Identification of modifiable risk factors for acute kidney injury after coronary artery bypass graft surgery in an Asian population

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Objective: Postoperative acute kidney injury (AKI) after cardiopulmonary bypass (CPB) with coronary artery bypass grafting is common and increases patient morbidity and mortality. Studies have identified the lowest hematocrit during CPB, preoperative anemia, and intraoperative transfusion as modifiable AKI risk factors. Because Asians are smaller in body size, the use of standard CPB circuits can result in excessive hemodilution and subsequent transfusion to maintain the desired hematocrit target of ≥21% during CPB. Thus, we aimed to ascertain whether the lowest hematocrit during CPB, preoperative anemia, and intraoperative transfusion remained as independent modifiable risk factors associated with AKI in our prospective cohort of Asians.

Methods: Data from 1448 patients who had undergone coronary artery bypass grafting with CPB from December 2008 to December 2010 at Singapore's 2 national heart centers were obtained. The perioperative risk factors were analyzed for their associations with postoperative AKI. AKI was defined using the Acute Kidney Injury Network stage 1 criteria.

Results: The incidence of AKI was 27.0% and mean lowest hematocrit during CPB was 24.5% ± 3.8%. The risk of AKI increased with a decreasing lowest hematocrit during CPB (relative risk, 0.933; 95% confidence interval, 0.899-0.968; $P < .001$), in particular with the lowest hematocrit of ≤22%. A 23% increased risk of AKI was found for preoperative anemia (relative risk, 1.225; 95% confidence interval, 1.022-1.468; $P = .028$). Intraoperative transfusion was related on univariate analysis ($P < .001$) but was not independently associated on multivariate analysis (relative risk, 0.961; 95% confidence interval, 0.782-1.180; $P = .702$).

Conclusions: The lowest hematocrit and preoperative anemia were potentially modifiable risk factors independently associated with AKI after cardiac surgery in our Asian population. Blood transfusion did not affect the development of AKI in our population. (J Thorac Cardiovasc Surg 2014;147:1356-61)

Postoperative acute kidney injury (AKI) after coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) is common and increases patient morbidity and mortality.[1,2] The perioperative risk factors for AKI include patient age, history of diabetes, intra-aortic balloon pump use, and CPB duration. Factors, such as the lowest hematocrit during CPB, intraoperative red blood cell (RBC) transfusion, and preoperative anemia, have been identified as independent modifiable risk factors that could contribute to postoperative AKI.[3-8]

The lowest acceptable hematocrit during CPB has not been definitively identified. However, it is generally agreed that a hematocrit of ≥21% during CPB decreases renal complications.[4,9] The current practice has been to maintain the hematocrit at or >21% during CPB. This can require blood transfusion. However, the transfusion of blood to ameliorate the effects of hemodilution can increase the risk of AKI.[3,4,6]

Preoperative anemia has been identified to be the single most important determinant of intraoperative blood transfusion.[10] Karkouti and colleagues[11] have shown that anemic patients are most likely to require multiple blood transfusions during cardiac surgery and are also most likely to be harmed by them. Preoperative anemia has therefore been shown to increase the risk of AKI.[6,7]

Our patient population was predominantly Asian, who are typically shorter and lighter than our Western counterparts.[12] Using Nadler's formula, the total blood volume is related to the cubed product of the height and directly to the weight.[13] Therefore, far greater hemodilution can occur in our patients from the fixed amount of blood-free prime in the CPB circuit, resulting in a lower hematocrit during CPB. This can

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Abbreviations and Acronyms
AKI = acute kidney injury
CABG = coronary artery bypass grafting
CI = confidence interval
CPB = cardiopulmonary bypass
RBC = red blood cell
RR = relative risk

necessitate a greater rate of intraoperative transfusion to conform to the hematocrit target, often requiring transfusions even for patients who were not anemic preoperatively.

We postulated that the smaller body sizes of our patients would compound the effect of preoperative anemia and increase the rate of transfusion, leading to postoperative AKI. We therefore embarked on the present study to determine the incidence of AKI after CPB in our patient population and to study the effect of known modifiable risk factors (ie, lowest hematocrit during CPB, preoperative anemia, and RBC transfusion) on the incidence of AKI after CABG.

METHODS

Study Design, Database, and Population Selection

With institutional review board approval, we prospectively followed up 1744 Asian patients who had undergone primary, isolated CABG from December 2008 to October 2011 at Singapore's 2 national heart centers (National University Health System and Singapore General Hospital). All patients provided written informed consent. The perioperative variables were collated and maintained in a cardiac database with regular audits. A total of 296 patients were excluded from the present study because they had had preoperative renal impairment (n = 237), had missing preoperative and postoperative creatinine values (n = 25), or undergone off-pump surgery (n = 34). The total number of patients who met the inclusion and exclusion criteria was 1448. The normal creatinine range provided by our laboratories was 60 to 105 μmol/L for men and 40 to 75 μmol/L for women. Renal impairment was defined as serum creatinine > 10 μmol/L greater than normal and/or dialysis. This corresponded to the cutoff values of serum creatinine of 115 μmol/L and 90 μmol/L that have been validated in men and women, respectively, in screening for early renal impairment.[14]

Renal Function Assessment and Perioperative Renal Data

The preoperative serum creatinine value used was that obtained closest to surgery, typically at preadmission testing within 1 week of surgery. If a material change had occurred in the patient's condition, the serum creatinine measurement would be repeated the day before surgery, and that value would be taken as the preoperative serum creatinine. The peak serum creatinine was the highest creatinine value obtained within the first 3 postoperative days. Stage I of the Acute Kidney Injury Network criteria was used as the primary outcome, defined as an absolute increase in serum creatinine of $\geq$26.4 μmol/L and/or a 50% increase in the serum creatinine to the peak serum creatinine from the preoperative serum creatinine. The creatinine levels typically peaked on postoperative day 2 and had returned to baseline by day 5.[15]

Hematocrit, Hemodynamic, and Transfusion Data

The hematocrit was measured at heparinization and every 20 minutes during CPB. Testing was performed using the routine arterial blood gas analysis protocols on the Siemens RAPIDlab 1265 (Siemens Healthcare Diagnostics, Tarrytown, NY). Blood transfusion was given to maintain a hematocrit of $\geq$21% during CPB and was guided by institutional protocol.

Preoperative Anemia Data

Preoperative anemia was defined according to the World Health Organization's gender-based definition of <12.0 g/dL for women and <13.0 g/dL in men.

Perioperative Anesthesia and Surgical and Perfusion Management

The perioperative surgical management and clinical practices at both institutions were similar and followed international practice. Typically, anesthesia was induced with intravenous induction agents (etomidate or propofol) and maintained with a balanced anesthesia regimen of low-dose fentanyl (10-20 μg/kg) and volatile agents (primarily sevoflurane). Conventional CPB circuits with roller pumps, membrane oxygenators, heat exchangers, venous reservoirs, cardiotomy suction, and arterial blood filters were used. The volume of prime used in the CPB circuits was typically 1300 to 1400 mL. The perfusion targets were mild-to-moderate hypothermia (32°-35°C), hematocrit levels of $\geq$21%, an activated clotting time of >400 seconds, a glucose level of <10 mmol/L, a nonpulsatile flow rate of 2.2 to 2.4 L/min/m^2, and mean arterial pressure of 50 to 70 mm Hg. Myocardial protection was achieved with cold blood cardioplegia. Aprotinin was not used in any of the patients.

Statistical Analysis

Population demographics, medical history, preoperative risk assessment, intraoperative variables, and postoperative outcomes were analyzed descriptively. Univariate analysis was performed using a 2-tailed unpaired *t* test or Mann-Whitney *U* test for numerical factors after normality assumption was checked. The chi-square test was performed for categorical factors on univariate analysis. The factors from the univariate analysis with $P < .1$ were included in the multivariate model. Multivariate analysis was performed using the Poisson regression model with robust estimator to estimate the adjusted relative risk (RR) of developing AKI after CPB for CABG patients. The interaction effect between the lowest hematocrit during CPB and the use of transfusion and the presence of preoperative anemia was checked. Only the main effects would be included in the model if no significant interaction was present. Collinearity among the factors was also checked. All statistical analyses were performed using IBM SPSS, version 20.0 (IBM, Armonk, NY). The data were plotted and logarithmic trend lines drawn using Microsoft Excel 2010 (Microsoft, Redmond, Wash).

RESULTS

A total of 1744 Asian patients underwent CABG during the study period. Of these, 1448 patients met the inclusion and exclusion criteria for our study. Of the 1448 patients, 391 developed AKI postoperatively. These patients were more likely to be older and to have a history of diabetes and hypertension. Other risk factors included preoperative anemia, high preoperative creatinine, poor heart function, the use of loop diuretics, urgent or emergent CABG surgery, intra-aortic balloon pump use, a lower European System for Cardiac Operative Risk Evaluation (EuroSCORE) logistic score, longer CPB time, longer aortic crossclamp time, and greater number of vein grafts harvested. They were also more likely to have a lower lowest hematocrit during CPB and to have received RBC transfusion (Table 1).

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