Blood transfusions are associated with urinary biomarkers of kidney injury in cardiac surgery

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Objective: Cardiac surgery is a major cause of acute kidney injury. In this setting, receipt of blood transfusions seems to be associated with a higher risk of acute kidney injury, as measured using serum creatinine values. We examined this association further by using urinary biomarkers of kidney injury.

Methods: A total of 1210 adults underwent cardiac surgery and were divided into 3 groups on the basis of the receipt of intraoperative packed red blood cell units: no blood (n = 894), 2 or less packed red blood cell units (n = 206), and more than 2 packed red blood cell units (n = 110). Acute kidney injury was defined as (1) doubling of serum creatinine from the preoperative value; (2) first postoperative urinary interleukin-18 in the fifth quintile; and (3) first postoperative urinary neutrophil gelatinase-associated lipocalin in the fifth quintile. We determined the relative risk for acute kidney injury outcome according to packed red blood cell units group after adjusting for 12 preoperative and surgical variables. By using the Sobel test for mediation analysis, we also evaluated the role of biomarkers in causing acute kidney injury through alternative pathways.

Results: Acute kidney injury was more common in those who received more than 2 packed red blood cell units. In patients receiving more than 2 packed red blood cell units, the adjusted relative risks were 2.3 (95% confidence interval, 1.2-4.4, *P* .01), 1.36 (95% confidence interval, 1.0-1.9, *P* .05), and 1.34 (95% confidence interval, 1.0-1.8, *P* .06) for doubling of serum creatinine, urinary interleukin-18 in the fifth quintile (>60 pg/mL), and urinary neutrophil gelatinase-associated lipocalin in the fifth quintile (>102 ng/mL), respectively. Furthermore, the effect of packed red blood cell units transfusion on acute kidney injury was partially mediated by interleukin-18.

Conclusions: Receipt of 2 or more packed red blood cell units during cardiac surgery is associated with a greater risk of acute kidney injury defined by serum creatinine and kidney injury biomarkers. (J Thorac Cardiovasc Surg 2014;148:726-32)

Cardiac surgery is one of the leading contributors to acute kidney injury (AKI) in patients admitted to intensive care.[1-3] It is estimated that more than 1.25 million cardiac surgeries are performed annually worldwide.[4] Given the large number of cardiothoracic surgeries and associated AKI, it is necessary to understand potentially modifiable risk factors for cardiothoracic surgeries and associated AKI.

Acute blood loss or decrease in hematocrit (HCT) because of hemodilution is common in cardiac surgery; thus, blood transfusion is frequently performed during surgery to improve oxygen delivery to kidneys and other vital organs with the assumption that it will prevent ischemic injury. However, blood transfusion is not a benign intervention and has been shown to be associated with multiorgan failure, including AKI in patients undergoing cardiopulmonary bypass (CPB).[5,6] Because blood transfusion is a potentially modifiable factor in cardiothoracic surgeries and associated AKI, the association between blood transfusion and outcomes in cardiac surgery has been widely investigated. More recently, data from a randomized controlled trial suggested that a restrictive protocol of blood transfusion was not inferior to a liberal protocol in patients undergoing cardiac surgery.[7] To date, however, most studies investigating the relationship between blood transfusion and AKI have used creatinine or dialysis as measures of AKI. Serum creatinine is not

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Abbreviations and Acronyms

AKI = acute kidney injury
CABG = coronary artery bypass grafting
CI = confidence interval
CPB = cardiopulmonary bypass
eGFR = estimated glomerular filtration rate
HCT = hematocrit
IL = interleukin
NGAL = neutrophil gelatinase-associated lipocalin
PRBC = packed red blood cell
RBC = red blood cell
RR = relative risk
TRIBE-AKI = Translational Research Investigating Biomarker Endpoints in AKI

considered a robust marker for timely diagnosis in AKI because of the effect of several nonrenal factors, such as fluids, drugs, and muscle metabolism, on serum creatinine levels. In addition, creatinine is a functional marker of renal clearance rather than direct injury. However, there are some novel urine proteins, neutrophil gelatinase-associated lipocalin (NGAL) and interleukin (IL)-18, that are associated with ischemia reperfusion injury in the kidney and have demonstrated improved sensitivity for AKI diagnosis when compared with serum creatinine.[8] In addition, animal studies have demonstrated that NGAL and IL-18 are not only early biomarkers but also mediators of AKI and contribute to apoptosis and necrosis of renal tubular cells.[9] Because the association between packed red blood cell (PRBC) transfusion and AKI has been examined by using serum creatinine, the objective of the present study was to determine the degree of functional and structural injury associated with transfusion of PRBCs and to determine whether urinary biomarkers of kidney injury mediate clinical AKI in this setting.

METHODS

Study Population

We performed a prospective analysis of the adult patient population who underwent coronary artery bypass grafting (CABG) or valve surgery at 6 academic medical centers in North America between July 2007 and December 2009. All the patients eligible for the study consented to the Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) protocol.[10] The main inclusion criteria required cardiac surgery with high risk for AKI defined by the presence of 1 or more of the following: emergency surgery, preoperative serum creatinine greater than 2 mg/dL (>177 μmol/L), ejection fraction less than 35% or grade 3 or 4 left ventricular dysfunction, age greater than 70 years, diabetes mellitus, concomitant CABG and valve surgery, or repeat revascularization surgery.[10,11] The cohort included patients undergoing off-pump coronary artery bypass and patients undergoing CPB. Patients with evidence of AKI before surgery, prior kidney transplantation, preoperative serum creatinine level greater than 4.5 mg/dL (>398 μmol/L), or end-stage renal disease were excluded.

Sample Collection

Urine and plasma specimens were collected preoperatively, and the first postoperative samples were collected soon after admission to the intensive care unit. The remaining daily blood and urine samples were obtained at the time of routine morning blood collection performed for clinical care. Serum creatinine values were recorded for every patient throughout the hospital stay. Further details on the sample collection and processing have been described.[10,11]

Acute Kidney Injury Biomarker Measurements

Urinary NGAL (ng/mL) and IL-18 (pg/mL) were measured with the ARCHITECT assay (Abbott Diagnostics, Abbott Park, Ill). Urine creatinine was measured by the modified Jaffe reaction. The intra-assay coefficient of variation for the urine creatinine assay was 5%, whereas the coefficients of variations for the NGAL and IL-18 assays were approximately 5% and 8%, respectively.

Study Variables

Published studies suggest a significantly increased risk of AKI with transfusion of more than 2 PRBC units.[12-15] We therefore analyzed the cohort by dividing into 3 groups as receiving no blood, 2 or less PRBC units, and more than 2 PRBC units intraoperatively. The primary outcome was the development of AKI, defined in 3 ways: (1) at least a doubling in serum creatinine from the baseline preoperative value; (2) urinary IL-18 concentration in the highest quintile; or (3) urinary NGAL in the highest quintile. We limited our analysis to first postoperative biomarker values because we have previously shown the association of these values with AKI in cardiac surgery cases.[10] Preoperative characteristics, operative details, and postoperative complications were collected. For postoperative complications, the definitions of the Society of Thoracic Surgeons database were used. The number of PRBC transfusions received intraoperatively was recorded for every patient. Cardiac catheterization if received within 48 hours of index surgery was recorded. Preoperative estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration equations.[16] All preoperative creatinine values were measured within 2 months before surgery.

Statistical Analysis

Patients' baseline characteristics were compared across the 3 groups. We analyzed categoric and continuous variables using chi-square and Kruskal–Wallis statistics, respectively. We assessed the outcome of severe AKI on the basis of serum creatinine and biomarkers as described earlier. We also examined the distribution of the urinary biomarkers across the 3 groups. We used the first postoperative values of urine biomarkers because these have been demonstrated to be associated with AKI in our prior observations.[10,17] Relative risk (RR) of severe AKI was calculated using Poisson regression with robust error variance in the 2 groups who received 2 or less PRBC units or more than 2 PRBC units, using the group with no blood transfusion as reference. We adjusted for various important covariates that are associated with AKI, including patient demographics (white race, age, sex), clinical risk factors (preoperative eGFR, diabetes, hypertension, congestive heart failure, cardiac catheterization in the last 48 hours), and operative characteristics (elective vs nonelective surgery, CPB time and type of surgery [CABG, CABG and valve, valve]). To minimize the indication bias that is associated with PRBC use, we also used propensity scores as a covariate and weighted propensity scores to calculate the RR. The RR was adjusted for propensity score, which provides a way to summarize covariate information about group bias (treatment selection) into a scalar value. The propensity score probability was calculated from logistic regression after accounting for covariates listed earlier, including PRBC groups.