:

Intraoperative and postoperative bleeding after corrective cardiac procedures in children under CPB and deep hypothermic cardiac arrest (dhCA) continue to be concerning issues. In multiple series, blood loss and transfusion requirements vary inversely with age, with neonates having the highest incidence of bleeding, increase chest tube drainage postoperatively, and amount of blood transfused relative to weight. In a prospective cohort study of 548 children undergoing cardiac surgery, children < 1 year of age had significantly more intraoperative blood loss compared to older children (22.2 *versus* 18.3 mL/kg), and required more blood product transfusion (60.6 *versus* 42 mL/kg)[6]. In a multivariate analysis, younger age, lower core temperature during CPB, complex lesions requiring dhCA were significant factors associated with bleeding and transfusion in children undergoing cardiac operations[6]. Although coagulation tests are not always predictive of bleeding risk following pediatric cardiac surgery, stepwise linear regression analysis in a series of 495 children indicated that platelet count (< 108,000/microL) and thromboelastography maximum amplitude (MA) during CPB were the variables most significantly associated with intraoperative blood loss and 12-hour chest tube output in children[7].

The risk of perioperative blood loss and increased transfusion requirements is also associated with the type of surgery and CPB conduct. Complex surgical repairs, performed under dhCA are associated with more bleeding compared to more simple procedures[8]. A review of our practice with dhCA at Cleveland Clinic comparing adults to children showed significantly more operations done with deep hypothermia in children (Table I), and more transfusion requirements.

WHY ARE CHILDREN WITH CONGENITAL HEART DISEASE AT INCREASED RISK FOR BLEEDING?

Pediatric patients are a susceptible population to microvascular injury and bleeding after dhCA and CPB[13-15]. Dysfunction of hemostasis caused by CPB and resulting in pronounced bleeding is of special significance in children. It can be explained by the immature coagulation system of the neonate, the influence of cyanosis in the overall hemostasis, and hemodilution and coagulopathy acquired with CPB and dhCA conduct.

The hemostatic system is not fully mature by 6 months of age, and remains abnormal even in healthy children. In a series of 246 children ages 1-16 years, plasma concentrations of seven coagulants (factors II, V, VII, IX, X, XI, XII) were significantly lower than adults. Mean values for inhibitors (α_2-macroglobulin, protein C, and protein C_1-inhibitor) were elevated throughout childhood, and bleeding time was prolonged during the first 10 years of life[9].

Patients with cyanotic congenital heart disease, arterial hypoxemia and decreased tissue oxygenation, have excessive release of renal erythropoietin. The resulting secondary polycythemia leads to coagulation defects including thrombocytopenia, platelet function abnormalities, factor deficiency and disseminated intravascular coagulopathy[10]. These children are also susceptible to excessive bleeding following dhCA due to accelerated fibrinolysis documented by raised levels of fibrin D-dimers and plasminogen activator inhibitor[16].

The coagulation defects in children are exaggerated by hypothermic bypass. In a series of 20 neonates undergoing deep hypothermic CPB, the initiation of CPB and dhCA resulted in a 50% decrease in circulating coagulation factors (V, VIII), antithrombin-III levels and a 70% decrease in platelet count[11]. The large priming volume, relative hemodilution, extreme cooling temperatures, and large non-endothelial CPB surface are all contributing factors. In addition, the empirical dosing of heparin in children on bypass results in lower plasma concentrations, and rapid decline in free heparin levels, due to the shorter biological half-life in children compared to adults[12].

PHARMACOLOGIC STRATEGIES FOR BLEEDING FOLLOWING DHCA IN CHILDREN

One of the major factors affecting hemostasis in children is the exacerbated response of inflammatory system and the imbalance between pro-coagulation and pro-fibrinolytic factors.

Aprotinin and other antifibrinolytics

Cardiopulmonary bypass and reperfusion after dhCA are responsible for the triggering of proteolytic enzymes cascade, including the following systems: blood coagulation, plasmin-fibrinolysis, complement and kallikrein-kinin[17]. Hypothermia activates kallikrein that converts kininogen to kinin[18]. Kinins are vasoactive peptides that induce a vasodilatory response and consequent hemodynamic instability. This substance is normally degraded in a single passage through the lungs by endothelial enzymes but this process is diminished as the CPB divertes the pulmonary artery flow[19]. Pediatric cardiac surgery, in comparison to other surgical procedures, is prone to generate high levels of kinins.

Aprotinin, a kinin inhibitor, is a particularly interesting tool in this scenario[20]. Aprotinin (trasylol; Bayer AG, Leverkusen, West Germany) is a broad base, nonspecific serine protease inhibitor purified from bovine lungs. This agent plays a role in hemostasis preservation by inhibition of contact and tissue factor pathways. It reversibly binds to the active serine sites in various proteases such as kallikrein, plasmin and trypsin[21]. It has been proven to inhibit the activation of the kallikrein-kinin and the plasmin fibrinolysis systems as well as the activation of complements and the activity of factor XIIa (by 20%) and factor IXa (by more than 50%). It has also been shown to preserve the integrity of platelet membranes via a reduction in glycoprotein loss (GPIb/GPIIb/IIIa) and inhibition of proteolytic alterations in Von Willebrand factor[15,22-25]. Aprotinin has a special affinity for plasmin, making it a potent inhibitor of fibrinolysis and it also prevents fibrin activation of platelets even at low doses[26].

Aprotinin attenuates the inhibitory effect of heparin on platelet function and decreases thrombin-mediated platelet consumption by inhibition of protease-activated receptor without affecting other receptors such as collagen, adenosine diphosphate or epinephrine. This selectivity protects platelets from undesired activation by thrombin and allows their participation in the hemostatic process[27-31].

Elliot et al[32] reported the pioneering use of aprotinin in pediatric cardiac surgery. They submitted 28 patients with high risk of bleeding to high doses of aprotinin, reporting a reduction in chest closure time with no significant side effects. No reduction in blood loss, however, was observed. More recently, a reduction in blood loss in pediatric patients has also been demonstrated in retrospective studies, with variable dosages of aprotinin[33,34]. Most aprotinin dosages are based on the Hammersmith[35] protocol that is directed for adults but has been adapted for children using either body surface area or body weight. Dosage decisions may be further affected by pump volume and individual patient size. The lack of efficacy of aprotinin in some studies may be partially explained by imprecise dosage calculations for each child[36].

Multiple groups have attempted to investigate the impact of aprotinin in pediatric patients undergoing cardiac surgeries with dhCA. Dietrich et al[37] investigated the effects of high-dose aprotinin on hemostatic function during CPB and

dhCA in children. Patients were assigned to a low-dose group, receiving 15,000 KIU/kg after induction of anesthesia and an additional dose to the pump-prime, and a high-dose group, receiving 30,000 KIU/kg. Patients in both groups received no continuous infusion of aprotinin. A dose-dependent reduction of clotting and fibrinolytic activity, leading to a hemostatic equilibrium was observed.

Tweddell et al[40] studied 115 children undergoing stage one palliation of hypoplastic left heart syndrome. Sixty-five of those patients received aprotinin. Deep hypothermic cardiac arrest was utilized for a mean time of 56 ± 25 minutes. The authors reported two cases of thromboses of the systemic to pulmonary artery (3%) and one early death, which did not correlate with aprotinin use. They concluded that strategies to reduce the inflammatory process caused by dhCA maybe of benefit to improve the postoperative support.

Although a few studies in adults showed possible deleterious effects of aprotinin in dhCA, it should be noted that the overall incidence of side effects reported with the use of aprotinin is low, despite its wide-scale use in adults or children. A recent observational study involving 4374 high-risk patients undergoing complex cardiac surgery, Mangano et al[39] used propensity-adjusted multivariable logistic regression to identify the risk of serious outcome with antifibrinolytics (aprotinin, aminocaproic acid, or tranexamic acid). In this controversial report, the authors link aprotinin use with a doubling in the risk of renal failure requiring dialysis (odds ratio 2.59), a 55% increase in the risk of myocardial infarction, and a 181% increase in the risk of stroke or encephalopathy. Despite having similar effects on reducing blood loss, neither aminocaproic acid nor tranexamic acid was associated with an increased risk of renal, cardiac or cerebral events. The report prompted the Food and Drug Administration to issue a public health advisory, to caution the use of aprotinin in high-risk patients, especially with dhCA, and require the manufacturer to further examine the safety and benefits of aprotinin in light of the recent data (http://www.fda.gov/cder/drug/advisory/aprotinin.htm).

However, other reports have examined the safety of aprotinin, especially in high-risk patients and with dhCA use. In systemic reviews and met-analysis of prior trials (n = 3,879 patients), aprotinin reduced transfusion requirements (relative risk 0.61), with no increase in mortality, or end organ damage. Pouard[40] described a lack of evidence of adverse effects of this drug in pediatric cardiac surgery. In a meta-analysis of aprotinin trials including 320 children submitted to dhCA, the author identifies benefits of decreased fibrinolysis and platelet activation, with no proven risk of a hypercoagulable state or thrombosis. These studies prompted the manufacturer (Bayer Pharmaceuticals) and the Society of Cardiovascular Anesthesiologists (March 2008 SCA Newsletter) to issue a response confirming the efficacy and safety of aprotinin in cardiac surgery, even in high-risk patients and with use of dhCA.

The most common complication of aprotinin, although rare, is an allergic reaction. Aprotinin is a polybasic polypeptide consisting of 58 amino acids. It has a molecular weight of 6500 daltons and it is rapidly eliminated from the circulation by glomerular filtration with temporary partial storage by the proximal tubular cells. As an allogenic protein it has antigenic properties and an adverse reaction to this agent has been reported. Dietrich et al reported three cases of allergic reaction over 147 pediatric patients submitted to cardiac reoperations and reexposures to high doses of aprotinin. CPB was done with moderate (26-28 °C) hypothermia or with dhCA. Despite the risk of allergic complications, the authors conclude that the use of protease inhibitors in patients with high risk of bleeding is justified[41]. Reported hypersensitive reaction in first exposure to aprotinin has an incidence of 1% (7/681), 1.3% (2/150) with the second exposure and 2.9% (1/34) severe reactions with three or more exposures. Skin tests and IgE assay are unreliable to predict these reactions.

Antifibrinolytics

Hypothermic CPB and circulatory arrest (core temperature < 25.6 ± 4.7 degrees °C) induces significant fibrinolysis (defined as thromboelastography of A30/MA less than 0.85) in over 16% of children following cardiac surgery. The urokinase-catalyzed plasminogen activation kinetics is similar in neonatal and adult blood, leading to significant fibrinolysis and bleeding postoperatively, and a clear role for various antifibrinolytic agents.

Aprotinin has been compared with other antifibrinolytic drugs for safety and efficacy in a few studies. Chauhan and coworkers[42] compared the effect of aprotinin and epsilon aminocaproic acid in sternal closure time and blood loss in cyanotic patients undergoing cardiac surgery with CPB. The patient's age ranged from 2.5 months to 14 years and they were randomly assigned to 4 groups: group 1 (n = 80), placebo; group 2 (n = 100) received low-dose of aprotinin; group 3 (n = 60) received epsilon aminocaproic acid; group 4 (n = 60), received both drugs. The authors reported that both drugs were effective in diminishing the sternal closure time and in reducing the postoperative blood loss. Combination of the two drugs was only slightly more effective than either of the two agents alone.

Chauhan also compared the use of aminocaproic and tranexamic acid with placebo in a pediatric group undergoing corrective surgery for cyanotic cardiac disease with CPB, showing no difference in those drugs regarding postoperative blood loss as well as blood product requirements[43].

Similar to the concerns with aprotinin, antifbrinolytic agents in children following dhCA and cardiac surgery raise the concern of creating a hypercoagulable state, especially in

a passive pulmonary circulation, as occurs with Bidirectional cavopulmonary shunts and Fontan repairs.

Desmopressin

Abnormalities of the hemostatic system following dhCA include low plasma levels of fibrinogen and other coagulant factors, and significant platelet membrane glycoprotein dysfunction leading to bleeding following cardiac surgery. The administration of the vasopressin analogue desmopressin (DDAVP) increases the large von Willebrand factor (vWF) multimers and Factor VIII levels from endogenous endothelial storage sites. DDAVP thus facilitates binding of platelet glycoprotein Ib receptors, augments platelet adhesion and aggregation. DDAVP has been used to decrease bleeding after dhCA in pediatric cardiac surgery, in a dose of 0.3 μg/kg over a period of 10 minutes following protamine administration. The peak effect of DDAVP on blood loss is seen in 30-60 minutes, with a half-life of six hours.

A meta-analysis of 17 double-blind, placebo-controlled trials involving 1,170 patients, showed that DDAVP significantly reduced postoperative blood loss by 9%[44]. The meta-analysis demonstrated a more significant effect in patients with risk for excessive blood loss, those on aspirin preoperatively, and an abnormal intraoperative thromboelastogram (TEG) [overall effect of 0.66 (95% confidence interval 0.57 to 0.77) indicating a saving in blood loss of 34% relative to placebo].

Activated recombinant Factor VII

Activated recombinant Factor VII (rFVIIa) is a hemostatic agent effective for the treatment of hemophilic patients with inhibitors to Factor VIII and IX, or with Factor VII deficiency. The mechanism of action of rFVIIa is through enhanced platelet activation, formation of Tissue factor-rFVIIa complex, activation of factor X, thrombin generation and formation of a stable fibrin clot resistant to premature fibrinolysis. Multiple case series have shown the effective use of rFVIIa in intractable bleeding following dhCA and congenital cardiac surgery[45]. Administered in a dose of 90 ug/kg over five minutes, rFVIIa is rapidly effective in decreasing blood loss (9.8 mL/kg/h pre, to 2 mL/kg/h post) and transfusion requirements. Compared to matched case-controls, Karkouti et al[46] showed significant decrease in bleeding in 51 cardiac patients with intractable postoperative blood loss, despite multiple transfusions.

The effects of rFVII require tissue injury, and thus should occur in the localized area of bleeding. However, multiple reports raised the possible risk of a hypercoagulable state with rFVII, especially in high risk patients following dhCA (coronary abnormalities, passive pulmonary circulation), where the risk of myocardial ischemia, strokes and acute renal insufficiency were reported[46]. Thus the use of rFVIIa should be reserved for intractable bleeding in children following CPB and dhCA, and only after other interventions (component transfusion, antifibrinolytics, surgical exploration) have failed.

Transfusion algorithms

The most important intervention in the management of post-CPB bleeding is the ability to identify the appropriate transfusion requirements in a child while managing a dynamic and ever-changing coagulopathy.

Two interventions can have a significant impact on bleeding following cardiac surgery in children: point of care testing and transfusion algorithms.

We are currently using ROTEM (rapid onset thromboelastography) and a transfusion protocol that has proven useful in the management of these patients and will present our data during the conference.

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