Leukoreduction program for red blood cell transfusions in coronary surgery: Association with reduced acute kidney injury and in-hospital mortality

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Objective: Leukocytes in allogeneic blood transfusions cause several immunomodulatory events. This before-and-after cohort study evaluated clinical outcomes after adoption of prestorage leukoreduction program for blood transfusions, with particular focus on acute kidney injury.

Methods: One thousand thirty-four consecutive patients who underwent on-pump coronary artery bypass grafting between January 2004 and December 2007 were included. Propensity score analysis for transfusion was performed in the whole population; patients who were actually transfused were then divided according to leukoreduction. From these 2 groups, 147 pairs matched for propensity score were considered to evaluate with bivariate and multivariable analyses the effects of leukoreduction, with all-cause in-hospital mortality and morbidity as main outcomes.

Results: Unadjusted in-hospital mortalities were 6.6% for the entire cohort and 44.2% for those with acute kidney injury. In the matched population, after introduction of leukoreduction, mortality rates decreased to 5.4% (vs 11.4%) and acute kidney injury (RIFLE [Risk, Injury, Failure, Loss of function, End-stage renal disease] class R or greater) dropped from 51.7% to 41.5% (relative risk –20%, $P < .045$). No difference emerged regarding other major complications. At multivariable analysis, intra-aortic balloon pump, RIFLE score, and propensity score for transfusion proved independent predictors of in-hospital mortality. Intra-aortic balloon pump and nonleukodepleted transfusion emerged as independent predictors of acute kidney injury. Multivariable analysis on the overall cohort of transfused patients confirmed that nonleukodepleted transfusion was an independent predictor of acute kidney injury.

Conclusions: Leukoreduction of allogeneic blood products is associated with decreased acute kidney injury and mortality in highly transfused patients. (J Thorac Cardiovasc Surg 2010;140:188-95)

Although allogeneic blood transfusions are commonly used in supportive care of cardiac surgical patients, they may be a double-edged sword. In addition to a lifesaving effect in hemorrhagic shock, transfusion of allogeneic packed red blood cells (RBCs) can be beneficial in situations of oxygen-supply dependency to avoid a critically low hematocrit. These benefits are countered by the risks of transfusion-associated lung injury, transfusion-associated immunomodulation, and cellular hypoxia, along with other well-known drawbacks.[1] Numerous studies have been performed to evaluate the impact of leukoreduction.[2] This possibility was suggested on the basis of studies evaluating the benefits obtained from white blood cell removal with specialized filters in reducing the unwanted effects of cardiopulmonary bypass.[3] Some studies revealed increased short-term postoperative mortality after transfusions containing allogeneic leukocytes relative to transfusions of blood leukoreduced by filtration. The precise mechanism behind such a survival benefit remains uncertain. No authoritative meta-analysis has yet provided convincing evidence for or against implementation of universal white blood cell reduction in this surgical setting.[2] Recently, an article by Blumberg and colleagues[4] questioned the validity of such a meta-analysis because it did not investigate medical sources of heterogeneity (intention to treat, as treated) and did not include the most recent randomized, controlled trials.

As part of our hospital's ongoing continuous quality improvement program, we performed a prospective cohort study designed to survey blood transfusion practice and its effects on outcomes in cardiac surgery. The relative database was later used to determine the impact of a universal leukoreduction program on hospital mortality and morbidity among patients referred for coronary artery bypass grafting (CABG) in a tertiary care, university-affiliated center.

MATERIALS AND METHODS

Study Setting and Patient Sample

The study was conducted at the Department of Cardiothoracic and Respiratory Sciences of the Second University of Naples, located in an affiliated

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CSA-AKI = cardiac surgery–associated acute kidney injury
GFR = glomerular filtration rate
IABP = intra-aortic balloon pump
RBC = red blood cell
RIFLE = Risk, Injury, Failure, Loss of function, End-stage renal disease

teaching hospital (V. Monaldi Hospital). At our institution, nearly 700 patients undergoing cardiac surgery annually are admitted to a dedicated 12-bed postoperative intensive care unit. Information from these patients is collected on a daily basis with standardized case report forms; all clinical perioperative data (including demographic data, laboratory tests, nature of surgery, blood product transfusions, reexploration, postoperative complications, and stays in the intensive care unit and the hospital) are collected. Data are entered into a computerized database that includes 100 variables and is programmed to accept only matching double-entry data falling within prespecified ranges. All queries are resolved by referring to the patients' original records. Of 1323 consecutive patients undergoing CABG between January 2004 and December 2007, a total of 1034 patients without preoperative transfusions who underwent on-pump procedures and survived longer than 24 hours after the completion of the index surgical procedure constituted the study sample.

Universal prestorage leukoreduction was implemented in our hospital starting from January 2006, fulfilling the European and German standard for leukoreduced blood products of less than 1×10^6 residual white blood cells. A total of 563 patients were enrolled during the control period, and 471 patients were enrolled after the advent of prestorage leukoreduction.

Study Design and Aims

In this before-and-after retrospective cohort study, the influence of leukodepletion on in-hospital mortality and morbidity was investigated in consecutive patients undergoing CABG. Research protocol was approved by the local ethics and research committee, which waived the need for informed consent.

Surgical and Clinical Care

All procedures were performed by the same 3 senior surgeons (G.N., M.C., M.S.) throughout the study period. Details on surgical strategy and postoperative care have been reported extensively elsewhere.[5,6] Aprotinin was never used for bleeding prevention, because it is not authorized in our country; tranexamic acid was given preoperatively to patients receiving dual antiplatelet therapy. Heparinization was managed by monitoring both heparin blood level and activated coagulation time. An intraoperative autologous blood salvage method was used for every patient with preoperative anemia. A specific perioperative transfusion algorithm was applied: patients received 2 units of packed RBCs before cardiopulmonary bypass whenever the preoperative hematocrit value was below 30%, and they received 2 or more units of packed RBCs during cardiopulmonary bypass in cases of excessive hemodilution (hematocrit <22%). After cardiopulmonary bypass, the patients received packed RBCs to maintain a hematocrit value higher than 25%. This target value was raised to a higher value according to the clinical condition, the hemodynamic status, the need for inotropic support, and the age of the patient. Fresh-frozen plasma was not used before the patient reached the intensive care unit. Platelets were usually not transfused, except for patients who reached the operating room with a full dose of ticlopidine or clopidogrel and had severe postoperative bleeding. Such a protocol complies with recently published guidelines.[7]

Baseline Data and Clinical Outcomes

All definitions were established as part of the original study design. Incidence of cardiac surgery–associated acute kidney injury (CSA-AKI) according to RIFLE (Risk, Injury, Failure, Loss of function, End-stage renal disease) criteria was investigated.[8] The change in kidney function was based on plasma creatinine concentration and defined as the difference between baseline concentration and the highest concentration during the stay in the intensive care unit.

Preoperative glomerular filtration rate (GFR) and nadir GFR during intensive care unit stay were calculated with the Modification of Diet in Renal Disease equation: estimated GFR $= 186 \times (\text{plasma creatinine level in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203}$. For women, the product of this equation was multiplied by a correction factor of 0.742.[9] The classification for acute kidney injury by the Acute Dialysis Quality Initiative Workgroup was constructed. This classification is named RIFLE for its grades of severity of renal impairment. The standard defines 3 grades of severity—risk (class R), injury (class I), and failure (class F)—and 2 outcome classes—loss of kidney function (class L) and end-stage renal disease (class E). This classification system includes separate criteria for creatinine and urinary output. A patient can fulfill the criteria through changes in serum creatinine, estimated GFR, or urinary output, with the criterion that leads to the worst possible classification being used. Class R is considered if there is a 1.5-fold increase in serum creatinine, a GFR decrease greater than 25%, or a urinary output less than 0.5 mL/(kg · h) for 6 hours; class I is considered if there is a 2-fold increase in serum creatinine, a GFR decrease greater than 50%, or a urinary output less than 0.5 mL/(kg · h) for 12 hours; and class F is considered if there is a 3-fold increase in serum creatinine, a GFR decrease greater than 75%, a serum creatinine greater than 4 mg/dL in conjunction with an acute rise in serum creatinine of at least 0.5 mg/dL, a urinary output less than 0.3 mL/(kg · h) for 24 hours, or anuria for 12 hours. The main parameters considered in this study for CSA-AKI definition were creatinine and GFR because of the heterogeneity of volemic status and diuretic use among the study patients, which obscured the relationship between renal status and urinary output.

Cardiac morbidity was defined as the occurrence of myocardial infarction or heart failure. The diagnosis of myocardial infarction required either the development of new Q waves, new and persistent ST-segment or T-wave changes associated with an elevation of creatine kinase MB isoenzyme values, or autopsy evidence of acute myocardial infarction. The diagnosis of heart failure required either the use of a ventricular assist device or the use of continuous inotropic support for at least 24 hours. Intra-aortic balloon pump (IABP) use was considered as a variable in itself, rather than as a criterion for heart failure definition, because IABPs were also implanted in cases of refractory angina or high-risk arrhythmias without pump deficit. Mediastinitis, bloodstream infection, and pneumonia were defined according to Centers for Disease Control and Prevention criteria.[6] Respiratory complications were defined as mechanical ventilation longer than 48 hours or need for tracheotomy. Fatality (in-hospital mortality) was defined as any death occurring after surgery and during the index hospitalization.

Statistical Analysis

Data analysis first addressed dissimilarities in clinical profile and course of patients transfused and not transfused, so that comparison would be fair and based on more extensive risk adjustment than has been done so far (Table 1). Bivariate analysis (with the χ^2 statistic for categoric variables and the t test and Wilcoxon rank-sum test for continuous variables) was used to identify significant preoperative, intraoperative, and postoperative factors associated with transfusion requirements in the general surgical population, with a dichotomous variable reflecting the prevalence of transfused patients used as a dependent variable. Variables that were not linearly

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