Journal of Cardiothoracic and Vascular Anesthesia ▮ (▮▮▮▮) ▮▮▮–▮▮▮

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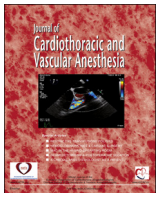

Original Article

Relationship Between Transfusion of Blood Products and the Incidence of Thrombotic Complications in Neonates and Infants Undergoing Cardiac Surgery

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Objectives: The authors hypothesized that transfusion of blood products in neonates and infants undergoing high-risk cardiac surgery in the absence of intraoperative coagulation monitoring increases the risk of thrombotic complications.

Design: Prospective observational study.

Setting: Neonates and infants undergoing cardiac surgery at a tertiary pediatric center.

Participants: Neonates weighing >2.5 kg and infants ≤ 12 months of age undergoing elective cardiac surgery with cardiopulmonary bypass were included in this prospective observational study.

Intervention: None.

Measurements and Results: Demographic data, surgical characteristics, transfusion data, and coagulation parameters (thromboeslatography and thromboelastometry) were collected. Logistic regression analysis was performed to identify potential determinants of postoperative thrombotic complication. Among the 138 neonates and infants included in the study, 12 (9%) developed a postoperative thrombotic complication. Unadjusted logistic regression analysis confirmed that the number and volume of blood products transfused was associated significantly with the increased incidence of thrombotic complication (odds ratio: 2.78, 95% confidence interval: 1.30-5.94, $p = 0.008$). This association persisted after adjustment for patient's age, the need for deep hypothermic cardiac arrest, and bypass time (odds ratio: 2.23, 95% confidence interval: 1.02-4.87, $p = 0.044$). The number of blood products transfused was associated with a significant increase in parameters of clot amplitudes measured at cardiac intensive care unit admission, while no difference was reported when measured after the administration of protamine.

Conclusions: This prospective observational study reports a significant association between transfusion of blood products in neonates and young infants undergoing cardiac surgery and an increased incidence of thrombotic complications in the absence of intraoperative coagulation monitoring.

Key Words: congenital heart disease; neonates; cardiac surgery; coagulopathy; bleeding

NEONATES AND INFANTS undergoing cardiac surgery with cardiopulmonary bypass (CPB) are at high risk for major perioperative bleeding, and regularly require the transfusion of

The authors have no conflict of interest.

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http://dx.doi.org/10.1053/j.jvca.2017.04.039

1053-0770/

large volumes of allogeneic blood products. Excessive postoperative bleeding in neonates after CPB has been shown to be independently associated with an increased incidence of major postoperative adverse events.[1]

Over the past decades, a variety of perioperative strategies have been used to improve perioperative management in this high-risk population. Most recently, attention has been directed toward the development of transfusion algorithms with point-of-care (POC)-testing used to guide patient-specific blood product administration.[2,3] Studies in adult cardiac surgical patients clearly demonstrate the efficacy of such POC-based algorithms in reducing the need for allogenic blood products transfusion, decreasing the incidence of major postoperative bleeding, and reducing costs.[4,5] To date, only 1 prospective study in children undergoing cardiac surgery has demonstrated the efficacy of a POC-based transfusion algorithm.[6]

Neonates and infants undergoing cardiac surgery also are at higher risk for postoperative thrombotic complications.[7] In a recent retrospective analysis of the Health Care Cost and Use Project (HCUP) Kid's Inpatient Database (KID), the authors reported that neonates and infants < 12 months of age were at higher risk to develop a thrombotic complication in the perioperative period of cardiac surgery.[8] Considering that blood product transfusion has been shown to contribute to the increased risk of thrombotic complication after adult cardiac surgery in a dose-dependent fashion,[9] the authors hypothesized that algorithm-based transfusion of blood products in neonates and infants undergoing high-risk cardiac surgery in the absence of coagulation monitoring could increase the risk of thrombotic complication through the development of a pro-coagulant profile.

Methods

The study design is prospective, observational study at a single institution. The authors' study protocol was approved by the institutional review board at Boston Children's Hospital (P00016625), and recorded on clinicaltrial.gov (NCT02410473). Written informed consent was obtained from the parents/guardians of each patient. Neonates weighing greater than 2.5 kg and infants equal to or less than 12 months of age undergoing elective cardiac surgery with CPB were eligible for this prospective study. Neonates and infants undergoing emergent procedure and/or those deemed to be in a moribund condition (American Society of Anesthesiology Physical Status [ASA PS 5]) were excluded from the study.

No specific interventions were required for this study. Anesthesia and CPB management were standardized per departmental protocols. The CPB circuit was primed with 1 unit of packed red blood cells (RBCs) and 1 unit of fresh frozen plasma (FFP). Target hematocrit during CPB was $> 30\%$. Following termination of CPB non-surgical, microvascular bleeding was treated with 1 to 2 units of volume reduced (20-30 mL/U) or non-volume reduced (40-50 mL/U) platelet concentrates. If microvascular bleeding continued 1 to 2 units of cryoprecipitate (20-30 mL/U) were transfused. If bleeding persisted despite these maneuvers, the sequence of platelets followed by cryoprecipitate transfusion was repeated. No FFP was transfused following CPB. Recombinant activated factor VII (rFVIIa) was administered at the discretion of the attending surgeon and anesthesiologist in cases where bleeding was deemed to be refractory to standard therapy. Target hematocrit following CPB was 40% in cyanotic patients and 35% in non-cyanotic patients. This algorithm has been utilized at the authors' institution for 10 years, and its use is supported by both clinical efficacy and laboratory investigation of the coagulation defects found to exist in the authors' neonatal and infant patient population.[10]

The authors' objective was to understand the relationship between transfusion of blood products and the incidence of thrombotic complication with their current transfusion protocol. Thrombotic complication was defined as any arterial or venous thrombosis diagnosed between Cardiac Intensive Care Unit (CICU) admission and hospital discharge. This included clinically symptomatic events (shunt thrombosis, stroke, or limb ischemia) as well as clinically occult thromboses detected by imaging studies (echocardiography, catheterization, or ultrasonography). Location of thrombosis and interval between surgery and thrombosis event were recorded. Demographic data and surgical characteristics were recorded: gender, age, diagnosis, date of surgery, type of procedure. Duration of the surgery was defined as the time between skin incision and the last surgical stitch. The authors recorded CPB characteristics (prime volume, CPB duration, aortic clamp duration, and duration of deep hypothermic cardiac arrest [DHCA]). Blood product transfusion was defined as any intraoperative exposure to RBCs, FFP, cryoprecipitate, and platelet concentrates (during or outside CPB). Administration of rFVIIa also was recorded. Blood samples were obtained at 3 different time points: after induction of anesthesia and placement of arterial line (Baseline), 3 minutes after protamine administration (post-protamine), and upon arrival to CICU admission (CICU admission). Each blood sample consisted of: 1 citrated tube (1.8 mL) used for coagulation analysis (TEG and ROTEM). Because ROTEM currently is not integrated in the authors' standard bleeding management strategy, the results obtained from the ROTEM analysis (EXTEM and FIBTEM) were not communicated to any caregivers. Bleeding management during the study period for all patients enrolled in the study were based on current available practices using standard coagulation assays.

The authors recorded the following ROTEM parameters on EXTEM and FIBTEM: clotting time (CT [min]), angle (α [degree]), clot formation time (CFT [min]), maximum clot firmness (MCF [mm]), clot amplitudes measured after 10 minutes (A10, mm) and 20 minutes (A20, mm), the clot lysis index at 30 min (LI30, %) which corresponds to the percentage of remaining clot stability in relation to the MCF value 30 minutes after the clotting time, maximal lysis (ML, %), and lysis onset time (LOT, min). In addition, the authors recorded the following TEG parameters: clotting time (r, sec), angle (degree), and maximal amplitude (MA, mm).

Please cite this article as: Faraoni D, et al. (2017), http://dx.doi.org/10.1053/j.jvca.2017.04.039