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 non-leukodepleted 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 colleagues⁴ 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-	= cardiac surgery–associated acute kidney
AKI	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 pre-specified 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 categorical 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

TABLE 1. Clinical overview of population undergoing isolated coronary artery bypass grafting and at risk for blood transfusion

	Total	Not transfused	Transfused	P value
No. of patients	1034 (100%)	563 (54.4%)	471 (45.6%)	
Age (y, mean $\pm$ SD)	63.2 $\pm$ 9.4	60.9 $\pm$ 8.7	65.9 $\pm$ 9.3	<.001
Female (no.)	193 (18.7%)	51 (9.1%)	142 (30.1%)	<.001
Body surface area (m ² , mean $\pm$ SD)	1.84 $\pm$ 0.16	1.89 $\pm$ 0.15	1.78 $\pm$ 0.15	<.001
Diabetes (no.)	316 (30.6%)	169 (30%)	147 (31.2%)	.538
Hypertension (no.)	724 (70.0%)	394 (70.0%)	330 (70.1%)	.977
Hypercholesterolemia (no.)	429 (41.5%)	234 (41.6%)	195 (41.4%)	.656
Chronic obstructive pulmonary disease	139 (13.4%)	71 (12.6%)	68 (14.4%)	.391
Preoperative glomerular filtration rate (mL/min, mean $\pm$ SD)	80.1 $\pm$ 22.4	84.2 $\pm$ 21.3	75.2 $\pm$ 22.7	<.001
Chronic renal disease (no.)	39 (3.8%)	13 (2.3%)	26 (5.5%)	.048
Ejection fraction $\geq$ 35% (no.)	158 (15.3%)	75 (13.3%)	83 (17.6%)	.034
Hematologic disorder (no.)	16 (1.5%)	5 (0.9%)	11 (2.3%)	.520
History of hemorrhagic gastropathy (no.)	71 (6.9%)	38 (6.7%)	33 (7.0%)	.844
Preoperative anemia (hemoglobin <12 g/dL, no.)	314 (30.4%)	91 (16.2%)	223 (47.3%)	<.001
Preoperative hemoglobin (g/dL, mean $\pm$ SD)	13.4 $\pm$ 1.7	14.1 $\pm$ 1.3	12.6 $\pm$ 1.8	<.001
Use of warfarin (no.)	7 (0.7%)	2 (0.4%)	5 (1.1%)	.255
Use of ticlopidine (no.)	46 (4.5%)	18 (3.2%)	28 (6.0%)	.023
Use of clopidogrel (no.)	148 (14.4%)	76 (13.5%)	72 (15.4%)	.396
Use of aspirin (no.)	468 (45.4%)	253 (45.0%)	215 (45.9%)	.767
Urgent or emergency setting (no.)	326 (31.6%)	140 (24.8%)	186 (39.5%)	<.001
Resternotomy (no.)	10 (1.0%)	5 (0.9%)	5 (1.1%)	>.999
No. of distal anastomoses (mean $\pm$ SD)	2.66 $\pm$ 0.85	2.58 $\pm$ 0.86	2.76 $\pm$ 0.80	<.001
Pump time (min, mean $\pm$ SD)	83.5 $\pm$ 33.1	77.0 $\pm$ 27.5	91.3 $\pm$ 37.4	<.001
Aortic crossclamp time (min, mean $\pm$ SD)	44.8 $\pm$ 20.2	42.1 $\pm$ 18.1	48.1 $\pm$ 22	<.001
Indexed pump flow (L/[m ² min], mean $\pm$ SD)	2.37 $\pm$ 0.20	2.37 $\pm$ 0.23	2.38 $\pm$ 0.17	.480
Lowest hemoglobin on pump (g/dL, mean $\pm$ SD)	8.83 $\pm$ 1.31	9.4 $\pm$ 1.10	8.13 $\pm$ 1.20	<.001
Lowest oxygen delivery on pump (mean $\pm$ SD)	297 $\pm$ 49	315 $\pm$ 47	276 $\pm$ 43	<.001
Blood loss in first 24 h (mL, mean $\pm$ SD)	715 $\pm$ 350	658 $\pm$ 266	784 $\pm$ 418	<.001
Resternotomy for bleeding (no.)	24 (2.3%)	0 (0%)	24 (5.1%)	<.001
Respiratory complication	34 (3.3%)	7 (1.2%)	27 (5.7%)	<.001
Intra-aortic balloon pump (no.)	87 (8.4%)	18 (3.2%)	69 (14.6%)	<.001
Cardiac complication (no.)	70 (6.8%)	16 (2.8%)	54 (11.5%)	<.001
Cerebral complication (no.)	20 (1.9%)	15 (3.2%)	5 (0.9%)	.007
RIFLE class R or worse (no.)	391 (37.8%)	183 (32.5%)	208 (44.2%)	<.001
Use of continuous venovenous hemofiltration (no.)	34 (3.3%)	2 (0.4%)	32 (6.8%)	<.001
Pneumonia (no.)	54 (5.2%)	20 (3.6%)	34 (7.2%)	.031
Bloodstream infection (no.)	28 (2.7%)	8 (1.4%)	20 (4.2%)	.002
Mediastinitis (no.)	21 (2.0%)	8 (1.4%)	13 (2.8%)	.100
Intensive care unit stay (d, mean $\pm$ SD)	3.3 $\pm$ 4.0	2.5 $\pm$ 1.4	4.2 $\pm$ 5.6	<.001
Hospital stay (d, mean $\pm$ SD)	8.1 $\pm$ 4.8	7.2 $\pm$ 2.5	9.2 $\pm$ 6.4	<.001
In-hospital mortality (no.)	32 (3.1%)	1 (0.2%)	31 (6.6%)	<.001
Red blood cells transfused (units, mean $\pm$ SD)				
Total		1.98 $\pm$ 2.74		
On pump		0.53 $\pm$ 1.03		
In operating room		0.77 $\pm$ 1.37		
In intensive care unit		1.03 $\pm$ 1.85		
Total fresh plasma transfused (units, mean $\pm$ SD)		1.49 $\pm$ 3.1		
Total platelets transfused (units, mean $\pm$ SD)		1.58 $\pm$ 3.9		

RIFLE, Risk, Injury, Failure, Loss of function, End-stage renal disease.

related were mathematically transformed, categorized along appropriate cut points, or converted into multiple dichotomous variables. A propensity score for the likelihood of receiving RBC transfusion was calculated for each patient with multivariable discriminant analysis by single-step entry method. All significant variables at bivariate analysis ($P \leq .05$) were included in the model. The C statistic for such a propensity model was 0.80. With the aim of preventing indication bias for transfusion, the propen-

sity score was used to match among patients who actually received blood transfusions ($n = 471$) those receiving leukodepleted RBCs with those receiving nonleukodepleted RBCs, and this yielded 147 well-matched pairs (294 patients; Table 2). The maximal accepted discrepancy between the scores of patient pairs to be matched was set at $\pm 1\%$. Details on propensity matching are reported in Appendix Tables 1 through 3. The latter patient subset was the final study sample in which bivariate analysis was used for

TABLE 2. Unmatched and matched transfused samples

	Unmatched			Matched		
	Not depleted	Depleted	P value	Not depleted	Depleted	P value
No. of patients	262 (55.6%)	209 (44.4%)		147 (50%)	147 (50%)	
Age (y, mean $\pm$ SD)	65.5 $\pm$ 9.3	66.3 $\pm$ 9.4	.372	66.7 $\pm$ 8.7	66.3 $\pm$ 9.3	.709
Female (no.)	77 (29.4%)	65 (31.1%)	.688	50 (34.0%)	40 (27.2%)	.127
Body surface area (kg/m ² , mean $\pm$ SD)	1.79 $\pm$ 0.15	1.77 $\pm$ 0.15	.178	1.78 $\pm$ 0.16	1.78 $\pm$ 0.15	.876
Diabetes (no.)	78 (29.8%)	69 (33.0%)	.340	37 (25.2%)	35 (23.8%)	.882
Hypertension (no.)	174 (66.4%)	156 (74.6%)	.053	98 (66.7%)	106 (72.1%)	.376
Hypercholesterolemia (no.)	105 (40.1%)	90 (43.1%)	.513	63 (42.9%)	64 (43.5%)	.500
Chronic obstructive pulmonary disease	34 (13.0%)	34 (16%)	.313	17 (11.6%)	23 (15.6%)	.198
Preoperative glomerular filtration rate (mL/min, mean $\pm$ SD)	75.5 $\pm$ 21.6	74.7 $\pm$ 24.2	.706	75.5 $\pm$ 21.8	75.9 $\pm$ 25.4	.892
Chronic renal disease (no.)	12 (4.6%)	14 (6.7%)	.317	7 (4.8%)	10 (6.8%)	.309
Ejection fraction $\geq$ 35% (no.)	54 (20.6%)	29 (13.9%)	.059	31 (21.1%)	19 (12.9%)	.062
Hematologic disorder (no.)	7 (2.7%)	4 (1.9%)	.588	6 (4.1%)	3 (2.0%)	.250
History of hemorrhagic gastropathy (no.)	19 (7.3%)	14 (6.7%)	.815	9 (6.1%)	10 (6.8%)	.500
Preoperative anemia (hemoglobin $<$ 12 g/dL, no.)	111 (42.4%)	112 (53.6%)	.015	70 (47.6%)	78 (53.1%)	.207
Preoperative hemoglobin (g/dL, mean $\pm$ SD)	12.8 $\pm$ 1.8	12.5 $\pm$ 1.7	.046	12.6 $\pm$ 1.9	12.5 $\pm$ 1.6	.770
Use of warfarin (no.)	2 (0.8%)	3 (1.5%)	.469	2 (1.4%)	2 (1.4%)	.684
Use of ticlopidine (no.)	19 (7.3%)	9 (4.4%)	.192	11 (7.5%)	7 (4.8%)	.243
Use of clopidogrel (no.)	31 (11.8%)	41 (19.9%)	.016	20 (13.6%)	25 (17.2%)	.243
Use of aspirin (no.)	116 (44.3%)	99 (48.1%)	.415	70 (47.6%)	66 (45.5%)	.404
Urgent or emergency setting (no.)	85 (32.4%)	101 (48.3%)	.001	51 (34.7%)	63 (42.8%)	.278
Resternotomy (no.)	4 (1.5%)	1 (0.5%)	.270	2 (1.4%)	0 (0%)	.249
No. of distal anastomoses (mean $\pm$ SD)	2.84 $\pm$ 0.82	2.67 $\pm$ 0.77	.031	2.78 $\pm$ 0.80	2.65 $\pm$ 0.70	.220
Pump time (min, mean $\pm$ SD)	87.8 $\pm$ 36.3	95.7 $\pm$ 38.4	.022	92.8 $\pm$ 40	94.5 $\pm$ 38	.717
Aortic crossclamp time (min, mean $\pm$ SD)	46.1 $\pm$ 21.5	50.5 $\pm$ 22.5	.032	47.3 $\pm$ 22	49.5 $\pm$ 21	.397
Indexed pump flow (L/[m ² min], mean $\pm$ SD)	2.37 $\pm$ 0.17	2.38 $\pm$ 0.17	.433	2.37 $\pm$ 0.19	2.38 $\pm$ 0.20	.719
Lowest hemoglobin on pump (g/dL, mean $\pm$ SD)	8.1 $\pm$ 1.14	8.20 $\pm$ 1.21	.321	8.0 $\pm$ 1.15	8.1 $\pm$ 1.20	.285
Lowest oxygen delivery on pump (mean $\pm$ SD)	274 $\pm$ 41	279 $\pm$ 44	.433	270 $\pm$ 42	275 $\pm$ 46	.278
Blood loss in first 24 h (mL, mean $\pm$ SD)	777 $\pm$ 397	792 $\pm$ 443	.682	783 $\pm$ 379	806 $\pm$ 422	.616
Red blood cells transfused (units, mean $\pm$ SD)						
Total	3.9 $\pm$ 3.1	4.2 $\pm$ 2.7	.448	4.2 $\pm$ 3.2	4.2 $\pm$ 2.7	.985
In operating room	1.53 $\pm$ 1.6	1.84 $\pm$ 1.6	.037	1.66 $\pm$ 1.5	1.78 $\pm$ 1.6	.247
In intensive care unit	2.20 $\pm$ 2.5	1.97 $\pm$ 2.0	.270	2.39 $\pm$ 2.7	2.1 $\pm$ 2.0	.174
Total fresh plasma transfused (units, mean $\pm$ SD)	2.6 $\pm$ 3.9	2.6 $\pm$ 3.4	.98	2.5 $\pm$ 4.1	2.7 $\pm$ 3.6	.606
Total platelets transfused (units, mean $\pm$ SD)	2.7 $\pm$ 5.8	2.7 $\pm$ 4.2	.97	2.7 $\pm$ 6.7	2.7 $\pm$ 4.3	.812
Resternotomy for bleeding (no.)	13 (5.0%)	11 (5.3%)	.883	7 (4.8%)	7 (4.8%)	.607
Respiratory complication (no.)	10 (3.8%)	17 (8.1%)	.045	9 (6.1%)	13 (8.8%)	.253
Cardiac complication (no.)	24 (9.2%)	30 (14.4%)	.079	10 (10.9%)	19 (12.9%)	.362
Intra-aortic balloon pump (no.)	26 (9.9%)	43 (20.6%)	.001	17 (11.6%)	31 (21.1%)	.020
Cerebral complication (no.)	11 (4.2%)	4 (1.9%)	.127	5 (3.4%)	2 (1.4%)	.224
RIFLE class R or worse (no.)	127 (48.5%)	81 (38.7%)	.039	76 (51.7%)	61 (41.5%)	.045
Use of continuous venovenous hemofiltration (no.)	17 (6.5%)	15 (7.2%)	.768	14 (9.5%)	11 (7.5%)	.338
Pneumonia (no.)	12 (4.6%)	22 (10.5%)	.048	10 (6.8%)	15 (10.2%)	.125
Bloodstream infection (no.)	11 (4.2%)	9 (4.3%)	.880	8 (5.4%)	7 (4.8%)	.545
Mediastinitis (no.)	9 (3.4%)	4 (1.4%)	.317	2 (1.4%)	3 (2.0%)	.652
Intensive care unit stay (d, mean $\pm$ SD)	3.9 $\pm$ 5.7	4.5 $\pm$ 5.3	.317	4.4 $\pm$ 5.7	4.7 $\pm$ 5.6	.557
Hospital stay (d, mean $\pm$ SD)	8.6 $\pm$ 6.9	9.9 $\pm$ 6.5	.034	9.2 $\pm$ 6.7	10.3 $\pm$ 6.6	.147
In-hospital mortality (no.)	21 (8.0%)	10 (4.8%)	.160	17 (11.6%)	8 (5.4%)	.046

RIFLE, Risk, Injury, Failure, Loss of function, End-stage renal disease.

outcome measurement. Finally, multivariable logistic regression analysis was used to identify predictors of CSA-AKI and in-hospital mortality, forcing the propensity score to enter the models as a covariate to distinguish between the real effects of transfusion and those of the conditions indicating transfusion. Because propensity score analysis, although improving specificity of the results, actually reduces statistical power, outcomes were also

analyzed with conventional multivariable regression model (backward stepwise) on the entire cohort of transfused patients ($n = 471$). Adjustment was made only for preoperative and intraoperative confounders, and nonleuko-depleted transfusion was forced as a covariate in the regression model to assess the direct and indirect effects of leukoreduction on outcomes. Data are expressed as mean $\pm$ SD for continuous variables and as percentages for

FIGURE 1. RIFLE (Risk, Injury, Failure, Loss of function, End-stage renal disease) scoring in matched pairs. *Not-D*, Nonleukodepleted; *D*, leukodepleted.

categoric variables. All statistical analyses were performed with SPSS 13.0 (SPSS Inc, an IBM Company, Chicago, Ill).

RESULTS

Study Sample Features

Transfused patient subsets in the 2 study periods proved inhomogeneous with respect to preoperative and perioperative features as well as in-hospital process of care characteristics. Propensity matching allowed analysis of 147 well-matched pairs (Table 2).

Study End Points in Unmatched and Propensity-Matched Groups

Both incidence of CSA-AKI class R or greater and in-hospital mortality were higher among unmatched patients

with nonleukodepleted transfusions, who otherwise were significantly less affected by respiratory complications and pneumonia. After propensity matching, patients in the nonleukodepleted group still showed significantly worse outcomes. Indeed, as reported in Table 2, they had a significantly higher incidence of CSA-AKI. RIFLE scores in the 2 groups are reported in Figure 1. Consistently, in-hospital mortality was higher. Differences in other in-hospital complications were not significant. The observed relative risk reductions for the measured outcomes were nearly 20% for CSA-AKI and 50% for in-hospital death after the introduction of the leukodepletion program.

Multivariable Regression Modeling for Study End Points

Multivariable logistic regression analysis for primary end points is reported in Table 3. In the entire cohort of transfused patients, predictors of in-hospital mortality were female sex, transfusion, and preoperative anemia; predictors of CSA-AKI were hypertension, IABP, crossclamp duration, and transfusion. Because the number of units transfused and the propensity score for transfusion were collinear variables, the former was not included in the adjusted model to avoid redundancy.

With respect to propensity-matched groups, IABP, RIFLE scoring, and propensity scoring for transfusion proved independent predictors of in-hospital mortality. IABP and nonleukodepleted transfusions emerged as independent predictors of CSA-AKI.

DISCUSSION

This before-and-after study aimed to evaluate the effects of the implementation of a universal leukoreduction

TABLE 3. Logistic regression modeling for cardiac surgery–associated acute kidney injury and in-hospital mortality

	β	Odds ratio	95% Confidence interval	P value
Renal dysfunction in transfused patients (n = 471)				
Nonleukodepleted transfusions	0.61	1.85	1.23–2.76	.003
Hypertension	0.49	1.63	1.06–2.50	.025
Intra-aortic balloon pump	0.67	1.95	1.10–3.46	.022
Aortic crossclamp time	0.013	1.01	1.004–1.023	.003
Transfusion (per unit)	0.13	1.14	1.05–1.23	<.001
In-hospital mortality among transfused patients (n = 471)				
Female sex	0.97	2.65	1.08–6.5	.033
Transfusion (per unit)	0.21	1.23	1.10–1.37	<.001
Preoperative anemia	0.95	2.6	1.0–6.7	.05
Renal dysfunction (n = 147 matched pairs)				
Intra-aortic balloon pump	0.764	2.147	1.128–4.085	.020
Leukodepleted transfusions	–0.493	0.611	0.381–0.979	.040
In-hospital mortality (n = 147 matched pairs)				
Propensity score for transfusions	0.958	2.606	1.930–3.851	<.001
Intra-aortic balloon pump	–1.704	0.182	0.047–0.798	.030
RIFLE class R or worse	2.300	9.970	8.710–50.082	<.001

RIFLE, Risk, Injury, Failure, Loss of function, End-stage renal disease.

program on morbidity and mortality after CABG. Transfused patient subsets in the 2 study periods proved inhomogeneous with regard to preoperative and perioperative features as well as in-hospital process of care characteristics. Indeed, patients operated on during the latter phase were sicker and more often in unstable condition preoperatively and thus more subject to cardiac and respiratory complications. Propensity-matching data processing allowed analysis of 147 well-matched pairs, which represented a subset of transfused patients homogeneous with regard to factors predisposing toward transfusion, thus excluding possible effects of arbitrariness in transfusional triggers. Main findings of the analysis were that the introduction of a leukoreduction program in a tertiary care cardiac surgery center yielded (1) similar incidences of major postoperative infections and of cardiac and respiratory complications, (2) significantly reduced incidence of CSA-AKI, and (3) reduced in-hospital mortality.

Data regarding infectious complications deserve some consideration. Incidences of surgical site infections and ventilator-associated pneumonia and bloodstream infections proved similar in matched pairs, and none of these emerged as a predictor in regression analysis for death. Such results are at odds with earlier reports on the benefits of leukoreduction, yet consistent with more recent experiences and reviews.^{2,4,6}

The incidence of CSA-AKI, according to a variety of historical definitions, usually ranges from 0.3% to 29.7%.¹⁰ In the overall study sample, a reduction of GFR greater than 50% was detected in as many as 5.3% of the patients, with a need for renal replacement therapy in 3.3%, with higher incidences in transfused subsets. The development of CSA-AKI is associated with increased morbidity and mortality and resource use. As authoritatively outlined, the pathophysiology of such a dreaded complication is likely to involve the following mechanisms, processes, factors, or pathways: (1) exogenous and endogenous toxins, (2) metabolic factors, (3) ischemia–reperfusion, (4) neurohormonal activation, (5) inflammation, and (6) oxidative stress.¹¹ Transfusion of allogeneic RBCs is increasingly recognized as a risk factor for adverse outcomes after cardiac surgery, including the development of CSA-AKI.¹² Leukocytes in transfused blood are associated with several posttransfusion immunomodulatory effects.¹³ Although leukocytes are known to play an important role in the development of acute kidney injury, the contribution of leukocytes in transfused blood products has not been fully investigated.^{14,15}

In this series, multivariable regression modeling revealed that RIFLE class R or higher independently predicted in-hospital death, consistent with previous studies in the cardiac surgical setting.¹⁶ Regression modeling for CSA-AKI disclosed the predictive roles of low output, severe ischemia, and cardiogenic shock conditions necessitating IABP placement and the protective effects of leukoreduced transfusion.

Although the former result is intuitively explained in the view of a more compromised hemodynamic state causing prerenal failure, the mechanism underlying the latter evidence, namely the pathophysiology of CSA-AKI, is complex and multifactorial.¹¹ Cardiopulmonary bypass–related ischemia–reperfusion injury initiates changes in vascular endothelial cells, tubular epithelial cells, and leukocytes that result in the loss of immune system homeostasis in the kidney. The ensuing inflammation leads to kidney parenchymal cell death and in severe cases to CSA-AKI.^{17,18} There is a growing body of basic science evidence demonstrating that whatever the prime etiology, the effectors of acute renal damage include immune mediators. On the other hand, in the clinical setting, it has been widely demonstrated that leukoreduction may improve outcomes.^{19–22} A recent review of the various types of leukocyte-depleting filtration strategies in cardiac surgery has further elucidated the interactions between leukocyte activation and renal dysfunction.³ In particular, the randomized, controlled trial by Tang and coworkers¹⁹ focusing on sensitive indicators such as urinary microalbumin and urinary retinol binding protein disclosed a significantly greater degree of injury to renal tubules and glomeruli in patients who did not have leukocyte depletion.¹⁹

In-hospital mortality in the overall patients subset was significantly higher among transfused patients than among their nontransfused counterparts (0.2% vs 6.6%), in accordance with other major series.^{1,12} To evaluate the effects on hospital outcomes of leukocytes in blood products administered during cardiac surgery, several authoritative studies are available.^{2,4,20–23} In most of them, leukoreduction was associated with lower mortality. Consistently, the introduction of a universal leukoreduction program was associated with a significant reduction in fatality rate in matched pairs at our institution. The exact mechanism associated with such decreased mortality has not yet been unraveled. In this series, as shown by multivariable modeling, the reduction in mortality was directly related to the preservation of renal function, impairment of which is known as one of the strongest independent predictors of death after CABG.^{10,11} The protective effect exerted by IABP support was consistent with major series.²⁴ Finally, it is noteworthy that the propensity score for the likelihood of receiving transfusion appeared as another independent predictor of in-hospital mortality. Data for hospital outcomes from the propensity-matched analysis confirmed those derived from multivariable regression models on the overall cohort of transfused patients and were consistent with those reported in most series.

Study Overview

Several study limitations should be considered for a thorough data interpretation. First, the single-center setting, although a guarantee of uniform processes of care, especially in terms of transfusion triggers, closely reflects the influence

of specific standards of clinical practice and a unique patient population that may have led to results not readily transferable to other patient populations. Second, before-and-after study designs are usually susceptible to selection and information biases. Indeed, the lack of blinding and the use of cohorts from different periods rather than prospective randomization do not prevent uneven distribution of patients with different demographic characteristics and risk factors and also overlook possible differences in the level of care with time. In this study, however, the inclusion of all consecutive patients admitted for CABG, prospective data mining through the hospital's quality assurance program, and correctness of statistical tools in balancing for confounders helped to make results objective and transferable.

Finally, no evaluation was performed of possible dose dependence of nonleukodepleted versus leukodepleted RBCs' effect on CSA-AKI and mortality. Patients with the highest propensity scores for transfusion, that is, those entering in matched comparison, were also those with the greatest numbers of units received, and this hampered any possible dose-dependence assessment.

CONCLUSIONS

To the best of our knowledge, this is the first time that the already reported lower mortality with leukodepleted transfusions has been demonstrated to be associated with a lower rate of CSA-AKI. The pathophysiologic mechanisms leading to these potential health benefits have not been elucidated. Further large, prospective clinical trials are warranted to demonstrate the efficacy of a leukoreduction strategy in the cardiac surgical setting. Cost-effectiveness of a universal application of prestorage leukodepletion needs further evaluation. Future clinical trials should be undertaken to verify in a prospective, randomized design the benefits of allogeneic RBC leukodepletion demonstrated in this study in terms of hospital outcomes, and in particular to elucidate the relationship between reduced mortality and decreased incidence of renal failure.

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APPENDIX TABLE 1. Variables used for propensity scoring

	Transfusion	
	No	Yes
Sex	28.529	29.787
Body surface area	90.114	87.062
Kidney disease	7.077	7.515
Preoperative estimated glomerular filtration rate	0.220	0.210
Diabetes	0.490	0.421
Continuous venovenous hemofiltration	1.479	2.572
First-day drainages	0.008	0.009
Hematologic disorders	−1.560	−1.481
Use of ticlopidine	2.762	3.578
Surgical indication criteria	−1.418	1.054
No. of bypass grafts	3.048	3.255
Low preoperative ejection fraction	1.845	1.961
Reoperation for infection	−4.860	−4.832
Reoperation for excessive bleeding	1.931	3.722
Intra-aortic balloon pump	1.193	2.044
Cardiopulmonary bypass time	0.054	0.064
Oxygen delivery	0.136	0.124
Preoperative anemia	4.600	6.163
Respiratory complications	3.770	3.978
Cardiac complications	0.992	1.618
Cerebral complications	−2.316	−1.681
Constant	−141.527	−136.399

Fisher’s linear discriminant functions.

APPENDIX TABLE 2. Test for risk score equality in matched pairs: Discriminant scores

	N	Mean	SD	SE	95% Confidence interval for mean		Minimum	Maximum
					Lower bound	Upper bound		
Not depleted	147	0.9760920	1.10574557	0.09120036	0.7958485	1.1563354	−1.38638	5.56434
Depleted	147	0.9745711	1.10126990	0.09083121	0.7950572	1.1540850	−1.36490	5.39681
Total	294	0.9753315	1.10162554	0.06424811	0.8488853	1.1017778	−1.38638	5.56434

APPENDIX TABLE 3. Test for risk score equality in matched pairs: Analysis of variance discriminant scores

	Sum of squares	df	Mean square	F	P value
Between groups	0.000	1	0.000	0.000	.991
Within groups	355.578	292	1.218		
Total	355.579	293			