Early postoperative bleeding is independently associated with increased surgical mortality in infants after cardiopulmonary bypass

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Objective: Infants undergoing cardiac surgery often have postoperative bleeding contributing to the occurrence of adverse events. A quantitative evaluation of postoperative bleeding has not been well described.

Methods: We identified 1071 infants who had undergone cardiopulmonary bypass from August 1, 2008 to December 31, 2011. The volume of postoperative bleeding and its effect on mortality were reviewed.

Results: Postoperative bleeding during the first 12 hours postoperatively was stratified by quartiles. Bleeding was significantly associated with increased mortality (odds ratio [OR], 1.15; 95% confidence interval [CI] 1.10-1.21; $P < .001$). Other risk factors significantly associated with mortality included greater Risk Adjustment for Congenital Heart Surgery score (OR, 1.5; 95% CI, 1.22-1.85; $P < .001$), single ventricle anatomy (OR, 3.09; 95% CI, 1.68-5.67; $P < .001$), younger age (OR, 0.99; 95% CI, 0.98-0.99; $P < .001$), and longer perfusion time (OR, 1.01; 95% CI, 1.01-1.02; $P < .001$). Subjects with greater bleeding volumes experienced a longer postoperative mechanical ventilation and intensive care unit stay. The overall hospital mortality was 4.1%. On multivariate analysis, adjusting for age, single ventricle anatomy, Risk Adjustment for Congenital Heart Surgery score, and perfusion time, an increasing bleeding volume was independently associated with increased mortality. Packed red blood cell transfusion was independently associated with an increased duration of mechanical ventilation ($P = .01$) and intensive care unit length of stay ($P = .003$).

Conclusions: Early postoperative hemorrhage was independently associated with an increased mortality in infants after cardiac surgery. The longer interval from surgery to death suggests that other factors, aside from the bleeding itself, including the transfusion volume, might contribute to mortality. Initiatives to limit postoperative bleeding and to critically appraise packed red blood cell transfusion practices are warranted. (J Thorac Cardiovasc Surg 2014;148:631-6)

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Supplemental material is available online.

Infants who undergo cardiac surgery within the first year of life often experience significant postoperative bleeding after admission to the intensive care unit (ICU).[1] In addition to the extensive suture lines, increased hemodilution, activation of the coagulation system, and hemostatic derangements after cardiopulmonary bypass (CPB) increase the risk of postoperative bleeding.[1-4] Inherent deficiencies in antithrombin and other coagulation proteins can also prevent adequate hemostasis during and after CPB.[5,6]

Excessive postoperative bleeding will often be treated with blood products, including packed red blood cells (PRBCs), fresh frozen plasma, platelets, and thawed cryoprecipitate. In cases of severe bleeding, activated factor VII will often be administered to achieve adequate hemostasis.[7] Laboratory tests, including the thromboelastogram, have allowed for specific targeting of deficient areas of the coagulation system during ongoing bleeding.[8] When factor and product replacement have failed to achieve hemostasis, surgical exploration will usually be undertaken.

Excessive postoperative bleeding requires replacement with blood transfusions. Although safe during administration, blood transfusions carry several risks that can affect morbidity and mortality after cardiac surgery. Adult data have demonstrated increased mortality risk in association with PRBC transfusion after coronary artery bypass grafting[9] and a significant effect on long- and short-term survival after all types of adult heart surgery.[10] Pediatric data have demonstrated an increased duration of mechanical ventilation and ICU length of stay in relation to blood transfusions, with no demonstrable survival benefit for aggressive transfusion strategies compared with conservative transfusion strategies.[11-17]

The primary goal of the present study was to examine the relationship of early postoperative bleeding in infants with

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Abbreviations and Acronyms

CPB = cardiopulmonary bypass
ICU = intensive care unit
PRBC = packed red blood cell
RACHS = Risk Adjustment for Congenital Heart Surgery

surgical mortality and adverse events. We hypothesized that increasing amounts of postoperative bleeding would be associated with an increased mortality risk and adverse events, including a prolonged duration of mechanical ventilation and ICU length of stay. In particular, we focused on a quantitative evaluation of early postoperative bleeding after infant cardiac surgery and its effect on mortality.

METHODS

Study Design

The Children's Healthcare of Atlanta institutional review board approved the present study. Data were collected from the individual medical records and our institutional surgical database. All infants <1 year of age who had undergone cardiac surgery with CPB from August 1, 2008 through December 31, 2011 were included in the present analysis. Early postoperative bleeding was defined as bleeding that occurred within the first 12 hours after ICU admission. All patients included in the analysis were treated in the cardiac ICU postoperatively.

In addition to the volume of postoperative bleeding, the data collected included age, weight, height, cardiac anatomy, presence of chromosomal anomaly, Risk Adjustment for Congenital Heart Surgery (RACHS) score, perfusion time in the operating room, blood products received in the operating room, blood products received in the ICU, mechanical ventilation duration, length of ICU stay, in-hospital mortality, postoperative cardiac arrest, postoperative infection confirmed by positive wound culture or blood culture findings, delayed sternal closure, need for surgical re-exploration, need for mechanical circulatory support, and need for continuous renal replacement therapy.

Each operative admission was treated separately. In patients who underwent >1 operation during an admission, the primary operation for which they had been admitted to the hospital was chosen for analysis. As such, the patients who underwent a stage I Norwood operation as a newborn and a subsequent cavopulmonary anastomosis at 4 months of age were included in the analysis as 2 unique encounters.

The CPB anticoagulation protocol at the Children's Healthcare of Atlanta during the entire study period consisted of a single bolus dose of 500 U/kg of unfractionated heparin immediately before the initiation of CPB. Monitoring was achieved with activated clotting times, with a goal of >500 seconds. Repeat doses of heparin (100 U/kg) were given to maintain the activated clotting time >500 seconds throughout the duration of CPB. Aminocaproic acid (Amicar; Clover Pharmaceuticals, Marietta, Ga) was routinely administered to infants undergoing repeat sternotomy. After CPB, a dose of protamine (5 mg/kg) was administered to reverse anticoagulation. Ongoing bleeding in the operating room was treated with platelets, thawed cryoprecipitate, and fresh frozen plasma. In cases of severe bleeding for which a surgical cause could not be identified, activated factor VII was used.

The vast majority of patients underwent bicaval cannulation and moderate hypothermia (28°-32°C), except for neonates undergoing aortic arch reconstruction or a first stage Norwood procedure, for whom hypothermia to 18°C was typically used with regional cerebral perfusion. The use of profound hypothermic circulatory arrest for >2 or 3 minutes was rare. The hematocrit was maintained at >28%, often with the use of hemofiltration during CPB. Modified venovenous ultrafiltration at the termination of CPB, particularly in neonates was commonly (but not universally) used, according to surgeon preference. The cell saver was also available for virtually all patients and was generally preferred over PRBCs both in the operating room and in the ICU.

Patients who continued to have significant bleeding on admission to the cardiac ICU were treated further with multiple blood products, including fresh frozen plasma, platelets, thawed cryoprecipitate, and PRBCs. In severe cases, repeat dosing of activated factor VII was used. The coagulation tests used included the prothrombin time, activated partial thromboplastin time, international normalized ratio, and anti-Xa assay. Thromboelastography and platelet mapping were also used more recently to help target specific areas of the coagulation system, if the bleeding was difficult to control. When the bleeding could not be controlled medically, or if signs or symptoms of pericardial tamponade developed, surgical exploration was undertaken to identify a specific source of bleeding.

The primary outcome of the present study was in-hospital mortality. Secondary outcomes were the mechanical ventilation duration and length of ICU stay.

Statistical Analysis

Statistical analysis was performed using STATA, version 12.0, software (StataCorp LP, College Station, Tex) and Statistical Analysis Software, version 9.3 (SAS Institute Inc, Cary, NC). Univariate analysis was performed using Student's t test or analysis of variance for continuous data and Fisher's exact test or χ^2 for categorical data. Multivariate logistic and linear regression analysis was undertaken to adjust for covariates. To predict the effect of postoperative bleeding on mortality risk, all variables with $P < .1$ on univariate analysis were entered into a multivariate logistic regression analysis.

RESULTS

A total of 1071 infants <1 year of age underwent cardiac surgery with CPB during the study period. To quantify the bleeding amounts, the patients were stratified by quartile according to the quantity of bleeding during the first 12 postoperative hours: 0 to 1.19, 1.20 to 2.00, 2.01 to 4.19, and ≥4.20 mL/kg/h. The patient characteristics are summarized in Table 1.

The patients in the higher quartiles were younger, weighed less, and had greater RACHS scores and longer perfusion times ($P < .001$). Patients in the highest quartile had a median age of 8 days (range, 0-346) compared with a median age of 103 to 158 days in the 3 lower quartiles ($P < .001$). The median weight in the highest quartile was 3.4 kg (range, 2.0-8.7) compared with a median weight of 4.4 to 5.8 kg in the 3 lower quartiles ($P < .001$). The median RACHS score in the 2 highest quartiles was 3 compared with a score of 2 in the 2 lower quartiles ($P < .001$). The perfusion time also increased with increasing quartile. The median perfusion time in the lowest quartile was 76 minutes (range, 18-211), increasing to 139 minutes in the highest quartile (range, 31-361; $P < .001$).

Single ventricle anatomy was present in 22% to 30% of the patients across the quartiles, with a trend toward statistical significance ($P = .08$). Chromosomal anomalies were present in 11% to 17%, and heterotaxy syndrome ranged