Transfusion associated complications in cardiac surgery : the swan song of the allogeneic leukocytes ?

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Chapter 3

Is Increased Mortality Associated with Postoperative Infections after Leukocytes Containing Red Blood Cell Transfusions in Cardiac Surgery? An Extended Analysis

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ABSTRACT

Background: In two randomized trials in cardiac surgery we observed that leukoreduced allogeneic red blood cell (RBC) transfusions (LR) compared with standard buffy-coat-depleted RBC transfusions (BCD) resulted in lower rates of postoperative infections and mortality.

Methods: To unravel whether this comprises two independent side effects or could be related complications of allogeneic leukocytes, we performed a re-analysis on the patients of these two trials.

Results: For all analyses, homogeneity tests were shown not to be significant. Data on characteristics of postoperative infections, nature of microorganisms, number of transfusions and causes of death in both studies were subjected to an integrated analysis. In both studies combined, 1085 patients had been assigned to prestorage leukoreduced RBCs (LR, n=542) or standard buffy-coat-depleted RBCs (BCD, n=543). Postoperative infections were significantly higher in the BCD group [BCD: 34.2% vs. LR: 24.0%, common odds ratios (COR): 1.65, 95% confidence interval (CI): 1.27-2.15], whereas the species of cultured microorganisms and the type of the infections were similar in both randomization arms. Mortality with the presence of infections in the postoperative period was significantly higher in patients receiving BCD compared with LR (BCD: 5.5% vs. LR: 2.2%, COR: 2.59, 95% CI: 1.31-5.14), whereas mortality without infections in the postoperative period was similar in both arms (BCD: 3.9% vs. LR: 3.1%, COR: 1.24, 95% CI: 0.65-2.38). The only cause of death that differed significantly between BCD and LR was the combination of multiple organ dysfunction syndrome with infections in the postoperative period.

Conclusions: This re-analysis shows that transfusion of leukocytes containing RBCs during cardiac surgery may be associated with more infections with fatal outcome. This should be confirmed in a larger extended analysis or a prospective study.

INTRODUCTION

The outcome of patients undergoing cardiac surgery is closely related with the development and the severity of postoperative complications such as systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS) and infections [1,2]. Moderate SIRS often develops after cardiac surgery and usually resolves with supportive care. However, severe SIRS can evolve to MODS, which may cause mortality, dependent on the number of failed organs [3].

Although in supportive care of cardiac surgery allogeneic blood transfusions are commonly used, these may act as a two-edged sword. On the one hand, patients with coronary artery disease compensate less for anemia and need a higher hemoglobin transfusion trigger [4-6]. On the other hand, allogeneic blood transfusions may be associated with more complications [7,8]. Several studies on intensive care unit (ICU) patients and cardiac surgery showed a dose-dependent relationship between allogeneic blood transfusions and the development of postoperative infections [9-11] and hospital mortality [12,13].

A meta-analysis of the three fully published [14-16] studies in cardiac surgery revealed an increased short-term postoperative mortality after transfusions containing allogeneic leukocytes as compared with transfusions of blood leukoreduced by filtration [17]. However, in different surgical settings a meta-analysis for postoperative infections demonstrated no clear evidence in favour of leukoreduced blood transfusions [18].

We conducted two randomized controlled trials (RCTs) [14,16] in cardiac surgery and observed in both studies a transfusion dose-dependent increase of postoperative infections as well as a higher mortality rate associated with MODS after the transfusion of standard, buffy-coat-depleted red blood cells (RBCs) compared with RBCs leukoreduced by filtration. We wondered whether postoperative infections and mortality might reflect different mechanisms or a common mechanism induced by allogeneic leukocytes. For this purpose we re-analysed the original data of patients who participated in two RCTs for the nature of infections and the influence of these infections on the course of postoperative outcome.

MATERIAL AND METHODS

Both studies were double-blinded, prospective RCTs. In both studies, the ethical review boards of the hospitals approved the trial protocols, and the local trial coordinators obtained informed consent from the patients. The design and outcome of both studies are described elsewhere in detail [14,16]. Study 1 was a single-center study conducted between 1992 and 1994 [16]. Patients undergoing coronary artery bypass surgery (CABG), valve surgery or a combination of both were randomized into three study arms: leukoreduced RBCs were either prepared prestorage from freshly drawn blood or were filtered after storage prior to transfusion. For the current analysis, we only included the patients who received prestorage leukoreduced RBCs (LR, n=305) and those who received buffy-coat-depleted RBCs (BCD, n=306) because these products were the common products used in both studies. Study 2 was conducted between 1999 and 2001 in two hospitals and included patients undergoing valve surgery with or without CABG (14). In this study, buffy-coat-depleted RBCs (n=237) were compared with prestorage filtered RBCs (n=237). In both studies, all patients received prophylactic antibiotics postoperatively for 24 hours in patients undergoing CABG and 48 hours in patients undergoing valve surgery. Postoperatively the patients were monitored at the ICU until there was no need for positive inotropes and intubation. Surgical and anesthetical procedures were according to the standards of the hospital in both studies.

Blood Products and Transfusions

The blood products and the quality control of blood products for both hospitals in the two studies fulfilled the requirements and the specifications of the Dutch standards for blood banks. Within 24 hours of withdrawal BCD-RBCs were prepared by centrifugation of whole blood at 3000 *g* for 10 min. Buffy coat and plasma were removed, and RBCs were reconstituted with 100 ml saline-adenine-glucose-mannitol. The average leukocyte count was in the first study 0.8 ± 0.5×10^9 per unit and in the second study 0.7 ± 0.4×10^9 per unit. Prestorage filtration of RBCs (LR) was performed within 24 hours after collection of blood by passage through a leukocyte filter. In both studies the same filter (Cellselect-Optima, NPBI International-Fresenius HemoCare, The Netherlands) was used. The residual leukocyte count in the filtered units was measured in study 1 using Nageotte counting chamber, revealing a leukocyte count of [mean ± standard deviation (SD)] 1.2 ± 1.4×10^6 per unit. In study 2, flow cytometry was used for quality control, more reliably detecting low leukocyte numbers. By this method the mean (±SD) residual leukocytes in the filtered units was 0.15 ± 0.02×10^6 per unit. All platelet concentrates in both studies

were prestorage leukoreduced by filtration. In both studies, there were no by-study-defined transfusion triggers. The decision to transfuse blood products was based on local policies, hemoglobin level (less than 8-8·5 g/dl), platelet count (less than 100×10^9/l), blood loss and bleeding disorders. In one centre participating in study 2 more patients received aprotinin for prevention of blood loss.

Mortality

In study 1, mortality was a secondary endpoint and was registered until day 60 postoperatively; in study 2, mortality at 90 days after surgery was the primary endpoint. For both studies, death at 60 days was monitored and used for this analysis. The cause of death in both studies was retrieved from the patient hospital records or from the referring cardiologist or general practitioner.

Postoperative Infections

In both studies infections in the postoperative period had been a secondary endpoint and were recorded according to the criteria of Center for Disease Control and Prevention [19]. In both studies the following infections were scored: respiratory tract infection (defined as positive sputum culture and/or pulmonary infiltrate on the radiograph), urinary tract infection (defined as positive urine culture with clinical signs of urine tract infection), wound infection (defined as positive wound culture and/or local symptoms) and bacteremia (defined as positive blood culture and fever). All information on infections and the identified microorganisms was collected by the trial coordinators from the patient records or electronically from the hospital computer system.

Multiple Organ Dysfunction Syndrome (MODS)

In study 1 MODS was not an endpoint. In this study, the causes of death were registered and MODS was diagnosed as cause of death by the treating physicians. In study 2 MODS was a secondary endpoint. The scoring of organ dysfunction was assessed by the local trial coordinators on the basis of the daily records according to a model described elsewhere [20]. The dysfunction of the following organ systems were scored: respiratory dysfunction (defined as respiratory frequency ≤5/min or ≥49/min, arterial $PaCO_2$ ≥6.65 kPa, $AaDO_2$ ≥46.7 kPa, or longer than 72 hours dependency of mechanical ventilation), cardiovascular dysfunction (defined as heart frequency ≤54/min or ≥ 150/min, mean arterial pressure ≤ 49 mmHg, serum pH ≤7.24 in combination with $PaCO_2$ ≤6.52 kPa, or dependency of positive inotropes), renal dysfunction (defined as urine production ≤ 479 ml per 24 hours or ≤159 ml per 8

hours, creatinine concentration ≥3.4 mg/dl, blood urea nitrogen concentration ≥50 mg/dl, or dependency of dialysis), hematological dysfunction (defined as white blood cell count ≤ 1.0×10^9/l, platelet count ≤20×10^9/l, or hematocrit ≤0.20) and insufficiency of the central nervous system (defined as Glasgow Coma Score ≤6). MODS was defined as the failure of 2 or more organ systems.

Statistics

These extended analyses were performed on intention-to-treat basis. Breslow-Day and Tarone's homogeneity tests were performed to verify that combined analyses were valid. Data were expressed as mean ±SD, number or percentage when appropriate. For comparison of qualitative parameters, the Fisher's exact test or χ^2 test was used, and for the comparison of quantitative parameters, the *t*-test or Mann-Whitney *U*-test was used. To analyse the differences, common odds ratios (COR) with 95% confidence intervals (95% CIs) were calculated using the Mantel-Haenszel estimation. Multivariate analysis of the risk factors was performed using logistic regression model. The survival was analysed with Kaplan-Meier curves. All p-values are two tailed. All analyses were performed in SPSS (SPSS Inc., Chicago, IL, USA).

RESULTS

In Table 1 the patient characteristics of both studies are summarized. Patients included in study 2 underwent CABG combined with valve surgery and were at higher risk with respect to age, gender, type of surgery and duration of surgery; this was reflected in longer ICU stay and hospital stay compared with study 1. In both studies more than 90% of the included patients received one or more RBC transfusions. Three patients in the LR group received solely BCD products, and in both groups 27 patients received both types of blood products. In the current analysis these patients remained in their original randomization arm. The homogeneity tests for all analyses were not significant.

In the BCD group 186 patients (34.2%) and in the LR group 130 patients (24.0%) had an infection. In total, 80 patients (7.4%) died, 51 patients (9.4%) in the BCD group and 29 patients (5.4%) in the LR group. The CORs for infections (COR: 1.65, 95% CI: 1.27-2.15, p<0.01) and for mortality (COR: 1.84, 95% CI: 1.15-2.96, p=0.01) showed significant differences between BCD and LR.

Table 1 | Characteristics of Included Patients

	Study 1		Study 2			Total	
	BCD	**LR**	**BCD**	**LR**	**p***	**BCD**	**LR**
Number	306	305	237	237		543	542
Female (%)	85 (27.8)	80 (26.2)	102 (43.0)	113 (47.7)	<0.01	187	193
Age (yrs±SD)	64.9 ± 9.4	63.5 ± 9.7	66.6 ± 12.5	65.4 ± 14.7	0.01	65.6 ± 10.9	64.3 ± 12.2
Type of surgery							
CABG (%)	234 (76.5)	225 (73.8)	-	-	<0.01	234 (43.1)	225 (41.5)
Valve (%)	49 (16.0)	58 (19.0)	164 (69.2)	156 (65.8)		213 (39.2)	214 (39.5)
CABG+valve (%)	23 (7.5)	22 (7.2)	73 (30.8)	81 (34.2)		96 (17.7)	103 (19.0)
Duration of surgery							
CPB (min±SD)	124 ± 48	123 ± 53	143 ± 62	139 ± 60	<0.01	132 ± 55	130 ± 57
Ao.clamping (min±SD)	66 ± 29	68 ± 33	95 ± 45	99 ± 47	<0.01	79 ± 39	82 ± 42
Transfusion characteristics							
Number transfused RBCs (mean±SD)	5.4 ± 5.6	5.4 ± 4.6	6.1 ± 7.1	5.9 ± 6.1	0.09	5.7 ± 6.3	5.6 ± 5.3
Median	4	4	4	4		4	4
Range	0-40	0-35	0-46	0-50		0-46	0-50
Storage time (days)	13.2 ± 6.0	12.9 ± 6.3	19.5 ± 5.4	17.4 ± 5.9	<0.01	16.1 ± 5.8	15.4 ± 6.2
Non-transfused (%)	12 (3.9)	20 (6.5)	21 (8.9)	21 (8.9)	0.02	33 (6.1)	41 (7.6)
Transfused plasma units (mean±SD)	4.3 ± 4.2	3.9 ± 3.1	4.5 ± 5.1	4.0 ± 4.5	0.83	4.4 ± 4.7	4.0 ± 3.8
Transfused platelet units (mean±SD)	1.3 ± 1.1	1.1 ± 0.9	1.2 ± 1.2	1.1 ± 1.3	0.89	1.2 ± 1.0	1.1 ± 1.1
ICU-stay (days)	4.2 ± 4.6	4.1 ± 4.7	5.5 ± 7.3	5.5 ± 7.2	<0.01	4.8 ± 5.9	4.7 ± 6.0
Hospital-stay (days)	11.1 ± 7.4	10.9 ± 7.9	13.9 ± 11.1	13.4 ± 14.5	<0.01	12.3 ± 9.3	12.0 ± 11.3

* p-values are calculated for differences between the study 1 and 2; BCD=Buffy-coat depleted red blood cells; LR=Leukocyte depleted red blood cells; CABG=Coronary artery bypass surgery; CPB=Cardiopulmonary bypass; Ao.Clamping=Aortic clamping; RBC=Transfused red blood cells

The most frequent type of infection was respiratory tract infection (48.7%) followed by urinary tract infection (33.2%), bacteremia (12.3%) and wound infection (11.1%). In the BCD group nine patients (4.8%) had two or more infections and in the LR group seven patients (5.4%). In the deceased patient group, respiratory tract infection was the most common type of infection (33.8%) followed by bacteremia (16.3%), urinary tract infection (8.8%) and wound infection (2.5%). The distribution of the types of infections was similar in both randomization groups (Table 2). There were more patients with more than 1 infection in the BCD group associated with mortality.

From 33 patients (17.7%) in the BCD group and 25 patients (19.2%) in LR group cultures revealed no microorganisms. The homogeneity test between the studies for type of microorganisms (p=0.49) was not significant. In the BCD group in 45 patients (24.2%) more than one microorganism was cultured. The isolated microorganisms in the BCD group were predominantly *Haemophilus influenzae* (16.8%), *Staphylococcus aureus* (16.8%) and *Escherichia coli* (15.4%). In the LR group, in 29 patients (22.3%) more than one microorganism was cultured. The most isolated microorganisms in this group were *E. coli* (23.1%), *H. influenzae* (18.5%), *Enterobacter* species (13.8%) and *S. aureus* (13.1%). There were more gram-negative (75.1%) than gram-positive (22.4%) microorganisms cultured in patients with infections. The cultured microorganisms in patients with infections and in deceased patients were not different between the randomization groups.

In Table 3 the causes of death are shown. The most common cause of death in the BCD group was MODS combined with infections in the postoperative period; this was significantly higher than that in the LR group. In the LR group cardiac complications (without MODS or infections) were the most common causes of death. Mortality, either from infections or other causes, tended to increase the more RBCs patients received (Table 4). The extent of the association between RBCs dose and mortality was not different between the trial arms for deaths not caused by infections but was significantly greater in the BCD arm compared with LR for deaths caused by infections (p=0.01 overall and p=0.02 if 8 or more units were transfused).

The association between infections in the postoperative period and mortality was analysed in a multivariate logistic regression model with pre-operative and per-operative risk factors. The following risk factors were found to be independently associated with mortality: cardiopulmonary bypass time (p<0.001), age at surgery (p=0.001), infections (p=0.004), type of surgery (p=0.012) and the randomization arm (p=0.03). Gender (p=0.07), study (p=0.99) and aortic clamping time (p=0.16) showed no independent association. Infections (p=0.43) and type of surgery (p=0.12) lost their significant association with

Table 2 | Types of Infections

	Infections			Infections associated with mortality			Not associated with mortality		
	BCD N (%)	LR N (%)	p	BCD N (%)	LR N (%)	p	BCD N (%)	LR N (%)	p
Patients with infections	186	130		30	12		156	118	
Patients with >1 infection	9 (4.8)	7 (5.4)		6 (20.0)	1 (8.3)		3 (1.9)	6 (5.1)	
Type of infections			0.73			0.31			0.44
Respiratory infections	90 (48.4)	64 (49.2)		20 (66.7)	7 (58.3)		70 (44.9)	57 (48.3)	
Urinary tract infections	61 (32.8)	43 (33.1)		5 (16.7)	2 (16.7)		56 (35.9)	41 (34.7)	
Bacteremia	25 (13.4)	14 (10.8)		9 (30.0)	4 (33.3)		16 (10.2)	10 (8.5)	
Wound infections	19 (10.2)	16 (12.3)		2 (6.7)	0		17 (10.9)	16 (13.5)	

p-values are calculated for differences between the randomization arms; BCD=Buffy-coat reduced red blood cells; LR=Leukoreduced red blood cells

Table 3 | Causes of Death

	BCD (N=543) N (%)	LR (N=542) N (%)	COR (95% CI)	p
MODS and infections (in the postoperative period)	20 (3.7)	7 (1.3)	2.92 (1.22-6.97)	0.02
Infections (without MODS)	9 (1.8)	5 (0.9)	2.01 (0.60-5.44)	0.42
MODS (without infections)	3 (0.6)	3 (0.6)	1.0 (0.20-4.97)	1.0
Cardiac complications (without MODS or infections)	16 (2.9)	11 (2.0)	1.47 (0.67-3.12)	0.44
Bleeding/Surgical complications	3 (0.6)	3 (0.6)	1.0 (0.20-4.97)	1.0
Total	51 (9.4)	29	1.84 (1.15-2.96)	0.01

p-values are calculated for differences between the randomization arms; BCD=Buffy-coat reduced red blood cells; LR=Leukoreduced red blood cells; MODS= Multiple-Organ-Dysfunction-Syndrome; COR=Common odds ratio

mortality when the number of erythrocyte transfusions was added to the model (p<0.001). Cardiopulmonary bypass time (p=0.01), age at surgery (p=0.005) and the randomization arm (p=0.03) remained independently associated with mortality.

Table 4 | Mortality, with and without Infection in the Postoperative Period Related to the Number of RBC Transfusions

		Mortality with Infection N (%)			Mortality without Infection N (%)		
No. of RBCs	**BCD/LR**	**BCD**	**LR**	**COR (95%CI) p**	**BCD**	**LR**	**COR (95% CI) p**
0	33/41	0	0		0	0	
1-3	208/188	2 (1.0)	1 (0.5)	1.82 (0.16-20.2) 1.0	3 (1.4)	3 (1.6)	0.90 (0.18-4.53) 1.0
4-7	188/198	7 (3.7)	2 (1.0)	3.79 (0.78-18.5) 0.10	8 (4.3)	4 (2.0)	2.16 (0.64-7.28) 0.25
≥8	114/115	21 (18.4)	9 (7.8)	2.66 (1.16-6.09) 0.02	10 (8.8)	10 (8.7)	1.01 (0.40-2.53) 1.0
Total	543/542	30 (5.5)	12 (2.2)	2.59 (1.31-5.14) 0.01	21 (3.9)	17 (3.1)	1.24 (0.65-2.38) 0.49

p-values are calculated for differences between the randomization arms; BCD=Buffy-coat reduced red blood cells; LR=Leukoreduced red blood cells;COR=Common odds ratios

The survival curves of patients with and without infections in the postoperative period are shown in Figure 1. The survival of patients without infections was not different between the randomization groups (p=0.28), and most deaths in this group occurred in the first 20 days after surgery. Most of the deaths in patients with infections occurred later; the difference between BCD and LR was mainly because of more deaths in the BCD group after an interval of 20 days or longer after surgery (p=0.09).

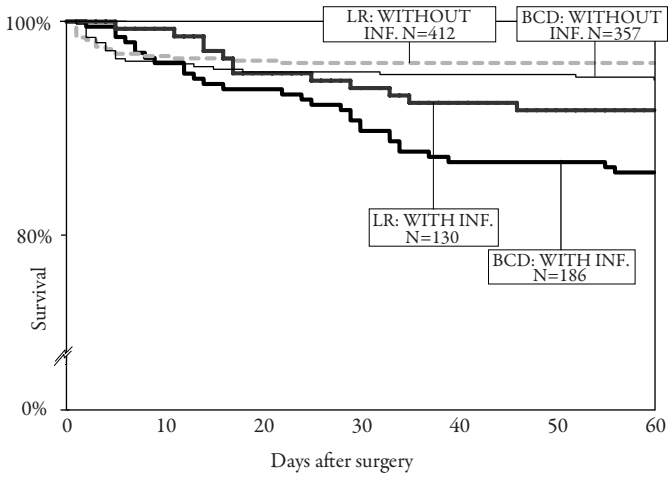

Figure 1 | The 60-day survival in after cardiac surgery in patients with or without infections in the postoperative period. Survival without infections was not different between BCD and LR (p=0.28). Difference in survival with infections between BCD and LR was mainly observed after 20 days (p=0.09).

DISCUSSION

To evaluate the role of leukocytes in blood products administered during cardiac surgery, three fully published RCTs [14-16] and two abstracts [21,22] are available. In four of the five studies, RBCs leukoreduced by filtration were associated with lower mortality. However, the exact mechanism associated with increased mortality has not been unravelled yet [23]. In all studies, postoperative infections had been evaluated as an independent endpoint with contradictory results. The current re-analysis was undertaken to explore whether infections in the postoperative period contributed to mortality in patients undergoing cardiac surgery after transfusion of leukocyte containing RBCs. This approach could be helpful to identify the possible role of infections in survival of patients receiving leukocytes containing RBCs. For this re-analysis we used the data of two previously published studies [14,16]. These studies were undertaken in cardiac surgery; however, there were also differences between the studies. Therefore, we tested the homogeneity of the results from both studies before analysing the

data. Because there were no significant differences between the studies in all homogeneity tests, we reported the results from the combined analysis.

Our finding that the mortality rate was increased in patients with the presence of infections in the postoperative period after cardiac surgery was in agreement with others [24]. The possible relationship between leukocytes containing RBCs and mortality associated with postoperative infections has not been described before. Mortality associated with or without infections increased with the number of units of RBCs transfused in both randomization arms. However, the difference in mortality between those receiving BCD or LR was more marked in patients receiving 8 or more units of RBCs, which suggests that transfusion-related immunomodulation may either be dose related or be more clinically significant in sicker patients. Because no differences in type of infections or type of microorganisms between BCD and LR were present, this points to an overall more reduced host resistance after non-leukoreduced RBC transfusions. No specific suspectibility for particular microorganisms, as has been suggested in an animal model, was seen [25]. Patients dying without infections did so mainly in the first 20 days after surgery, whereas patients with infections often died later. This was reflected in the growing difference in mortality between BCD and LR beyond 20 days. This is in agreement with other observations on a possible long-standing suppression of the innate immune system caused by leukocytes containing RBCs [26,27]. Patients with infections in the postoperative period appear to have a higher mortality associated with MODS when they receive leukocytes containing RBCs instead of leukoreduced RBCs. This difference in mortality associated with infections could be explained by increase of pro-inflammatory mediators by production or release induced by leukocytes containing RBCs. It has been shown that transfusion of RBCs in cardiac surgery leads to higher concentrations of pro-inflammatory mediators and is associated with more postoperative infections [28]. It is possible that such a postoperative inflammatory response (which could lead to MODS and a worse outcome) is more pronounced in patients receiving leukocytes containing RBCs compared with leukoreduced RBCs. More studies are necessary to investigate the role of allogeneic blood transfusions in the pathophysiology of postoperative inflammatory responses and organ dysfunction.

There are several restrictions in this analysis. First, this is not a new RCT but an extended analysis of two double-blind RCTs conducted in different patient populations. The RCTs were designed to investigate the potential effect of leukocytes containing RBCs in a highly transfused patient group. In the second study only patients undergoing valve surgery (with or without CABG) were included. This group was older, underwent longer surgery and stayed longer in ICU and in hospital. This high-risk patient group was selected because

the first study indicated the greatest deleterious effects of leukocytes containing RBC transfusions in the more heavily transfused patients who underwent valve surgery combined with CABG, which was confirmed in the second study. Second, the studies had different endpoints. The first published study found no difference in alloimmunization (primary endpoint). The secondary endpoints (postoperative infections and mortality) were higher in patients transfused with leukocytes containing RBCs compared with patients transfused with leukoreduced RBCs. These differences were associated with the number of RBC transfusions. The second study found a non-significant difference for mortality at 90 days (the primary outcome). However, in patients transfused with leukocytes containing RBCs, in-hospital mortality was twice as high and postoperative infections (secondary endpoints) were significantly higher compared with patients transfused with leukoreduced RBCs. For this re-analysis these outcomes were not double-checked or adjudicated by independent investigators. Third, both studies had been performed 7 years apart. Between the first study conducted in 1992-1994 and the second in 1999-2001, surgical procedures, application of aprotinin and transfusion practice changed, although cardiac surgery patients remained at risk to receive a large number of blood products. Fourth, the first study did not score MODS as an independent outcome but only as a cause of death. Therefore, exact incidence and severity of MODS in all participating patients is not known. Also, detailed data on pre-operative risk status of the patients were not recorded in the first study. Furthermore, the data had been collected in the same way by the same investigators in the same country. All these factors could have influenced this extended analysis. However, their influence affects both randomization arms equally because randomization had resulted in a balanced distribution of patients in both studies.

In summary, this extended analysis suggests a possible common pathway to postoperative death because of a higher incidence of presence of infections in the postoperative period associated with mortality, which might be elicited by long-standing immune suppression as a result of the presence of leukocytes in allogeneic blood transfusions. It is necessary to confirm these findings, preferentially by similar analysis on patients enrolled in all five RCTs conducted in cardiac surgery or (if possible) by a prospective study in countries that have not implemented universal leukoreduction.

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