Double-Blind, Randomized Controlled Trial on the Effect of Leukocyte-Depleted Erythrocyte Transfusions in Cardiac Valve Surgery

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Background—Leukocytes in allogeneic blood transfusions are believed to be the cause of immunomodulatory events. A few trials on leukocyte removal from transfusions in cardiac surgery have been conducted, and they showed inconclusive results. We found in a previous study a decrease in mortality rates and number of infections in a subgroup of more heavily transfused patients.

Methods and Results—Patients (n=496) undergoing valve surgery (with or without CABG) were randomly assigned in a double-blind fashion to receive standard buffy coat–depleted (PC) or prestorage, by filtration, leukocyte-depleted erythrocytes (LD). The primary end point was mortality at 90 days, and secondary end points were in-hospital mortality, multiple organ dysfunction syndrome, infections, intensive care unit stay, and hospital stay. The difference in mortality at 90 days was not significant (PC 12.7% versus LD 8.4%; odds ratio [OR], 1.52; 95% confidence interval [CI], 0.84 to 2.73). The in-hospital mortality rate was almost twice as high in the PC group (10.1% versus 5.5% in the LD group; OR, 1.99; 95% CI, 0.99 to 4.00). The incidence of multiple organ dysfunction syndrome in both groups was similar, although more patients with multiple organ dysfunction syndrome died in the PC group. LD was associated with a significantly reduced infection rate (PC 31.6% versus LD 21.6%; OR, 1.64; 95% CI, 1.08 to 2.49). In both groups, intensive care unit stay and hospital stay were similar, and postoperative complications increased with the number of transfused units.

Conclusions—Mortality at 90 days was not significantly different; however, a beneficial effect of LD in valve surgery was found for the secondary end points of in-hospital mortality and infections. **(*Circulation*. 2004;109:2755-2760.)**

Key Words: leukocytes ■ infection ■ mortality ■ bypass ■ valves

Despite blood-sparing developments, blood transfusions still play a pivotal role in many large operations. Because of advances in transfusion medicine, allogeneic blood transfusions carry minimal risks for transmission of diseases. However, as it has been shown that allogeneic blood transfusions impair the immune response against cadaver kidney grafts,[1] there is concern that blood transfusions could also suppress the recipients immune response against cancer and infections.[2,3] These effects are often referred to as transfusion-related immunomodulation (TRIM).[4] Many factors in transfusions might contribute to TRIM, but leukocytes and soluble factors mediated by leukocytes in blood transfusions are considered of possible importance.[5,6] The depletion of leukocytes by filtration of blood products has been applied for many years to reduce human leukocyte antigen (HLA) alloimmunization and cytomegalovirus transmission for patients at risk. A limited number of clinical studies investigated whether leukocyte-depleted erythrocyte concentrates diminish TRIM.[6] The only prospective, randomized controlled trial (RCT) that compared the recurrence of colorectal cancer after perioperative transfusions with leukocyte-depleted versus buffy coat-depleted erythrocytes found no benefit.[7] The effect of leukocyte-depleted erythrocytes on postoperative infections after abdominal surgery has been studied in 5 RCTs, with conflicting results.[8–12]

Generally, in complex cardiac surgery, more erythrocyte concentrates are transfused than in abdominal surgery.[13] Two RCTs on cardiac surgery have been performed, and they showed inconclusive results on the incidence of postoperative infections.[14,15] Two other studies were not focused on cardiac surgery.[16,17] In one study, a nonsignificant beneficial difference of leukocyte-depleted erythrocytes in severe infections was found[16]; the other found no decrease in antibiotic usage, their parameter for infections.[17] We observed in one RCT

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comparing leukocyte-depleted versus buffy coat–depleted erythrocytes in patients undergoing coronary artery bypass grafting (CABG), with or without valve replacement, a significant reduction in postoperative infections only in the patients receiving ≥4 U.[15] Unexpectedly, in this study, a reduced mortality rate in the group receiving leukocyte-depleted erythrocytes was found. This difference was due to the near absence of death by multiple organ dysfunction syndrome (MODS) in the patients receiving leukocyte-depleted erythrocytes. These results were the reason to initiate a prospective double-blind, 2-center RCT to detect possible differences in postoperative complications. This trial was performed in adults undergoing cardiac valve surgery (with or without CABG) because these patients do have a high probability of receiving ≥4 U erythrocytes and have an increased risk on postoperative complications.[15]

Methods

Patients and Design

A prospective, randomized, double-blind controlled trial was conducted between June 1999 and May 2001 in adult patients >18 years undergoing valve surgery (with or without CABG) in 2 university hospitals (Academic Medical Center and Leiden University Medical Center) in The Netherlands. The ethics review boards of both hospitals approved the trial protocol. The local trial coordinator collected written informed consent. Patients with a medical indication for leukocyte-depleted erythrocytes (LDs) and patients who had received blood transfusions within the previous 3 months were ineligible. When blood for compatibility testing of the participating patients was sent to the hospital transfusion service, the technicians randomly assigned the patients by opening a sealed and numbered envelope. The patients were randomly assigned into 2 groups: when there was an indication for transfusions, one group received buffy coat–depleted packed cells (PCs), which was at that time the standard product in The Netherlands, and the other group received prestorage by filtration of LDs. The patients, surgeons, anesthesiologists, and the trial coordinators were blinded to the random assignment, as the technicians placed uniform study labels on the description on the erythrocyte bags. In the hospital electronic information system, a code was used during the study period to hide the random assignment.

For the assessment of the preoperative risk of the patients, the score model described by Parsonnet was applied.[18] Surgical and anesthetic procedures were performed according to the standards of the hospitals. The hospitals used similar transfusion triggers for erythrocytes, plasma, and platelets. Not all patients underwent induced hypothermia (29° to 33°C). In one hospital, aprotinin was used in some patients; this hospital had a medium-care ward. Prophylactic antibiotics were given to all patients for 48 hours. After surgery, the patients were monitored at the intensive care unit (ICU); they were discharged from the ICU when there was no more need for inotropes and intubation.

Blood Products

PCs were prepared by centrifugation of whole blood at 3000 rpm for 10 minutes within 20 hours after withdrawal. Buffy coat and plasma were removed, and erythrocytes were reconstituted with 100 mL saline-adenine-glucose-mannitol. The average leukocyte content was $0.7\pm0.4\times10^9$ per unit. The average hemoglobin content was 59±5 g/unit. LDs were prepared before storage within 24 hours after withdrawal by passage of the buffy coat–depleted erythrocytes through a leukocyte filter (Cellselect-Optima, NPBI International-Fresenius HemoCare). The average leukocyte content was $0.15\pm0.02\times10^6$ per unit and the average hemoglobin content was 54±4 g/unit. The quality controls of the blood products were according to the requirements of the blood product specifications in The Netherlands.

Platelet concentrates were prepared from pooled buffy coats and were all leukocyte-depleted by filtration ($<1\times10^6$ leukocytes per product) before storage.

Data Collection

Preoperative and postoperative clinical and laboratory data and transfusion data were registered daily and collected by the local trial coordinator from the patient records and the hospital electronic information systems. The scoring of organ dysfunction was assessed retrospectively on the basis of the daily records. We used parameters for organ dysfunction as described by Knaus et al.[19] MODS was defined as the failure of ≥2 organ systems. Infections were scored

TABLE 1. Baseline Characteristics

	PC (n=237)	LD (n=237)
Age, y	66.6±12.5	65.3±14.7
Hospital A/B, n	126/111	130/107
Female	102 (43.0)	113 (47.7)
Myocardial infarction	30 (12.7)	29 (12.2)
Hypertension	60 (25.3)	68 (28.7)
Diabetes mellitus	33 (13.9)	22 (9.3)
Heart failure	48 (20.3)	59 (24.9)
Parsonnet score	13.5±8.6	13.5±8.0
0 to 4	31 (13.1)	19 (8.0)
5 to 9	53 (22.4)	61 (25.7)
10 to 14	57 (24.0)	65 (27.4)
15 to 19	39 (16.5)	36 (15.2)
≥20	57 (24.0)	56 (23.6)
Surgery		
Valve	164 (69.2)	156 (65.8)
Valve+CABG	73 (30.8)	81 (34.2)
Aortic valve	160 (67.5)	172 (72.6)
Mitral valve	79 (33.3)	64 (27.0)
Other valves	16 (6.8)	16 (6.8)
Multivalves	12 (5.1)	17 (7.2)
Reoperations	18 (7.6)	12 (5.1)
Cardiopulmonary bypass, min	143±62	139±60
Aortic cross-clamping, min	96±45	99±47
Rethoracotomy	36 (15.2)	26 (11.0)
Normothermia	44 (18.6)	48 (20.3)
Use of aprotinin	88 (37.1)	86 (36.3)
Erythrocyte transfusions		
Units, n	6.2±7.1	5.9±6.1
0	21 (8.9)	21 (8.9)
1 to 3	85 (35.9)	71 (29.9)
≥4	131 (55.3)	145 (61.2)
Storage time of the units, d	19.7±5.4	17.4±5.9*
Preoperative hematologic values		
Hemoglobin, g/dL	12.2±4.1	12.4±3.7
Platelets, $\times10^9$/L	232±72	232±71
Leukocytes, $\times10^9$/L	6.9±2.9	6.7±2.7

Values are mean±SD or numbers (%).
*$P<0.05$.

TABLE 2. Intention-to-Treat Analysis

	PC	LD	OR (95% CI)
Mortality at day 90	30 (12.7)	20 (8.4)	1.52 (0.84 to 2.73)
In-hospital mortality rate	24 (10.1)	13 (5.5)	1.99 (0.99 to 4.00)*
Causes of death			
During initial operation	0	2 (0.8)	
MODS	17 (7.2)	10 (4.2)	
Cardiac events	4 (1.7)	1 (0.4)	
During second operation	3 (1.3)	0	
Infections	75 (31.6)	53 (22.6)	1.64 (1.08 to 2.49)*
No. infections	79	58	
Type of infections			
Respiratory tract infections	39	25	
Urinary tract infections	14	14	
Wound infections	11	10	
Bacteremia	12	8	
Type unknown	3	1	
MODS	49 (20.7)	48 (20.4)	1.07 (0.67 to 1.68)

Values are numbers (%).
*$P \leq 0.05$.

according to the criteria of the Centers for Disease Control and Prevention.[20] Causes of in-hospital mortality were obtained from the hospital patient records, report of mortality at 90 days from the referring cardiologist, or the general practitioner.

End Points and Statistical Analysis

The primary end point of the study was mortality at 90 days after surgery. Secondary end points were incidence of in-hospital mortality and the causes of death, incidence of MODS, infections during the hospital stay, duration of ICU stay, and hospitalization. An independent safety committee monitored the interim results of the primary end point.

Based on the results of the subpopulation in a previous study,[15] the trial was designed to detect a significant difference in mortality between both trial arms of 10% (15% versus 5%). To reach statistical significance ($P<0.05$) and a power of 90%, 210 evaluable patients were needed in each arm . To compensate for nonevaluable patients, the target number of included patients was 500.

Patients were stratified by the type of surgery (valve with or without CABG) and by hospital. Within each of these strata, a straightforward randomization was performed by using a fixed block size (n=24) to ensure a balance between the randomization groups. The final analysis incorporated the stratification structure (2×2) when estimating the relation between the randomization variable and the various outcomes. The analysis for all end points was on an intention-to-treat basis. All patients were analyzed according to the original random assignment, and no patients were re-assigned. Based on the results of the previous study,[15] subgroup analysis was performed according to transfusions. For comparison of qualitative parameters, the Fisher's exact test or χ^2 test was used, and for comparison of quantitative parameters, the *t* test or Mann-Whitney *U* test was used. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to compare the differences of mortality, infections, and MODS, calculated according to the Mantel-Haenszel procedure. The CI obtained by the Mantel-Haenszel procedure is based on a normal approximation. ICU stay, hospital stay, and duration of MODS were analyzed by means of the Student's *t* test. Multivariate analysis of the risk factors was performed with the use of an enter/backward logistic regression model. For statistical analysis, the SPSS program was used.

Results

In total, 496 patients were enrolled in the study. Twenty-two patients were excluded for various reasons: 8 withdrew consent before the surgery, 6 canceled surgery, 3 had no valve replacement performed, 3 had received blood transfusions in the past 3 months, and 2 died before the operation. In each arm, 237 patients were evaluable for the primary end points. Two patients (both randomly assigned into the LD group) died during the initial operation. These 2 patients were ineligible for the analysis of the secondary end points. Three patients (all of them randomly assigned into the PC group) died in a second operation (performed >24 hours later); these patients remained in the study for the secondary end points. As shown in Table 1, both groups were comparable with respect to baseline characteristics, with an exception for the storage time of the erythrocytes. Based on their Parsonnet score, the patients in both trial arms are considered to be at high-risk (mean±SD: 13.5±8.3). The majority (58.2%) of the patients received ≥4 U erythrocytes (mean±SD: 6.1±6.6). Forty-two (8.9%) of the patients did not receive any transfusion. Four (0.8%) patients received both types of blood products; these patients remained in their original randomization arm.

Intention-to-Treat Analysis

As shown in Table 2, in total, 50 (10.5%) patients died within the first 90 days after surgery. The total mortality rate at day 90 was higher in the PC group than in the LD group (12.7% versus 8.4%, respectively). This difference was not significant (OR, 1.52; 95% CI, 0.84 to 2.73; $P=0.16$). In the hospital, 37 (7.8%) patients died; in the PC group the in-hospital mortality rate was almost twice as high as in the LD group (10.1% versus 5.5%, respectively; OR, 1.99; 95% CI, 0.99 to 4.00; $P=0.05$).

TABLE 3. Mortality at Day 90 According to Number and Type of Transfusions

	No.		Mortality at Day 90			
	PC	LD	PC	LD	OR	95% CI (*P*)
Total	237	237	30 (12.7)	20 (8.4)	1.52	0.84 to 2.73 (0.16)
No. of transfusions						
0	21 (8.9)	21 (8.9)	0	0		
≥1	216 (91.1)	216 (91.1)	30 (13.9)	20 (9.3)	1.63	0.90 to 2.98 (0.11)
1 to 3	85 (35.9)	71 (29.9)	4 (4.7)	2 (2.8)		
≥4	131 (55.3)	145 (61.2)	26 (19.9)	18 (12.4)	1.82	0.94 to 3.52 (0.08)

Values are numbers (%).

TABLE 4. In-Hospital Mortality Rates According to Number and Type of Transfusions

	No.		In-Hospital Mortality			
	PC	LD	PC	LD	OR	95% CI (*P*)
Total	237	237	24 (10.1)	13 (5.5)	1.99	0.99 to 4.00 (0.05)
No. of transfusions						
0	21 (8.9)	21 (8.9)	0	0		
≥1	216 (91.1)	216 (91.1)	24 (11.1)	13 (6.0)	2.00	0.99 to 4.02 (0.05)
1 to 3	85 (35.9)	71 (29.9)	1 (1.2)	1 (1.4)		
≥4	131 (55.3)	145 (61.2)	23 (17.6)	12 (8.3)	2.43	1.16 to 5.12 (0.02)

Values are numbers (%).

In 128 of 472 patients (27.1%), 137 postoperative infections were diagnosed. In the PC group, 75 (31.6%) of 237 patients had infections, as did 53 (22.6%) of 235 patients in the LD group (OR, 1.64; 95% CI, 1.08 to 2.49; $P=0.02$). In total, 97 (20.6%) patients had MODS in the postoperative period. In both trial arms, there was a similar incidence of MODS (20.7% in PC versus 20.4% in LD group). The duration of MODS in days (mean±SD) was also not different in both groups (6.3±8.8 in PC versus 6.1±8.0 in LD; $P=0.98$).

ICU stay in the PC group was 5.6±7.2 (mean±SD) days and 5.5±7.3 days in the LD group ($P=0.88$). The median ICU stay in both groups was 3 days. The postoperative hospital stay was 13.8±10.7 days and 13.3±13.7 days in the PC and LD groups, respectively ($P=0.66$). The median duration of the hospital stay in both groups was 10 days.

Analysis According to Transfusion

In both groups, the mortality rate at 90 days was higher in patients who had received ≥4 U: PC, 19.9% versus LD, 12.4%; OR, 1.82; 95% CI, 0.94 to 3.52; $P=0.08$ (Table 3). The causes of death after discharge in both groups were predominantly cardiac. Both for mortality at day 90 and in-hospital, there were no deaths in the non-transfused patients. In the patients who received 1 to 3 U, there was no difference in mortality rates between both groups. The in-hospital mortality rate increased markedly with transfusion of ≥4 U (Table 4) (PC, 17.6% versus LD, 8.3%; OR, 2.43; 95% CI, 1.16 to 5.12; $P=0.02$). In both groups, most of the patients with in-hospital death had MODS. Mortality rate associated with MODS was higher in the PC than in the LD group (Table 2).

Most patients with infections were in the group receiving ≥4 U (Table 5) (PC, 44.3% versus LD, 28.7%; OR, 1.93; 95% CI, 1.17 to 3.20; $P=0.01$). The types of infections are shown in Table 2. In both groups, the number of transfused erythrocyte concentrates was correlated with the incidence of MODS; however, this was not different between the groups (Table 6).

Multivariate Analysis

For the primary end point and the secondary end points, the following preoperative and peroperative risk factors were analyzed: Hospital, sex, age, Parsonnet score, type of surgery, duration of cardiopulmonary bypass and aortic-cross clamping, randomization arm, and number of erythrocyte transfusions. For mortality at day 90, Parsonnet score ($P=0.001$), the number of erythrocyte transfusions ($P<0.001$), and sex ($P=0.04$) were significant prognostic factors; for in-hospital mortality, the number of erythrocyte transfusions ($P<0.001$), Parsonnet score ($P=0.01$), sex ($P=0.03$), and the randomization arm ($P=0.01$) were significant prognostic factors (Table 7). For postoperative infections, the number of erythrocyte transfusions ($P<0.001$) and randomization arm ($P=0.02$) were significant prognostic factors. For MODS, only the number of erythrocyte transfusions ($P<0.001$) was significant prognostic factor.

Discussion

In this study, a large group of patients undergoing complex cardiac surgery were enrolled. These patients were heavily

TABLE 5. Postoperative Infections According to Number and Type of Transfusions

	No.		Infections			
	PC	LD	PC	LD	OR	95% CI (*P*)
Total	237	235	75 (31.6)	53 (22.6)	1.64	1.08 to 2.49 (0.02)
No. of transfusions						
0	21 (8.9)	21 (8.9)	2 (9.5)	1 (4.8)		
≥1	216 (91.1)	214 (91.1)	73 (33.8)	52 (24.3)	1.61	1.06 to 2.47 (0.03)
1 to 3	85 (35.9)	71 (30.2)	15 (17.6)	11 (15.5)		
≥4	131 (55.3)	143 (60.9)	58 (44.3)	41 (28.7)	1.93	1.17 to 3.20 (0.01)

Values are numbers (%).

TABLE 6. MODS According to Number and Type of Transfusions

	No.		MODS			
	PC	LD	PC	LD	OR	95% CI
Total	237	235	49 (20.7)	48 (20.4)	1.07	0.67 to 1.68 (0.79)
No. of transfusions						
0	21 (8.9)	21 (8.9)	2 (9.5)	2 (9.5)		
≥1	216 (91.1)	214 (91.1)	47 (21.8)	46 (21.5)	1.05	0.65 to 1.68 (0.85)
1 to 3	85 (35.9)	71 (30.2)	5 (5.9)	6 (8.5)		
≥4	131 (55.3)	143 (60.9)	42 (32.1)	40 (28.0)	1.24	0.73 to 2.11 (0.42)

Values are numbers (%).

transfused with erythrocyte concentrates, which were randomly allocated between standard PCs and LDs. The overall mortality rate within the first 90 days after surgery was 10.5% and the in-hospital mortality rate was 7.8%. These rates were comparable with other studies in valve surgery.[21,22] In agreement with others,[23] we found that most of the patients who died after discharge from the hospital died from cardiac causes. This was similar between both trial arms. We observed a high rate of rethoracotomy in this study with a difference between the hospitals: 7% in hospital A (256 patients) and 20% in hospital B (218 patients). A possible explanation is the policy of administration of aprotinin in one hospital. The use of aprotinin was equally distributed in both trial arms.

The major findings of this study were (1) a nonsignificant difference for the primary outcome of the study, mortality at 90 days (12.4% versus 8.4%); (2) an in-hospital mortality rate in the PC group (10.1%) that was almost twice as high as that in the LD group (5.5%), largely caused by deaths associated with MODS; and (3) a significantly higher incidence of postoperative infections in the PC group (31.6%) compared with the LD group (22.6%). The incidence of MODS was not different, nor was the ICU stay or hospital stay between the groups. This lower in-hospital mortality rate in the LD group, as well as the strong relation with the number of transfusions, extends the results of the previous study.[15] This earlier study was primarily designed to evaluate the effect of leukocyte-depleted erythrocytes on alloimmunization and infections but revealed an unexpected difference in mortality rates in patients transfused with PCs. In a similarly designed study in patients with CABG (with infections as primary end point), a nonsignificant difference in mortality rate was observed; however, total mortality rate was low.[14] In 2 other randomized studies performed in different patient groups, the subgroup analyses of cardiac surgery patients failed to show a beneficial effect of LD on mortality rate.[16,17]

TABLE 7. Multivariate Analysis for Mortality at Day 90 and In-Hospital Mortality Rates

	P	
	Mortality at Day 90	In-Hospital Mortality
No. of erythrocyte transfusions	<0.001	<0.001
Parsonnet score	0.001	0.01
Sex	0.04	0.03
Randomization arm	0.16	0.01
Type of surgery	0.07	0.12
Hospital	0.12	0.85
Age	0.24	0.28
Duration of cardiopulmonary bypass	0.22	0.42
Duration of aortic cross-clamping	0.77	0.91

The present study in high-risk cardiac surgery was primary designed to detect possible differences in mortality rates. Patients who received 1 to 3 U showed a similar mortality rate between both trial arms, whereas the difference was favorable for LD when ≥4 U were transfused. However, the difference in mortality rate at 90 days did not reach statistical significance between the 2 study populations. Based on results of 60-day mortality in the previous study,[15] the present study was powered to detect a difference in mortality rate of 10%. We observed a smaller difference in mortality rates between the groups, in particular that caused by cardiac mortality after discharge, which was equal in both trial arms.

The reduction in postoperative infections in favor of LDs was solely present in patients who received ≥4 U. It has been shown that transfusion of whole blood during surgery is associated with prolonged impairment of macrophages and natural killer cell function. This effect appears to be dependent on the dosage of leukocytes or on the leukocyte-aggregates in the transfused concentrates.[11]

This is the first prospective trial in which the development of MODS in relation to blood products was studied. Overall incidence of MODS was 20.7%; this was highly associated with the number of transfusions but not with the randomization groups. The mortality rate associated with MODS was higher in the PC group compared with the LD group; whether the beneficial effects of LD on MODS-related survival and to postoperative infections remains unclear and must be investigated further.

LD transfusions are widely implemented in Western Europe and Northern America. The clinical benefits other than prevention of HLA alloimmunization and cytomegalovirus transmission have been difficult to demonstrate.[6] Taking previous studies[6] into account, leukocytes appear to be particularly important as a risk for infections when larger numbers of erythrocyte concentrates are administered. In this study, a large, homogeneous and multiple transfused patient group was enrolled. We demonstrated in this population that

LDs result in a decrease in postoperative infections and in-hospital mortality rates. Therefore, our study supports the transfusion of LD in patients at high risk for receiving multiple transfusions in cardiac surgery.

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