Patient Blood Management in Pediatric Cardiac Surgery

Feride Karacer[1]

1 Department of Anesthesiology and Reanimation, Cukurova University Faculty of Medicine, Adana, Türkiye

Abstract
Children undergoing open heart surgery are often exposed to allogeneic blood products due to developmental changes in their hemostatic system and inflammation, use of anticoagulants, hemodilution and coagulopathy due to CPB. The complexity of surgical procedures, complex cardiopulmonary interactions and the risk of inadequate oxygen delivery and postoperative bleeding increase the use of blood products. Patient blood management aimed at minimizing blood product transfusion is associated with improved patient outcomes. Safe conservative blood management practices covering the pre-, intra- and postoperative periods result in reduced blood product transfusion. This review summarizes the current evidence on anemia management and blood transfusion practices in the perioperative care of children undergoing cardiac surgery.
Keywords: *Pediatrics, patient's blood management, cardiopulmonary bypass*

1. Introduction

Pediatric cardiac surgery is associated with a significant risk of bleeding and often requires allogeneic blood transfusion. Anemia and coagulopathy are observed perioperatively in neonates and children undergoing cardiac surgery due to complex congenital heart disease and prolonged cardiopulmonary bypass (CPB)[1]. Corrected gestational age, weight, degree of cyanosis and/or intracardiac mixing, immaturity of the hemostatic system, degree of hemodilution, hemostatic alterations and activation of the coagulation system induced by CPB are central features in the management of bleeding and coagulopathy in this special group of patients. Excessive blood loss and consumption of blood products are inevitable in patients with complex congenital heart disease. However, anatomical and physiological variations in children and differences in surgical approaches, CPB techniques and perioperative management between centers make it difficult to generalize patient blood management[2-4]. Studies in children undergoing cardiac surgery are mainly observational and the results do not provide high quality evidence.

Allogeneic blood transfusion can be a life-saving intervention for neonates and children with massive hemorrhage or severe anemia. However, transfusion of blood products is associated with pulmonary complications, thrombosis, transfusion-associated circulatory overload, allergic reactions, prolonged mechanical ventilation, prolonged ICU and hospital stay, infectious risks and mortality[5-7]. Children are also at higher risk of transfusion-related complications than adults[8]. Therefore, minimizing transfusion may be beneficial in pediatric cardiac surgery patients.

Patient blood management strategies aim to optimize the care of patients who require transfusion. Efforts to correct preoperative anemia and coagulopathy, improve homeostasis, reduce bleeding, limit blood collection and incorporate blood-sparing techniques are important points of PBM[9,10]. Pediatric patients are exposed to potential complications associated with red blood cell (RBC) transfusion because of the higher transfusion threshold for children than adults. PBM proposes the restrictive transfusion approach and should be applied to the pediatric cardiac surgical population[11]. Pediatric patients are exposed to potential complications associated with red blood cell (RBC) transfusion because the transfusion threshold is higher in children than in adults. PBM proposes the restrictive transfusion approach and should be applied to the pediatric cardiac surgical population[11].

This review aims to present the current literature on PBM in children with CHD undergoing open heart surgery.

Preoperative Patient Blood Management

Preoperative assessment includes evaluation of patient risk factors, surgical approach, staffing and equipment requirements and should be discussed by a multidisciplinary care team (cardiac surgery, anesthesia, cardiology and intensive care)[12]. The involvement of perfusionists and transfusion center staff in the management of these patients is essential for successful PBM[13]. In order to assess the risk of coagulopathy and intraoperative bleeding, a detailed history should be taken, inquiring about medications and supplements taken, relevant medical history, previous surgery and family history. Laboratory tests for anemia and coagulation parameters should be performed and abnormal results should be treated preoperatively in elective cases[13].

One of the pillars of PBM programs is the diagnosis and treatment of preoperative anemia. Children with CHD range from neonates to adolescents with cyanotic or non-cyanotic heart defects resulting in variable baseline hemoglobin (Hb) and ferritin levels. The

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optimal preoperative Hb concentration for these children is uncertain, especially in patients younger than 6 months or with chronic cyanosis[14].

Iron deficiency (ID) is the most common nutritional deficiency in children and has been defined as a comorbidity in children with chronic conditions such as CHD, heart failure, chronic inflammation, hematological disorders[15]. In addition, ID is a known risk factor for perioperative blood transfusion in the pediatric surgical population[16]. Gao et al.[17] investigated preoperative ID and its association with clinical outcomes in 314 children undergoing cardiac surgery with CPB. They reported that ID was associated with preoperative anemia and cyanotic heart disease and was an independent risk factor for postoperative blood transfusion.

As preoperative anemia and perioperative blood transfusion are associated with poor postoperative outcomes in neonates and pediatric noncardiac and cardiac surgical patients, correction of ID and anemia may reduce perioperative transfusion and is recommended in several guidelines[18-21]. However, this association may be difficult to detect in cyanotic children, who may have ID anemia even with elevated hemoglobin levels.

Preoperative iron supplementation has been studied in adult patients undergoing cardiac surgery in many trials[20,22]. In these studies, hemoglobin levels increased significantly and blood transfusions decreased perioperatively. However, such studies in pediatric cardiac patients are scarce. Otsuka et al.[15] administered oral iron supplementation to children with CHD for 3-12 weeks preoperatively and found that preoperative hemoglobin levels were significantly higher in children treated with iron. Although oral iron treatment has advantages such as low cost, ease of access and relative safety, a treatment period of 2-4 weeks is required to increase hemoglobin levels. The choice of oral or intravenous (IV) iron therapy should therefore be based on patient preference, degree of anemia and timing of surgery. Newer IV iron preparations such as ferumoxytol and ferric iron gluconate are reliable options for rapid iron replacement[23]. Hassan et al.[23] administered IV iron (ferumoxytol) to 54 children with ID anemia and demonstrated that ferumoxytol was effective in the treatment of IDA. In addition, the slow infusion rate and close monitoring allowed early detection of the rare adverse drug reactions.

The use of erythropoiesis-stimulating agents such as erythropoietin in the preoperative period in adult and pediatric patients is limited and poorly studied. Ootaki et al.[24] administered recombinant human erythropoietin subcutaneously to 82 children (72 with noncyanotic heart disease and 10 with cyanotic heart disease) 7 days before surgery. They reported that a single dose of erythropoietin without autologous blood donation increased hemoglobin levels. The Network for the Advancement of Patient Blood Management, Hemostasis and Thrombosis (NATA) guidelines recommend diagnosis and treatment of preoperative iron deficiency anemia with oral or intravenous iron (Grade 1C) and suggest consideration of preoperative erythropoietin (Grade 2C) in pediatric cardiac surgery patients[25].

Intraoperative Patient Blood Management

Acute Normovolemic Hemodilution

Acute normovolemic hemodilution (ANH) is a blood conservation strategy in which one or more units of the patient's own whole blood are replaced with an equal volume of crystalloid or colloid fluid before surgery and reinfused at the end of surgery. The collected blood contains clotting factors, red blood cells and platelets and is not subject to the harmful effects of the CPB machine. Intraoperative bleeding is diluted and the reinfusion of collected blood reduces the amount of blood lost at the end of surgery as a source of clotting factors and platelets[26].

The use of ANH in the pediatric surgical population is limited. However, in major pediatric surgery, great care must be taken to maintain normovolemia, as hypovolemia due to blood loss is the most recognized cause of anesthesia-related cardiac arrest in pediatric patients[27]. Sebastian et al.[28] studied ANH in 50 pediatric patients undergoing cardiac surgery with CPB and demonstrated that ANH protected platelets from the deleterious effects of CPB and improved hemostasis with autologous whole blood at the end of surgery. However, higher ANH volumes (ml/kg) and longer storage times increased the need for intraoperative transfusion. In a small study of 12 pediatric cardiac surgery patients, ANH was safe as a strategy to reduce blood component therapy; however, the study failed to demonstrate a reduction in perioperative transfusion or improvement in postoperative outcomes[29]. Overall, there is no clear recommendation that ANH is effective in children undergoing cardiac surgery with CPB due to conflicting results. The NATA guideline recommends against the use of routine ANH in children undergoing cardiac surgery with CPB (Grade 1C)[25].

Cell Salvage

Intraoperative cell salvage (ICS) is another method of reducing allogeneic red blood cell (RBC) transfusion. It recovers and purifies blood lost in the surgical field and returns the resulting red blood cell concentrate to the patient[30]. Due to the minimal blood volume required for the washing process in cell salvage, this method has limited use in infants and young children during pediatric cardiac surgery[31]. However, new cell salvage devices with small volume centrifugal beakers allow blood salvage even in neonates and small infants. Golab et al.[32] demonstrated that the use of a cell saver significantly reduced postoperative allogeneic blood transfusion in infants undergoing CPB surgery with a body weight of less than 10 kg. In addition, erythrocyte washing may reduce inflammatory biomarkers and systemic inflammation[33]. The NATA guideline recommends the use of cell salvage in pediatric cardiac surgery to reduce perioperative transfusion (grade 1C) and suggests active salvage of residual blood from the CPB circuit (grade 2C)[25].

Antifibrinolytic Agents

Antifibrinolytic agents such as tranexamic acid (TXA) or ε-aminocaproic acid (EACA) competitively inhibit the conversion of plasminogen to plasmin and reduce fibrin degradation. Activation of fibrinolysis is a major cause of bleeding in open heart surgery and antifibrinolytic agents significantly reduce blood loss and transfusion[34]. A meta-analysis of 30 trials (aprotinin n = 14, TXA n = 12 and EACA n = 2) reported that all agents reduced mean 24-hour blood loss and blood product transfusion[34]. Therefore, the agent with the best safety profile should be used, but sufficient data are lacking.

Intraoperative TXA dosing regimens used in different centers are quite variable due to various concerns regarding pharmacokinetic mechanisms and adverse effects. Some centers have used 3 boluses of 10 to 100 mg/kg, while others have used a loading dose of 10 to 100 mg/kg followed by continuous infusion[35]. To maximize the antifibrinolytic effect of TXA and avoid dose-related side effects, including seizures, it is important to use the lowest effective dose possible. Recent studies in children undergoing cardiac surgery have suggested the following dosing regimen: intravenous loading dose of 30 mg/kg (age <12 months) or 10 mg/kg (age ≥12 months); followed by infusion of 10 mg/kg/hr[36]. Therefore, large comparative studies are needed to investigate the relative safety and appropriate dosing regimens in children.

The NATA guideline recommends prophylactic administration of lysine analogues (either TXA or EACA) to all neonates and children undergoing surgery with CPB to reduce perioperative bleeding

and transfusion (Grade 1B) and discourages the administration of high doses of lysine analogues (either TXA or EACA) because of the risk of clinical seizures (Grade 1C)[25].

Coagulation Assessment

Systemic anticoagulation is provided by unfractionated heparin (UFH) during CPB. UFH inhibits thrombin, Factor Xa and activated intrinsic coagulation factors via antithrombin[37]. Monitoring of ACT, heparin concentration (anti-Factor Xa [aFXa] activity) or whole blood heparin concentrations can be used to adjust UFH dosing[38]. ACT and automated protamine titration devices are generally preferred for rapid point-of-care assessment. 400 U/kg heparin is effective in prolonging the activated clotting time (ACT) >480 seconds in infants and children[37]. However, due to low antithrombin levels in neonates and infants, weight-based doses have been shown to inadequately suppress thrombin generation[39]. In addition, differences in anticoagulant efficacy have been reported between different commercial heparins[40]. If heparin resistance is present and antithrombin deficiency is excluded, an additional 100 U/kg is recommended. In the presence of heparin resistance secondary to antithrombin deficiency, fresh frozen plasma (10 mL/kg) or antithrombin supplementation is recommended[25].

Protamine is used to neutralize heparin after CPB and the dose of protamine is usually administered as a 1:1 ratio of protamine to heparin. However, a 1:1 ratio may lead to protamine overdose and bleeding. The use of a protamine-heparin ratio of 1:1 or higher is not recommended as excess protamine may increase the risk of bleeding[25]. Thus, age-related differences and heparin-protamine interactions complicate heparin dosing and protamine reversal in pediatric cardiac patients[41].

Bivalirudin, a direct thrombin inhibitor, is the anticoagulant of choice when heparin is contraindicated or must be avoided. The recommended dose to maintain an ACT of more than 480 seconds was 1 to 2 mg/kg followed by a 2 to 3 mg/kg/h infusion[42].

Cardiopulmonary Bypass

Hemodilution and Target Hemoglobin

Patient size and bypass circuit volume ratio determine the degree of hemodilution during CPB. In infants weighing less than 8 kg, severe hemodilution occurs, causing fluid shifts and reducing platelets and coagulation factors[43]. Therefore, the bypass circuit in pediatric patients is generally primed with blood to maintain a predefined Hct[44].

Total priming volume is directly related to the amount of perioperative transfusion, and lower priming volumes are associated with lower transfusion volumes during CPB[45]. In addition, lower priming volume leads to improved water balance and reduced need for postoperative mechanical ventilation[46]. Consequently, miniaturization of the circuit and use of ultrafiltration, hemoconcentrator and cell saver can reduce hemodilution and the need for blood product transfusion and improve clinical outcomes[47].

Jonas et al.[48] administered 2 different target hematocrit (Htc) values (20% vs 30%) to infants < 9 months. The lower Htc group (20%) had a lower cardiac index, higher post-CPB lactate levels and increased total body water on postoperative day 1. Although there was no difference in the amount of blood product transfusion and adverse events between the 2 groups, the low Hct group had significantly worse psychomotor development scores at 1 year. In another study, Newburger et al.[49] compared target Hct values of 25% vs 35% during hypothermic CPB in infants. The 25% group had a more positive fluid balance but similar blood product transfusions, adverse events and developmental outcomes. As a result of these studies, a target Hct value of >25% during CPB is recommended for optimal neurodevelopmental outcome.

Priming Fluid

Since the 1990s, physiological salt solutions (commonly Plasmalyte) or lactated Ringer's (LR) have been used as the crystalloid priming solution in pediatric cardiac surgery[50,51]. Albumin is often added to the priming solution because of the inability of crystalloid solutions to provide oncotic pressure and reduce the inflammatory response[52]. In a study of 105 children under the age of 3 years, patients were randomized into 3 groups[53]. One group received 10 mL/kg albumin in the priming solution, the second group received 20 mL/kg synthetic colloid in the priming solution and the third group received LR priming solution. The albumin group had significantly higher postoperative platelet counts and plasma colloid oncotic pressures, and significantly less postoperative blood loss and blood product requirements than the other groups. According to the results of this study, albumin may have some advantages in terms of postoperative blood parameters.

The decision to add RBCs to the prime solution depends on the patient's body weight, pre-operative hematocrit, prime volume and acceptable hematocrit after dilution on CPB[54]. Asanginous prime is generally used in infants weighing more than 5-6 kg[55]. Whole blood, erythrocytes or erythrocytes plus FFP can be added to the blood-based prime volume[56]. Fresh whole blood (FWB) has historically been used in pediatric cardiac surgery to stabilize and correct coagulopathy and reduce inflammation. However, FWB is difficult to obtain and test in a timely manner, limiting its use. In pediatric patients younger than 2 years undergoing complex cardiac surgery, the use of FWB has been shown to reduce blood loss[57]. Mou et al.[58] compared FWB with RBC plus FFP for CPB priming in children undergoing cardiac surgery. They found that FWB in CPB priming reduced ICU length of stay and fluid overload.

FFP is often used in CPB priming as a source of fibrinogen and clotting factor[59]. In a study of children aged 1 to 16 years with congenital heart disease, 20% albumin or FFP was used in the CPB prime[60]. Immediately after heparin reversal, hemostatic test results improved in the FFP group, but these results were not maintained 24 hours after CPB. There were no other clinical differences between the groups. In a study of neonates with CHD, Bianchi et al.[61] compared FFP in the prime volume with 5% albumin with erythrocytes in the prime volume. They found that postoperative bleeding was reduced and fibrinogen levels improved in the FFP group. Another study in acyanotic infants under 10 kg compared a 5% FFP priming solution with an albumin priming solution. The FFP priming solution group received more perioperative blood transfusions than the albumin group, but total blood product consumption did not differ between the two groups[62]. The content of the priming solution is usually surgeon and institution dependent, but further study is needed in pediatric cardiac surgery.

The addition of FFP to the prime solution has been suggested in neonates (<30 days) undergoing cardiac surgery (grade 2C). There is no evidence in infants and children undergoing cardiac surgery (C). NATA Colloids (e.g. albumin) should be preferred to crystalloids for clear priming in children undergoing cardiac surgery (Grade 1C).[25]

Ultrafiltration

Ultrafiltration in pediatric cardiac surgery is used to concentrate erythrocytes and coagulation factors and reduce inflammatory mediators by removing excess fluid[63]. Conventional ultrafiltration (CUF) techniques (continuous ultrafiltration and zero balance ultrafiltration) remove fluid from the circulation during CPB and reverse hemodilution[64]. Modified ultrafiltration (MUF) is administered im-

mediately after cessation of CPB, provides maximal hemoconcentration and reduces early postoperative blood transfusion[65]. MUF has been shown to improve pulmonary compliance and gas exchange, increase hematocrit and blood pressure levels. However, Kuranti et al. reported in a meta-analysis that CUF and MUF were safe and effective hemoconcentrators and there was no difference in clinical outcomes[66].

The authors recommend conventional ultrafiltration or ≥10 minutes of modified ultrafiltration for neonates and infants undergoing cardiac surgery with CPB (Grade 1B)[25].

Intraoperative Monitoring of Hemostasis

From birth to adulthood, the concentration of coagulation factors increases while the hepatic synthesis of natural anticoagulants decreases, a phenomenon termed developmental hemostasis[67,68]. Perioperative bleeding and coagulopathy are the major causes of morbidity and mortality in neonates and children undergoing cardiac surgery. Cyanotic heart disease may increase the risk of bleeding by altering the preoperative coagulation profile. In the intraoperative period, major surgery and CPB induce an inflammatory response and coagulopathy. In addition, prime solution causes hemodilution[69]. Blood transfusions are often necessary, but may also be a risk factor for acute lung injury, prolonged extubation time, and prolonged ICU and hospital stay[3,4]. Therefore, clinicians should be prepared to manage blood loss and coagulopathy in pediatric cardiac surgery. Appropriate and timely use of blood products and hemostatic agents according to hemodynamic parameters, laboratory and coagulation tests is one of the key points of patient blood management.

Conventional coagulation tests (aPTT, PT, fibrinogen) are used to diagnose factor deficiencies and the normalized ratio (INR) is used as a guide for vitamin K antagonists in both adults and children[70]. However, as patients are uncoagulable during CPB, these tests cannot be used[25]. In addition, it takes 30-45 minutes to obtain results and the limited information provided does not include platelet count and function and fibrinolysis.

Viscoelastic tests (thromboelastography (TEG) and ROTEM) provide real-time global coagulation status and aid in the management of blood product transfusion in the setting of acute hemorrhage[71]. Viscoelastic assays measure clot initiation, strength and stability by providing a rapid assessment of coagulopathy and have been widely used in adult patients undergoing cardiac surgery[72]. Nakayama et al conducted a study in children undergoing cardiac surgery and found that ROTEM-guided early hemostatic management reduced blood loss, erythrocyte transfusion requirements and ICU length of stay[73]. However, a meta-analysis of 47 articles reported that there is insufficient data in the literature to establish viscoelastic testing as a "gold standard" for the management of bleeding and coagulopathy in pediatric cardiac surgery[74]. In addition, similar to conventional coagulation screening, viscoelastic tests cannot predict bleeding preoperatively in children undergoing cardiac surgery[25].

In the presence of excessive bleeding, the use of intraoperative hemostasis monitoring is recommended (Grade 1B). Viscoelastic tests may be an alternative to standard coagulation tests for intraoperative bleeding management (Grade 2C)[25].

Postoperative Red Blood Cell Transfusion and Thresholds

A prospective multicentre study reported that 79% of pediatric cardiac surgery patients received at least 1 RBC transfusion postoperatively[75]. The amount of RBC transfusion in these patients could not be determined based on intraoperative blood loss or preoperative hematocrit alone[76]. Children under 1 year of age, low birth weight, complex and/or cyanotic congenital heart disease, CPB and preoperative anemia are independent risk factors for RBC transfusion[77]. Although previous studies have shown that RBC transfusion after pediatric cardiac surgery is associated with increased morbidity and prolonged hospital stay, optimal transfusion thresholds have not been defined in these patients. The TRIPICU (The Transfusion Requirements in the Pediatric Intensive Care Unit) study, which investigated transfusion requirements in the pediatric intensive care unit, reported that Hb: 7 mg/dl was tolerated by children without adverse effects[78-80]. In the subgroup analysis, there was no difference in the incidence of multisystem organ dysfunction between children who received a restrictive transfusion strategy (Hb: 7 mg/dl) and a liberal transfusion strategy (Hb: 9.5 mg/dl) in postoperative cardiac surgery patients[81]. However, randomized controlled trials reported that pediatric patients with 20% hematocrit during CPB had a lower postoperative cardiac index, higher lactate levels and poorer neurological outcomes than those with 30% hematocrit[82]. Recent studies suggest that 24% hematocrit may be sufficient in terms of clinical outcomes and neurological outcome[81]. However, higher hematocrits may be required in neonates, cyanotic patients and those with complex cardiac anomalies. Therefore, goal-directed transfusion therapy aimed at a physiological target may be associated with improved clinical outcomes[83]. NATA recommends a postoperative hemoglobin threshold for transfusion in stable, acyanotic cardiac infants of Hb 70 g/L or 80 g/L in the presence of clinical signs suggesting symptomatic anemia (Grade 1B). This threshold is recommended to be 90 g/L in stable, cyanotic cardiac infants with clinical signs suggestive of symptomatic anemia (Grade 1C)[25].

Platelet Transfusion

Thrombocytopenia and platelet dysfunction are consequences of CPB and are associated with postcardiotomy bleeding in neonates and infants[84]. In addition, cyanotic cardiac patients with a hematocrit >50% usually have preoperative thrombocytopenia[85]. Platelet count and function at the end of CPB depend on the duration of CPB, hemodilution and hypothermia[86,87]. The threshold and/or volume of platelet transfusion in pediatric cardiac surgery has not been evaluated in any study and recommendations for platelet transfusion are mainly based on consensus. Group-matched platelet transfusion of 10-20 ml/kg may be given as a first step to restore hemostatic function in the setting of clinical bleeding and/or thrombocytopenia. Clinical assessment, platelet count and VET parameters are helpful in guiding platelet transfusions[11].

Fibrinogen

Decreased plasma fibrinogen has been associated with postoperative bleeding in pediatric cardiac surgery[88]. Fibrinogen can be replenished by administration of cryoprecipitate or fibrinogen concentrate. In bleeding neonates and children, hypofibrinogenemia diagnosed by the Clauss method (<1.5 g/L) or viscoelastic test (class 1C) should be treated with cryoprecipitate or fibrinogen concentrate (class 2C). FFP should be considered ONLY when cryoprecipitate or fibrinogen concentrate is not available (Class 2C)[25].

2. Conclusion

In pediatric cardiac surgery, blood conservation methods including the use of low priming volume circuits, ultrafiltration, microsampling of blood, antifibrinolytics, point-of-care testing and cell salvage blood reinfusion are recommended to reduce blood product consumption. These methods both reduce blood product transfusion and improve clinical outcomes. Patient blood management aims to transfuse the right product, in the right dose, to the right patient, at the right time, for the right reason. A comprehensive and multidisciplinary patient blood management Programme optimizes

patient care, avoids unnecessary blood product transfusions and limits side effects.

Statement of ethics

The author declares that this article does not require ethics committee approval

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