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 mortality⁶ 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 categorical 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 categorical 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 collinearity, 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 $\times \geq 1$ RBC units) in the regression models. Finally, given that more patients did not, versus did,

receive transfusion, and illness severity is known to differ as a result of transfusion, we repeated the analysis, including an equal number of nontransfused patients who had been selected based on a propensity score for RBC transfusion. Nontransfused patients with the highest propensity score, based on 35 variables associated with RBC transfusion, were selected for the time periods before and after leukocyte depletion. The analysis comparing outcomes pre- and post-ULD was then repeated for transfused and an equal number of non-transfused patients selected based on the propensity score.

All analyses were performed using the statistical software package Stata 11.2 (Stata Corporation, College Station, Tex). This study had approval from the human research ethics committees at participating institutions.

RESULTS

During the study period, 16,253 patients underwent cardiac surgery. Laboratory information system data were available for 14,980 (92%) of these patients, and these were included in the final analysis. Of these, 8857 (59%) had surgery before introduction of ULD.

Patient and Transfusion Characteristics

Patient and surgical characteristics before and after ULD was introduced are shown in Table 1. A slightly higher proportion of patients were transfused with ≥ 1 RBC units within 48 hours of surgery before ULD (3799 [43%] vs 2525 [41%], $P = .044$). The median number of RBC units transfused was 3 (IQR: 2-5), both before and after ULD ($P = .167$), with the range for all patients being 0 to 280.

A total of 1933 (25%) patients received ≥ 3 RBC units before ULD, and 1280 (25%) received ≥ 3 RBC units after ULD ($P = .902$). Of the 8656 who did not receive any RBC units within 48 hours of surgery, 1068 (12%) received >1 RBC unit subsequently during their admission. Of the 6324 patients transfused with ≥ 1 RBC unit within 48 hours of surgery, 2794 (44%) received exclusively leukodepleted RBCs; 2702 (43%) received exclusively nonleukodepleted RBCs; and 828 (13%) received a mixture. Only 480 (17%) of the group receiving exclusively leukodepleted RBCs had their surgery before the introduction of ULD.

Association Between Leukodepletion and Mortality, Infection, and Acute Kidney Injury

The overall rates of mortality, infection, and AKI were 445 (3.5%), 1181 (9%), and 904 (7%), respectively. In transfused patients, no statistically significant reduction was found in in-hospital mortality or infection after the introduction of ULD (Table 2); however, a reduction was found in the proportion of patients with AKI (10.5% vs 8.5%, $P = .01$).

After adjusting for the following factors, no difference in mortality or infection was found: hospital; age; gender; body mass index; prior myocardial infarction; comorbidities (diabetes, lung disease, peripheral or cerebrovascular disease, heart failure, dialysis); New York

Heart Association class; ejection fraction; preoperative laboratory parameters (hemoglobin level, platelet count, and creatinine level); surgical history; type and urgency of procedure; preoperative shock; preoperative medications (nitrates, antiplatelets, immunosuppressives); perfusion time; drain output in first 4 hours; and number of RBC units transfused. However, a reduction was found in AKI in post-ULD, compared with pre-ULD, patients (adjusted odds ratio [OR] 0.80, 95% confidence interval [CI] 0.68-0.93, $P = .003$) (Table 3).

To determine whether the OR differed for pre-ULD versus post-ULD transfused patients, compared with nontransfused patients, we assessed whether there was an interaction between RBC transfusion and having cardiac surgery pre- or post-ULD for each of the outcomes. We found no significant differences in the adjusted ORs for mortality, infection, or AKI (timing of surgery $\times \geq 1$ RBC interaction: OR 0.77 [95% CI 0.44-1.36, $P = .370$]; OR 1.22 [95% CI 0.93-1.60, $P = .155$]; and OR 0.85 [95% CI 0.63-1.14], $P = .269$, respectively). Therefore, the effect of timing of surgery (pre- or post-ULD) was not different in transfused, compared with nontransfused, patients.

The analysis was repeated to examine differences in mortality, AKI, and infection, according to those who received exclusively leukodepleted, versus nonleukodepleted, RBCs. The results were similar to those from the comparison of pre-ULD versus post-ULD transfused patients, with no difference in mortality or infection, but with a reduction in AKI (adjusted OR 0.80 [95% CI 0.65-0.98], $P = .035$) (Table 4).

Association Between Leukodepletion and Intensive Care Unit Length of Stay

The overall median ICU LOS in survivors was 25 hours (IQR: 21-49 hours) before ULD, and 27 hours (IQR: 21-56 hours) after ULD. For transfused patients, the median ICU LOS in survivors was 39 hours (IQR: 22-74 hours) before ULD, and 39 hours (IQR: 21-74 hours) after ULD. The median ICU LOS in survivors was 39.5 hours (IQR: 22-73 hours) in those who received exclusively nonleukodepleted RBCs, and 36.5 hours (IQR: 21-72 hours) in those who received exclusively leukodepleted RBCs.

After adjusting for characteristics (as outlined earlier), both timing of surgery (adjusted coefficient 0.103 [95% CI 0.077-0.129], $P < .001$) and RBC transfusion were associated with ICU LOS. However, no significant interaction was found between timing of surgery and RBC transfusion (timing of surgery $\times \geq 1$ RBC interaction: coefficient -0.005 [95% CI -0.055 to 0.045], $P = .846$), again implying that the effect of timing of surgery (ie, before vs after ULD) was not different in transfused, versus nontransfused, patients.

TABLE 1. Characteristics of all cardiac surgery patients and transfused cardiac surgery patients before and after introduction of universal leukodepletion

Characteristic	All patients		Transfused patients		Nontransfused patients	
	Pre-ULD n = 8857 (59%)	Post-ULD n = 6123 (41%)	Pre-ULD n = 3799 (60%)	Post-ULD n = 2525 (40%)	Pre-ULD n = 3801 (60%)	Post-ULD n = 2527 (40%)
Age (y)	67 (58-75)	68 (59-75)	70 (61-76)	70 (61-77)	65 (12)	65 (12)
Gender, male	6438 (73)	4410 (72)	2358 (62)	1562 (62)	2932 (77)	1932 (77)
Body mass index (kg/m ²), mean (SD)	28 (25-31)	28 (25-31)	27 (24-30)	27 (24-31)	28 (5)	29 (5)
Diabetes	2605 (29)	1824 (30)	1183 (31)	811 (32)	1146 (30)	769 (30)
Lung disease	1026 (12)	761 (12)	507 (13)	355 (14)	404 (11)	298 (12)
Prior myocardial infarction	3807 (43)	2421 (40)	1726 (45)	1069 (42)	1674 (44)	1013 (40)
Dialysis	166 (2)	99 (2)	114 (3)	77 (3)	42 (1)	19 (1)
Congestive heart failure	2675 (30)	1316 (21)	1435 (38)	707 (28)	1049 (28)	487 (19)
EF severely reduced	580 (7)	327 (5)	334 (9)	168 (7)	213 (6)	131 (5)
Clopidogrel within 5 d	671 (8)	442 (7)	310 (8)	185 (7)	265 (7)	176 (7)
Aspirin within 7 d	4127 (47)	3327 (54)	1913 (50)	1384 (55)	1754 (46)	1374 (54)
Anticoagulants at time of surgery	1576 (18)	1091 (18)	825 (22)	586 (23)	625 (16)	407 (16)
Steroids at time of surgery	156 (2)	116 (2)	96 (3)	77 (3)	43 (1)	30 (1)
Immunosuppressive	195 (2)	182 (3)	121 (3)	115 (5)	60 (2)	53 (2)
Inotropes	241 (3)	159 (3)	191 (5)	119 (5)	41 (1)	32 (1)
Intravenous nitrates	592 (7)	279 (5)	332 (9)	141 (6)	224 (6)	97 (4)
Infective endocarditis	233 (3)	162 (3)	170 (4)	109 (4)	53 (1)	39 (2)
IABP	473 (5)	326 (5)	337 (9)	208 (8)	120 (3)	89 (4)
Shock	226 (3)	154 (3)	176 (5)	111 (4)	43 (1)	30 (1)
Blood products in 48 h						
Transfused ≥1 RBC unit	3799 (43)	2525 (41)			NA	NA
Number of RBC units	0 (0-2)	0 (0-2)	3 (2-5)	3 (2-5)	NA	NA
Transfused ≥1 PLT unit	1733 (20)	1100 (18)	1412 (37)	935 (37)	292 (8)	137 (5)
Transfused ≥1 cryoprecipitate unit	811 (9)	576 (9)	711 (19)	520 (21)	89 (2)	52 (2)
Transfused ≥1 FFP unit	1661 (19)	1170 (19)	1379 (36)	1007 (40)	254 (7)	142 (6)
Laboratory parameters before surgery						
APTT (sec)	36 (29-50)	36 (30-48)	40 (31-60)	40 (32-58)	34 (29-45)	35 (29-43)
Platelet count × 10 ⁹ /L	279 (221-365)	280 (219-367)	282 (218-378)	288 (219-384)	276 (221-354)	275 (219-356)
Hemoglobin (g/L)	140 (125-150)	138 (123-149)	130 (115-143)	129 (115-142)	143 (131-152)	141 (130-151)
Creatinine, mmol/L	90 (80-110)	85 (72-103)	90 (80-120)	89 (74-110)	90 (80-110)	84 (71-100)
Surgical characteristics						
Procedure other than isolated CABG or valve	2198 (25)	1731 (28)	1195 (31)	946 (37)	804 (21)	625 (25)
Procedure urgency greater than for elective	3785 (43)	1659 (27)	1955 (51)	787 (32)	1498 (39)	613 (24)
Previous cardiac surgery	688 (8)	525 (9)	477 (13)	395 (16)	179 (5)	101 (4)
Perfusion time (min)	106 (83-138)	112 (87-146)	118 (92-154)	123 (94-161)	103 (83-131)	107 (84-136)
Drain output in first 4 h (mls)	195 (120-320)	202 (126-330)	240 (140-420)	250 (145-420)	190 (125-280)	184 (120-285)

Values are n (%) or median (IQR), unless otherwise specified. The nontransfused patients were selected based on propensity score for RBC transfusion. ULD, Universal leukodepletion; SD, standard deviation; EF, ejection fraction; IABP, intra-aortic balloon pump; NA, not applicable; RBC, red blood cell; PLT, platelet; FFP, fresh frozen plasma; APTT, activated partial thromboplastin time; CABG, coronary artery bypass graft.

Effect of the Number of RBC Unit Transfusions

To test whether leukocyte depletion had a dose-response effect on outcomes, we repeated the analysis, this time considering whether the timing of surgery interacted with the number of RBC units. As in the previous analysis, no significant difference was found in the adjusted ORs in transfused, versus nontransfused, patients, including for AKI (interaction of timing of surgery × number of RBC transfusions: OR 1.01 [95% CI 0.99-1.02], $P = .537$).

Propensity-Matched Analysis

Finally, given the differences between nontransfused patients, compared with transfused patients, we repeated the analysis, selecting an equal number of nontransfused patients based on a propensity score for RBC transfusion. Comparison of patients before and after ULD, who did not receive a transfusion, is shown in Table 1. The median propensity score for RBC transfusion was 0.58 (IQR: 0.39-0.77) for transfused patients, and 0.31 (IQR: 0.21-0.46) for nontransfused patients ($P < .001$).

TABLE 2. Comparison of outcomes from before and after introduction of universal leukodepletion, and for patients who received leukodepleted, versus nonleukodepleted, red blood cells in cardiac surgery transfusions

Outcome	All patients, N = 14,980			Transfused n = 6296			Transfused leukodepleted or nonleukodepleted RBCs* n = 5496		
	Pre-ULD	Post-ULD	P	Pre-ULD	Post-ULD	P	Nonleukodepleted	Leukodepleted	P
	n = 8857 (59%)	n = 6123 (41%)		n = 3799 (60%)	n = 2525 (40%)		n = 2702 (43%)	n = 2794 (44%)	
In-hospital mortality	294 (3.3)	177 (2.9)	.139	240 (6.3)	136 (5.4)	.125	145 (5.4)	143 (5.1)	.680
Infection	792 (8.9)	495 (8.1)	.066	510 (13.4)	310 (11.9)	.080	347 (12.8)	318 (11.4)	.097
AKI	615 (7.0)	110 (6.1)	.027	398 (10.5)	215 (8.5)	.010	284 (10.5)	236 (8.5)	.011
ICU LOS (h), median (IQR)	25 (21-49)	27 (21-56)	.004	39 (22-74)	39 (21-74)	.127	39.5 (22-73)	36.5 (21-72)	.0323

Values are n (%), unless otherwise indicated. RBC, Red blood cell; ULD, universal leukodepletion; AKI, acute kidney injury; ICU, intensive care unit; LOS, length of stay; IQR, interquartile range. *Excludes patients who received both leukodepleted and non leukodepleted RBCs.

Repeated analysis in this subset still showed no difference in the adjusted ORs for mortality, infection, or AKI before, versus after, ULD implementation, between transfused and nontransfused patients (timing of surgery $\times \geq 1$ RBC interactions: OR 0.75 [95% CI 0.42-1.32, $P = .313$]; OR 1.16 [95% CI 0.89-1.54, $P = .290$]; and OR 0.89 [95% CI 0.65-1.23, $P = .495$], respectively). In addition, no difference was found for ICU LOS after adjustment (timing of surgery $\times \geq 1$ RBC interaction: coefficient -0.017 [95% CI -0.07 to 0.35 , $P = .510$]).

DISCUSSION

Key Findings

In this study of 14,980 consecutive cardiac surgery patients from 6 hospitals, introduction of ULD was independently associated with a reduction in AKI and ICU LOS, but not in in-hospital mortality or infection. However, these changes in outcomes were not significantly different in transfused patients from those seen in nontransfused patients, and therefore, other changes in care, over time, most likely explain such changes in renal outcomes and LOS. Although patients who received exclusively nonleukodepleted RBCs were less likely to develop AKI, most had their surgery after the introduction of ULD, and therefore, these differences in outcomes could be attributable to other changes in care, over time.

TABLE 3. Adjusted odds ratios for post-, versus pre-universal leukodepletion, for all patients

Outcome	Adjusted OR	95% CI	P value
In-hospital mortality	0.96	0.76-1.21	.730
Infection	0.90	0.79-1.03	.142
Acute kidney injury	0.80	0.68-0.93	.003

Odds ratios are adjusted for hospital site, patient comorbidities, surgery type, surgery urgency and prior surgery history, preoperative medications, preoperative status (including shock and use of an intra-aortic balloon pump), preoperative laboratory values, perfusion time, drain loss, and number of red blood cells transfused. OR, Odds ratio; CI, confidence interval.

Relationship to Previous Studies

Previous randomized controlled studies in cardiac surgery have reported benefits from transfusion of leukodepleted RBCs, compared with nonleukodepleted RBCs. These studies have included reduction in postoperative infection⁷ and mortality,⁶ perhaps through an effect on the postoperative pro-inflammatory state, with previous studies reporting higher interleukin-6 levels and an associated increased risk of multi-organ dysfunction (which included renal impairment) with transfusion of nonleukodepleted RBCs.¹⁴

However, studies after the introduction of ULD have reported conflicting results with regard to mortality, infection, and LOS in cardiac surgery patients. A Canadian before-and-after study, conducted during the implementation of ULD, of 14,786 patients who received transfusion after cardiac surgery, or repair of hip fracture, or during ICU admission after surgery or trauma, reported a reduction in the adjusted odds of mortality after ULD.⁸ However, in the subgroup analysis of the 9525 cardiac surgery patients, no significant reduction in mortality was found (adjusted OR 0.88, [95% CI 0.72-1.07]). In contrast, a before-and-after study of 2095 consecutive patients undergoing elective coronary artery bypass grafting, or total hip and/or knee replacement in the United Kingdom, found no difference in postoperative LOS or the proportion of patients with suspected and proven postoperative infections. In the 852 transfused cardiac surgery patients, mortality was higher after introduction of ULD (OR 3.05 [95% CI 1.11-8.37], $P = .031$).

More recently, the effect of leukocyte depletion on the risk of developing AKI has been investigated. Both transfusion and anemia have been independently associated with risk of AKI after cardiac surgery.¹⁵ Whether RBC transfusion is causally related is unknown; however, possible mechanisms proposed include promotion of a pro-inflammatory state, impaired tissue oxygen delivery, and exacerbation of oxidative stress.¹² Romano and colleagues¹⁶ studied 147 matched pairs of transfused patients over a period of 4 years, during which ULD was

TABLE 4. Adjusted odds ratios for red blood cells that are exclusively nonleukodepleted versus exclusively leukodepleted

Outcome	Adjusted OR	95% CI	P value
In-hospital mortality	0.97	0.72-1.30	.844
Infection	1.11	0.91-1.34	.299
Acute kidney injury	0.80	0.65-0.98	.035

Odds ratios are adjusted for hospital site, patient comorbidities, surgery type, surgery urgency and prior surgery, preoperative medications, preoperative status (including shock and use of an intra-aortic balloon pump), preoperative laboratory values, perfusion time, drain loss, and number of red blood cells transfused. *OR*, Odds ratio; *CI*, confidence interval.

introduced, and reported a reduction in AKI from 51.7% to 41.5%. Their study was a single-institution study and did not account for any trends in rates of AKI over the course of the 4-year period.

The rate of AKI in that study¹⁶ was much higher than the rate in our study, which may be partly a result of the definition used, which was a RIFLE (risk, injury, failure, loss of function, end-stage renal disease) grade of R (risk: least-severe grade) or greater. In our study, although ULD was associated with a reduction in the proportion of cardiac surgery patients who developed AKI, this reduction seemed to be attributable to changes in care over time, because the OR for AKI in transfused patients was not significantly different than the OR in nontransfused controls.

Strengths and Limitations

Our study has several strengths. It included a large cohort of consecutive cardiac surgery patients from 6 institutions, using prospectively collected and validated data. We addressed the issue of change in care over time, by testing for an interaction between transfusion and timing of surgery. Through this analysis, we found that the reduction in AKI observed in the transfused cohort was not significantly different than that seen in nontransfused patients and could therefore not be attributed to benefits of ULD alone. Without this comparison, we might have overestimated the potential benefits of ULD in regard to AKI. In addition, we attempted to address the inherent differences between nontransfused “control” patients, compared with transfused patients, via selection of nontransfused patients based on a propensity score for RBC. This approach did not change the findings of our study.

The study has limitations that should be considered in interpreting the results. The study is observational and uses registry data that are not designed to address this particular study question. However, the registry data used were collected prospectively on all patients, reducing the risk of observation bias and laboratory information system data were used, which provide reliable information on transfused blood products in this population.¹⁷

Despite our attempts to adjust for many important patient and procedural factors in the multivariable analysis,

adjusting for all potential confounders, both measured and unmeasured, is not possible, and these may have influenced the outcomes of interest. Potential confounders include the use of antifibrinolytics, intravenous fluids, and antibiotics, which were not available for our analysis. Finally, we excluded patients who received a mixture of RBCs that were or were not leukodepleted from the subgroup comparison between patients receiving exclusively leukodepleted, versus nonleukodepleted, RBCs. By doing so, we likely excluded a cohort of higher-risk patients, because those who received both types of RBC were more likely to have received more RBCs. However, including these patients with the cohort who received only nonleukodepleted RBCs may have exaggerated the benefit of leukodepleted RBCs.

Implications of Study Findings

Studies into potential benefits of ULD are relevant, because provision of ULD is accompanied by substantial manufacturing costs, and although many countries have already adopted ULD routinely, this is not standard practice in all countries. For example, in the United States, according to the 2011 National Blood Collection and Utilization Survey Report,¹⁸ approximately 70% of whole blood/RBCs transfused in 2011 were leukodepleted. In this report, approximately 73% of US transfusing facilities responded that they had a policy of ULD. In the remaining 27% of facilities, without a policy of ULD, only 10% had a policy of transfusing only leukodepleted RBCs for cardiac surgery.¹⁸ Our study did not demonstrate a benefit of ULD for cardiac surgery patients that could not be attributed to other changes in care over time. For this reason, we recommend that future before-and-after studies in transfusion include a matched cohort of nontransfused patients for this reason.

CONCLUSIONS

In our large cohort study, we did not find an association between introduction of ULD and additional improvements in mortality, infection, or AKI beyond those that probably result from other changes in care over time. Our findings are in contrast to the results of other before-and-after studies, and randomized but smaller trials, and challenge the notion that ULD provides clinically important advantages in cardiac surgery patients.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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