Introduction of universal prestorage leukodepletion of blood components, and outcomes in transfused cardiac surgery patients

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Objective: To assess whether introduction of universal leukodepletion (ULD) of red blood cells (RBCs) for transfusion was associated with improvements in cardiac surgery patient outcomes.

Methods: Retrospective study (2005-2010) conducted at 6 institutions. Associations between leukodepletion and outcomes of mortality, infection, and acute kidney injury (AKI) were modeled by logistic regression, and intensive care unit length of stay (LOS) in survivors was explored using linear regression. To examine trends over time, odds ratios (ORs) for outcomes of transfused were compared with nontransfused patients, including a comparison with nontransfused patients who were selected based on propensity score for RBC transfusion.

Results: We studied 14,980 patients, of whom 8857 (59%) had surgery pre-ULD. Transfusions of RBCs were made in 3799 (43%) pre-ULD, and 2525 (41%) post-ULD. Administration of exclusively leukodepleted, versus exclusively nonleukodepleted, RBCs was associated with lower incidence of AKI (adjusted OR 0.80, 95% confidence interval [CI] 0.65-0.98, $P = .035$), but no difference in mortality or infection. For post-ULD patients, no difference was found in mortality (OR 0.96, 95% CI 0.76-1.22, $P = .76$) or infection (OR 0.91, 95% CI 0.79-1.03, $P = .161$); however, AKI was reduced (OR 0.79 95% CI 0.68-0.92, $P = .003$). However, ORs for post-ULD outcomes were not significantly different in nontransfused, versus transfused, patients. Furthermore, those who received exclusively nonleukodepleted RBCs were more likely to have surgery post-ULD.

Conclusions: Universal leukodepletion was not associated with reduced mortality or infection in transfused cardiac surgery patients. An association was found between ULD and reduced AKI; however, this reduction was not significantly different from that seen in nontransfused patients, and other changes in care most likely explain such changes in renal outcomes. (J Thorac Cardiovasc Surg 2015;150:216-22)

See related commentary on pages 223-4.

Transfusion of red blood cells (RBCs) has been independently associated with adverse outcomes, including mortality, infection, multi-organ dysfunction, and increased hospital length of stay (LOS) in patients undergoing cardiac surgery.[1-4] Whether RBC transfusion is causally related to these outcomes is unknown, but one proposed mechanism for these effects is transfusion-related immunomodulation from leukocytes in RBC units.[5]

Previous randomized studies have reported benefits of leukodepleted RBCs, compared with nonleukodepleted RBCs, in cardiac surgery, including reduced postoperative mortality[6] and infection.[7] However, studies evaluating potential benefits after the introduction of universal

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Abbreviations and Acronyms
AKI = acute kidney injury
CI = confidence interval
LOS = length of stay
ICU = intensive care unit
OR = odds ratio
RBC = red blood cell
ULD = universal leukodepletion

leukodepletion (ULD), including cardiac surgery patients, have reported conflicting results. A Canadian study performed during the implementation of ULD reported a reduction in mortality, febrile events, and antibiotic use in a cohort of cardiac surgery, orthopedic, intensive care unit (ICU), and trauma patients.[8] In contrast, a United Kingdom study failed to demonstrate any reduction in infection rates or LOS in cardiac surgery and orthopedic patients after ULD was instituted.[9] A before-and-after study in France, in patients undergoing abdominal aortic surgery, demonstrated no reduction in postoperative infections.[10] In addition, a single-center randomized controlled study of 2780 patients in the United States found no difference in the primary outcomes of in-hospital mortality, LOS, or costs.[11]

Transfusion of RBCs has recently been reported to be independently associated with development of renal failure in cardiac surgery patients.[12] Although the potential mechanism for this association is unknown, an inflammatory basis has been proposed.[12] However, acute kidney injury (AKI) has not been widely studied as an outcome in the larger studies on potential benefits of implementation of ULD. In Australia, ULD was introduced in July 2008. We investigated whether the implementation of ULD was associated with a reduction in in-hospital mortality, infection, new renal failure, and ICU LOS in a cohort of cardiac surgery patients.

METHODS

Patients and Data Collection

All patients aged ≥18 years who underwent cardiac surgery at the 6 major teaching hospitals within the Australian state of Victoria (population approximately 5.3 million) that perform this surgery, between 2005 and 2010, were included in the analysis. The Australian and New Zealand Society for Cardiac and Thoracic Surgeons Cardiac Surgery Database collects data prospectively on all patients undergoing cardiac surgery at participating sites, using a standardized dataset and definitions. Information collected includes patient demographics, comorbid conditions, preoperative medications, surgery (type, urgency, and prior surgical history), intraoperative details, and patient outcomes.[13]

Laboratory results, including preoperative hemoglobin level, platelet count, coagulation profile, and creatinine level, were obtained from the laboratory information system at each of the 6 hospitals. Data on the type and number of blood products transfused (including modifications such as leukodepletion) were obtained for each patient from this system. These data were merged using the hospital site, and a unique hospital identifier within the database, for each patient.

Definitions

Patients who underwent surgery between 2005 and 2010 were categorized as having had surgery either before or after the introduction of ULD. From July 1, 2008, all RBC components manufactured in Australia were leukodepleted. Before this, leukodepleted RBCs were provided to patients with specific indications, which did not include cardiac surgery, or to other patients, if extra leukodepleted units were in inventory.

Given that the individual hospital blood bank inventory would have held nonleukodepleted units, for up to 42 days after the introduction of ULD, patients were classified as being post-ULD if their surgery occurred after August 11, 2008. Patients were classified as being transfused if they received ≥1 RBC units within 48 hours of surgery. This time period was chosen because previous studies have demonstrated effects of nonleukodepleted RBCs, within this perioperative time period,[14] and to ensure that transfusion occurred before the outcomes of interest. In addition, patients were categorized as having received either exclusively leukodepleted RBCs, exclusively nonleukodepleted RBCs, or a mixture of the 2.

Postoperative outcomes analyzed were in-hospital mortality, infection, AKI, and ICU LOS. Definitions for the outcomes were based on the Cardiac Surgery Database.[13] Infection included ≥1 of the following: pneumonia, deep sternal wound infection, and septicemia. Diagnosis of pneumonia required positive cultures of sputum or transtracheal aspirate combined with consistent clinical findings of pneumonia, including radiologic changes. Deep sternal wound infection required muscle and bone involvement as demonstrated by surgical exploration with positive cultures or treatment with antibiotics. Septicemia required positive blood cultures supported by ≥2 of the following: fever, elevated white cell count, elevated and increasing C-reactive protein, or an elevated and increasing erythrocyte sedimentation rate. The definition used for AKI was acute postoperative renal insufficiency resulting in ≥2 of the following: increased serum creatinine to >200 micromol/L; a doubling or greater increase in creatinine, compared with baseline preoperative value; or a new requirement for dialysis and/or hemofiltration.

Statistical Analysis

Summary statistics for continuous data are reported as mean and SD or median and interquartile range (IQR; 25th centile to 75th centile), as appropriate, and as number and percentage for categoric variables. Comparisons were performed using the Student t test for normally distributed data, the Wilcoxon rank-sum test for non-normally distributed data, and Pearson's χ^2 analysis for categoric data.

Logistic regression analyses explored the association between leukocyte depletion and the outcomes of mortality, infection, and renal failure, using a backward, step-wise approach. This association was analyzed by evaluating: (1) whether cardiac surgery was performed before or after ULD introduction; and (2) whether patients received only leukodepleted RBCs, compared with only nonleukodepleted RBCs (patients who received a mixture were excluded).

Variables associated with the outcomes of interest, with a P value of <.25, were considered for the multiple logistic regression models. Pearson's correlation was used to assess variables for potential colinearity, with the more clinically relevant variable selected, when present. A total of 35 patient and procedural variables were considered for inclusion, as well as hospital site. The relationship between leukocyte depletion and ICU LOS among survivors was explored using linear regression. Natural logarithmic transformation of LOS was used for regression.

Because changes in outcomes after the introduction of ULD may have been a result of other changes in care over time, we investigated whether statistical evidence showed a differential effect of the timing of surgery on outcomes in transfused, compared with nontransfused, patients, by including an interaction term (timing of surgery × ≥1 RBC units) in the regression models. Finally, given that more patients did not, versus did,

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