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

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Chapter 8

# Postoperative Complications Associated with Transfusion of Platelets and Plasma in Cardiac Surgery

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## ABSTRACT

**Background:** Studies in cardiac surgery have reported increased postoperative morbidity and mortality after allogeneic red blood cell (RBC) transfusions. Whether platelet and/or plasma transfusions are a marker for more concomitant RBC transfusions or are independently associated with complications after cardiac surgery is unknown.

**Study design and methods:** Data from two randomized controlled studies were combined to analyze the effects of platelet and/or plasma transfusions on postoperative infections, length of stay in the intensive care unit (ICU), all-cause mortality and mortality in the presence or absence of infections in the postoperative period.

**Results:** After adjusting for confounding factors, plasma units and not RBC transfusions were associated with all-cause mortality. Leukocyte-containing RBC transfusions and platelet transfusions were associated with mortality occurring in the presence of or after infections. Number of (leukocyte-containing) RBC transfusions was also significantly associated with postoperative infections and with ICU-stay for 4 or more days.

**Conclusion:** Although it is difficult to separate the effects of blood components, we found that in cardiac surgery peroperative plasma transfusions are independently associated with all-cause mortality. Leukocyte-containing RBC transfusions and platelet transfusions are independently associated with mortality in the presence of infections in the postoperative period. Future transfusion studies in cardiac surgery should concomitantly consider the possible adverse effects of all the various transfused blood components.

## INTRODUCTION

Patients undergoing cardiac surgery are at increased risk for bleeding, because of thrombocytopenia secondary to hemodilution, platelet dysfunction and consumption of platelets in the extracorporal circuit. In addition, intra-operatively anticoagulant medication is administered to these patients. To improve hemostasis, platelets and fresh-frozen plasma (FFP) are often transfused in the peri-operative and postoperative periods. However, neither the efficacy nor the safety of platelet and plasma transfusions has been demonstrated.

Retrospective studies in cardiac surgery have shown that allogeneic red blood cell (RBC) transfusions are associated with an increased risk of postoperative infections and mortality in a dose-dependent manner [1-4]. In two randomized controlled trials (RCTs) of patients undergoing cardiac surgery [5,6], we found an increase in postoperative infections and mortality related to the number of transfused RBCs. Postoperative infection and mortality were significantly higher in patients receiving buffy-coat-depleted (BCD) RBCs than in patients receiving leukocyte-reduced (LR; filtered) RBCs, which suggested a role of allogeneic leukocytes in provoking postoperative infections and mortality. However, patients receiving multiple RBC transfusions often receive platelets and plasma transfusions as well. Whether platelet and plasma transfusions contribute to such postoperative complications or are just a surrogate marker for the need for a higher number of RBC transfusions is unknown. Previous retrospective studies yielded conflicting results concerning the association between platelet and plasma transfusions and outcome in cardiac surgery [7-13]. The purpose of this current analysis of the combined data from our two RCTs [5,6], is to investigate whether transfusion of platelet concentrates and FFP are independently associated with postoperative infection and mortality in cardiac surgery, after adjusting for the effect of the number of RBC transfusions and other confounders.

## MATERIAL AND METHODS

Our two double-blinded RCTs had been conducted at two university hospitals in the Netherlands. The ethical review boards of the hospitals approved the trial protocols and informed consent was obtained from the patients. The design of these studies have been reported elsewhere in detail [5,6]. In summary, the first study [5] was a single-center study conducted between 1992 and 1994. Patients undergoing coronary-artery-bypass-graft (CABG) or cardiac valve surgery or a combination of both, were randomised to receive,

when transfusion was necessary, BCD RBCs or LR RBCs (randomly assigned to receive either before storage from freshly drawn RBCs or filtered after storage before transfusion RBCs). For the current analysis we included only the patients who had received prestorage LR RBCs (n=305) and those who had received BCD RBCs (n=306), because these were the randomization arms also transfused in the second study. The second study [6] was conducted between 1999 and 2001 at two hospitals and included patients undergoing valve surgery with or without CABG. In this study BCD RBCs (n=237) were compared with pre-storage LR RBCs (n=237). In both studies oral anticoagulants and aspirin were stopped at least 5 days before surgery. Heparin (3 mg/kg) was administered before initiation of bypass with a target activated clotting time of 400 seconds. The priming of the cardiopulmonary bypass circuit was comparable in both studies. After termination of bypass, heparin was antagonized by protamine sulphate at a 1:1 ratio. In both studies, all patients received prophylactic antibiotics postoperatively for 24 hours (for subjects undergoing CABG) or 48 hours (for subjects undergoing valve surgery). In the second study, only patients considered to be at high risk for bleeding received aprotinin at one hospital. Postoperatively, all patients were admitted to the intensive care unit (ICU) until they had been extubated and had no longer needed positive inotropes. In one hospital, in the second study, patients without complications were transferred to a medium care unit before they were transferred to the department of cardiothoracic surgery.

**Blood Products and Transfusions**

The blood products in both studies were similar and fulfilled the requirements and the specifications of the Dutch standards for Blood Banks. Platelet concentrates were prepared from five pooled buffy coats and were prestorage LR by filtration. BCD RBCs were prepared by removal of the buffy coat and plasma, followed by reconstitution with 100 mL saline-adenine-glucose-mannitol. Prestorage filtration of RBC units was performed within 24 hours after whole-blood collection, by passage through a leuko-reduction filter (Cellselect-Optima, NPBI International-Fresenius HemoCare, the Netherlands). FFP was prepared by separation from whole donor-blood by hard spin and freezing within 6 hours at < -23°C. Women with a history of pregnancy were excluded from plasma donations, except in one hospital in the second study. In both studies the precise number of transfused RBCs, plasma units and platelet concentrates was recorded. At the time of both studies no documented guidelines for blood transfusions were present. The decision to transfuse blood products was based on the hemoglobin level (less than 8-8.5 gr/dl), platelet count (less than 100 x $10^9$/l), total amount of blood loss and/or presence of bleeding disorders.

### Endpoints

In both studies, postoperative infections had been a secondary endpoint based on the criteria of Centers for Disease Control and Prevention [14] and were scored during the hospital stay of the patients. In both studies, the length of stay in the ICU had been recorded in days. Because respiratory failure was not documented in the first study, length of ICU-stay for at least 4 days was considered to indicate need for prolonged mechanical ventilation. In the first study, mortality was a secondary endpoint and it was registered until day 60 postoperatively. In the second study mortality at 90 days postoperatively was the primary endpoint, although 60-days mortality was also recorded.

### Statistical Analysis

Breslow-Day and Tarone's tests were used to examine whether the data from two RCTs were sufficient homogeneous to permit combined analyses of both studies. Data were expressed as mean ± SD, number or percentage as appropriate. For comparison of qualitative parameters, the Fisher's exact test or chi-square test was used and for the comparison of quantitative parameters, the t-test or Mann-Whitney *U* test. To estimate risk factors for postoperative infection, ICU-stay for 4 or more days, overall mortality and mortality occurring in the presence or in the absence of postoperative infections known variables associated with these postoperative complications were included in a univariate analysis. Multivariate analysis of the risk factors was performed using a logistic regression enter/backward stepwise model to estimate independent predictors for postoperative complications. The following variables were eligible for inclusion in this model: study (our 1992-1994 versus our 1999-2001 RCT), age, gender, type of surgery (CABG, valve or the combination of both), cardiopulmonary bypass time, number of transfused RBC's, randomization arm (BCD vs. LR RBCs) and number of transfused plasma units and number of transfused platelet units. Time on cardiopulmonary bypass was analyzed as a categorical variable (in hr). The number of transfused RBC units, transfused plasma units and transfused platelet units were forced into the multivariate analysis. The results of the univariate analysis are reported as p values and the results of the multivariate analysis as odds ratios (ORs) with 95% confidence intervals (CIs). All p values are two tailed. Analyses were performed using the SPSS 17.0 (SPSS Inc, Chicago IL, USA).

## RESULTS

The data from the two studies comprised 1.085 patients; 611 from the first study and 474 from the second study. Testing for homogeneity indicated that it was legitimate to pool the data from both studies. Only ICU-stay was different between both studies which was due to the presence of a medium care in one hospital in the second study. In the combined population of 1.085 patients; 316 patients (29.1%) had developed postoperative infection and 80 patients (7.4%) had died. Of the patients who died, 41 patients (51.3%) died who had developed infections in the postoperative period, while 27 patients (33.8%) died from a cardiac cause without any postoperative infection. In total 12 patients (15.0%) died from other reasons (e.g., bleeding or multiple-organ-dysfunction-syndrome) without any postoperative infection.

In Table 1 the attributes of the patients are presented who developed postoperative infections and of the patients who died. Compared with patients who did not develop infections or patients who survived, patients who developed infections and patients who died were older, more often female; they had a longer duration of surgery and received more units RBCs and plasma and they had received platelet transfusion more often. The patients who received plasma and/or platelet transfusions were older, had a longer duration of surgery, and had received more RBC transfusions than patients who did not receive plasma or platelet transfusions. More infections and more deaths were observed in patients who received plasma or platelet transfusions (Table 2). As shown in Figures 1 and 2 patients who received more RBC units also received more plasma units (of 615 patients receiving 4 or more units RBCs, 403 patients [65.5%] had received 4 or more units plasma units as well) and patients who received more RBC units also received platelet transfusion more often (of 615 patients receiving 4 or more units RBCs, 233 patients [37.9%] had received also platelet transfusions).

Table 3 shows the results of univariate analyses concerning risk factors for the development of postoperative infection, length of ICU-stay at least 4 days, overall mortality, mortality in the presence (and absence) of infections in the postoperative period. Multivariate analysis showed that study, age, and number of RBC units transfused were associated with both postoperative infection and ICU-stay for at least 4 days. In addition to these factors, randomization arm and sex were associated with postoperative infections and the time on cardiopulmonary bypass with ICU-stay for at least 4 days (Table 4). Plasma or platelet transfusions were not associated with postoperative infections or ICU-stay for at least 4 days. All-cause mortality was associated with age, time on cardiopulmonary bypass,

**Table 1** | Attributes of All Patients and Patients Developing Postoperative Infections and Patients who died in the Hospital

| Attributes | Patients without infections N=769 | Patients with infections N=316 | p | Patients who survived N=1005 | Patients who died N=80 | p |
|---|---|---|---|---|---|---|
| First study (%) | 421 (54.7) | 190 (60.1) | 0.10 | 578 | 35 (43.8) | 0.01 |
| Female (%) | 246 (32.0) | 134 (42.4) | 0.001 | 338 | 42 (52.5) | 0.001 |
| Age (years) | 63.8 ± 11.9 | 67.9 ± 10.1 | <0.001 | 64.5 ± 11.6 | 70.8 ± 9.0 | <0.001 |
| Type of surgery (%) | | | | | | |
| CABG | 324 (42.1) | 135 (42.7) | 0.19 | 440 | 19 (23.7) | <0.001 |
| Valve | 313 (40.7) | 114 (36.1) | 0.20 | 396 | 31 (38.7) | 0.55 |
| CABG + valve | 132 (17.2) | 67 (21.2) | 0.48 | 169 | 30 (37.5) | <0.001 |
| Preop. Aspirin (%) | 226 (29.4) | 87 (27.5) | 0.55 | 290 | 23 (28.7) | >0.90 |
| Preop. Anticoagulans (%) | 236 (30.7) | 115 (36.4) | 0.07 | 330 | 21 (26.2) | 0.26 |
| Preop. Heparin (%) | 15 (2.0) | 6 (1.9) | >0.90 | 21 | 0 | 0.39 |
| Aprotinin use (%) | 135 (17.6) | 39 (12.3) | 0.11 | 159 | 15 (18.8) | 0.74 |
| Cardiopulmonary bypass time (min) | 128 ± 50 | 143 ± 62 | <0.001 | 129 ± 52 | 173 ± 70 | <0.001 |
| Aortic clamping time (min) | 78 ± 39 | 86 ± 44 | 0.003 | 79 ± 40 | 100 ± 46 | <0.001 |
| No. RBC transfusions | | | | | | |
| Mean ± SD | 4.5 ± 4.1 | 8.5 ± 8.1 | <0.001 | 5.1 ± 4.8 | 13.2 ± 10.7 | <0.001 |
| Units of RBCs (%) | | | | | | |
| 0 | 69 (9.0) | 5 (1.6) | | 73 | 1 (1.2) | |
| 1-3 | 333 (43.3) | 67 (21.2) | <0.001 | 390 | 10 (12.5) | <0.001 |
| ≥4 | 367 (47.7) | 244 (77.2) | <0.001 | 542 | 69 (86.2) | <0.001 |
| Randomization arm (%) | | | | | | |
| BCD | 357 (46.4) | 186 (58.9) | <0.001 | 492 | 51 (63.7) | <0.001 |
| LR | 412 (53.6) | 130 (41.1) | | 513 | 29 (36.2) | |
| Plasma transfusions (%) | 654 | 301 (95.2) | <0.001 | 877 | 78 (97.5) | 0.004 |

| Attributes | Patients without infections N=769 | Patients with infections N=316 | p | Patients who survived N=1005 | Patients who died N=80 | p |
|---|---|---|---|---|---|---|
| No. plasma transfusions | | | | | | |
| Mean ± SD | 3.4 ± 3.2 | 5.9 ± 6.3 | <0.001 | 3.6 ± 3.3 | 10.5 ± 9.8 | <0.001 |
| Units of plasma (%) | | | | | | |
| 0 | 115 (15.0) | 15 (4.7) | | 128 | 2 (2.5) | |
| 1-3 | 340 (44.2) | 98 (31.0) | <0.001 | 422 | 16 (20.0) | <0.001 |
| ≥4 | 314 (40.8) | 203 (64.2) | <0.001 | 455 | 62 (77.5) | <0.001 |
| Platelet transfusions (%) | 177 (23.0) | 120 (38.0) | <0.001 | 242 | 55 (68.8) | <0.001 |
| Mean ± SD | 0.4 ± 0.9 | 0.9 ± 1.9 | <0.001 | 0.4 ± 0.9 | 2.3 ± 3.5 | <0.001 |
| 0 | 592 (77.0) | 196 (62.0) | <0.001 | 763 | 25 (31.3) | <0.001 |
| 1 | 118 (15.3) | 59 (18.7) | 0.18 | 156 | 21 (26.2) | 0.02 |
| ≥2 | 59 (7.7) | 61 (19.3) | <0.001 | 86 | 34 (42.5) | <0.001 |

*For patients with or without infections or who died and survived. RBC=Red blood cells, BCD=Buffy-coat depleted, LR=Leukocyte-depleted

**Table 2 |** Attributes of Patients Transfused (Versus not Transfused) with Platelets or Plasma

| Attributes | Patients with platelet transfusions N=297 | Patients without platelet transfusions N=788 | p | Patients with plasma transfusions N=955 | Patients without plasma transfusions N=130 | p |
|---|---|---|---|---|---|---|
| First study (%) | 57 (19.2) | 554 (69.0) | <0.001 | 608 (63.6) | 3 (2.3) | <0.001 |
| Female (%) | 133 (44.8) | 247 (31.3) | <0.001 | 324 (33.9) | 56 (43.1) | 0.05 |
| Age Mean ± SD (yrs) | 68.0 ± 11.7 | 63.9 ± 11.3 | <0.001 | 65.5 ± 11.1 | 61.5 ± 14.3 | < 0.001 |
| Type of surgery (%) | | | | | | |
| CABG | 34 (11.4) | 425 (53.9) | <0.001 | 457 (47.8) | 2 (1.5) | <0.001 |
| Valve | 152 (51.2) | 275 (34.9) | <0.001 | 325 (34.0) | 102 (78.5) | <0.001 |
| CABG + valve | 111 (37.4) | 88 (11.2) | <0.001 | 173 (18.1) | 26 (20.0) | <0.001 |
| Preop. Aspirin (%) | 80 (26.9) | 233 (29.6) | 0.41 | 286 (29.9) | 27 (20.8) | 0.03 |
| Preop. Anticoagulans (%) | 88 (29.9) | 263 (33.4) | 0.25 | 319 (33.4) | 32 (24.6) | 0.04 |
| Preop. Heparin (%) | 7 (2.3) | 14 (1.8) | 0.62 | 17 (14.6) | 4 (3.1) | 0.30 |
| Aprotonin use (%) | 82 (27.6) | 92 (11.7) | 0.22 | 124 (13.0) | 50 (38.5) | 0.52 |
| Cardiopulmonary bypass time (min) | 166 ± 66 | 120 ± 43 | <0.001 | 135 ± 56 | 112 ± 38 | <0.001 |
| Aortic clamping time (min) | 107 ± 46 | 70 ± 33 | <0.001 | 80 ± 34 | 80 ± 42 | 0.84 |
| No. RBC transfusions, Mean ± SD | 9.9 ± 8.5 | 4.1 ± 3.3 | <0.001 | 6.1 ± 6.0 | 2.3 ± 2.2 | <0.001 |
| Units of RBC (%) | | | | | | |
| 0 | 3 (1.0) | 71 (9.0) | <0.001 | 44 (4.6) | 30 (23.1) | <0.001 |
| 1-3 | 59 (19.9) | 341 (43.3) | <0.001 | 332 (34.8) | 68 (52.3) | <0.001 |
| ≥4 | 235 (79.1) | 376 (47.7) | <0.001 | 579 (60.6) | 32 (24.6) | <0.001 |
| Randomization arm (%) | | | | | | |
| BCD | 152 (51.2) | 391 (49.6) | 0.68 | 486 (50.9) | 57 (43.8) | 0.14 |
| LR | 145 (48.8) | 397 (50.4) | | 469 (49.1) | 73 (56.2) | |

| Attributes | Patients with platelet transfusions N=297 | Patients without platelet transfusions N=788 | p | Patients with plasma transfusions N=955 | Patients without plasma transfusions N=130 | p |
|---|---|---|---|---|---|---|
| Infections (%) | 120 (40.4) | 196 (24.9) | <0.001 | 301 (31.5) | 15 (11.5) | <0.001 |
| Respiratory tract infections (%) | 65 (21.9) | 89 (11.3) | <0.001 | 144 (15.1) | 10 (7.7) | 0.02 |
| ICU-stay ≥4 days (%) | 169 (56.9) | 183 (23.2) | <0.001 | 323 (33.8) | 29 (22.3) | 0.009 |
| Mortality (%) | 55 (18.5) | 25 (3.2) | <0.001 | 78 (8.1) | 2 (1.5) | 0.004 |
| Mortality with infections(%) | 33 (11.1) | 9 (1.1) | <0.001 | 41 (4.3) | 1 (0.8) | 0.05 |
| Mortality without infections (%) | 22 (7.4) | 16 (2.0) | <0.001 | 37 (3.9) | 1 (0.8) | 0.07 |

RBC=Red blood cells, BCD=Buffy-coat depleted, LR=Leukocyte-depleted

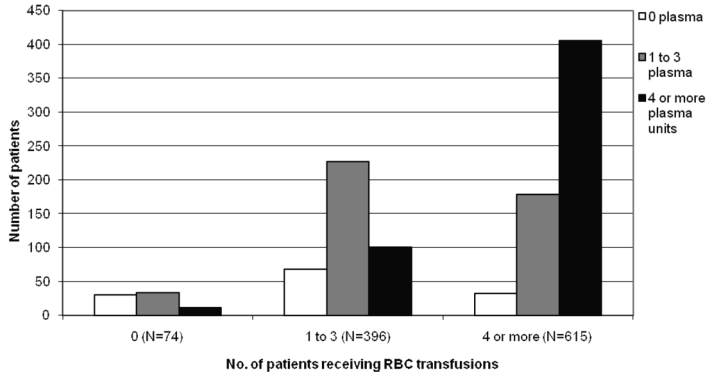


**Figure 1 |** Distribution of number of patients receiving red blood cell (RBCs) transfusions (0,1-3 or ≥4 units) with plasma transfusions (0,1-3 or ≥4 units).

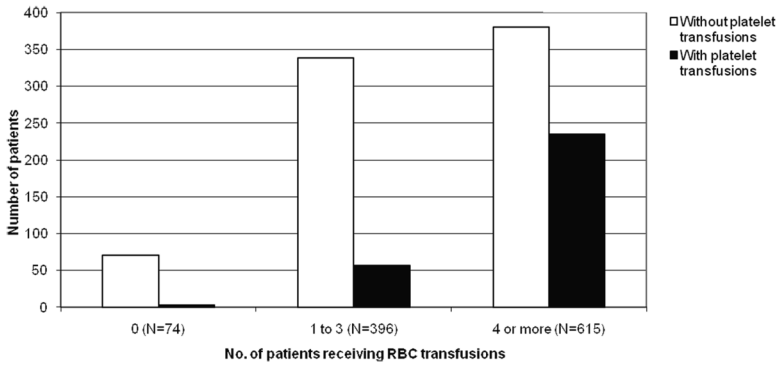


**Figure 2 |** Distribution of number of patients receiving red blood cell (RBCs) transfusions RBCs (0,1-3 or ≥ 4 units) with (or without) platelet transfusions.

**Table 3 |** Risk Factors for Postoperative Infections, ICU-stay ≥4 days, Overall Mortality and Deaths occurring in the Presence (or Absence) of Infections Based on Univariate Analyses

| Risk factors | Infections | ICU-stay ≥4 days | Mortality | Mortality with infection | Mortality without infection |
|---|---|---|---|---|---|
| Study (first/second) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Age | <0.001 | <0.001 | <0.001 | <0.001 | 0.06 |
| Gender (male/female) | 0.001 | <0.001 | 0.003 | 0.04 | 0.03 |
| Type of surgery (CABG/valve/both) | 0.39 | <0.001 | <0.001 | <0.001 | 0.02 |
| Cardiopulmonary bypass | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Number of RBC transfusions | <0.001 | <0.001 | <0.001 | <0.001 | 0.003 |
| Randomization (BCD/LR) | <0.001 | 0.41 | 0.004 | 0.005 | 0.24 |
| Platelet transfusions | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Number of plasma transfusions | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

RBC=Red blood cells, BCD=Buffy-coat depleted, LR=Leukocyte-depleted

**Table 4 |** Results of Multivariate Analyses for Postoperative Infections and ICU-stay for ≥4 days.

| Risk factors | Infections | | | ICU-stay ≥4 Days | | |
|---|---|---|---|---|---|---|
| | MVA OR | MVA 95% CI | p | MVA OR | MVA 95% CI | p |
| Study (first/second) | 0.62 | 0.41-0.93 | 0.02 | 1.81 | 1.20-2.73 | 0.01 |
| Age (years) | 1.03 | 1.01-1.04 | <0.001 | 1.02 | 1.01-1.03 | 0.01 |
| Gender (male/female) | 1.43 | 1.06-1.93 | 0.02 | 1.18 | 0.86-1.60 | 0.30 |
| Type of surgery | 0.97 | 0.75-1.25 | 0.80 | 1.16 | 0.89-1.52 | 0.27 |
| Cardiopulmonary bypass time (hours) | 1.08 | 0.91-1.28 | 0.38 | 1.21 | 1.01-1.44 | 0.04 |
| Number of RBC transfusions | 1.12 | 1.07-1.17 | <0.001 | 1.21 | 1.15-1.28 | <0.001 |
| Randomization arm (BCD/LD) | 1.67 | 1.25-2.23 | <0.001 | 0.86 | 0.64-1.15 | 0.30 |
| Number of platelet transfusions | 1.05 | 0.89-1.24 | 0.54 | 1.16 | 0.76-1.76 | 0.50 |
| Number of plasma transfusions | 1.01 | 0.96-1.07 | 0.61 | 0.99 | 0.94-1.06 | 0.94 |

RBC=Red blood cells, BCD=Buffy-coat depleted, LR=Leukocyte-depleted

plasma transfusions, platelet transfusions and randomization arm, but not with the number of RBC units transfused (Table 5). Randomization arm, age, platelet transfusions and plasma transfusions were associated with deaths occurring in the presence of infections in the postoperative period. Time on cardiopulmonary bypass and number of transfused plasma units were associated with deaths without postoperative infections (Table 5).

**Table 5 |** Results of Multivariate Analyses for Overall Mortality and Deaths occurring in the Presence (or Absence) of Infections

| | Mortality | | | Mortality with infection | | | Mortality without infection | | |
|---|---|---|---|---|---|---|---|---|---|
| | MVA OR | MVA 95% CI | p | MVA OR | MVA 95% C I | p | MVA OR | MVA 95% CI | p |
| Study (first/second) | 0.61 | 0.31-1.22 | 0.16 | 0.66 | 0.26-1.64 | 0.37 | 0.60 | 0.24-1.49 | 0.27 |
| Age (Years) | 1.05 | 1.02-1.08 | 0.003 | 1.07 | 1.02-1.11 | 0.01 | 1.02 | 0.99-1.06 | 0.18 |
| Gender (male/female) | 1.55 | 0.90-2.66 | 0.12 | 1.41 | 0.67-2.94 | 0.37 | 1.87 | 0.90-3.88 | 0.10 |
| Type of surgery (CABG/Valve/Both) | 1.30 | 0.86-1.98 | 0.22 | 1.31 | 0.75-2.29 | 0.34 | 1.26 | 0.73-2.19 | 0.41 |
| Cardiopulmonary bypass time (hours) | 1.39 | 1.08-1.78 | 0.01 | 1.15 | 0.82-1.61 | 0.42 | 1.80 | 1.34-2.43 | <0.001 |
| Number of RBC transfusions | 0.99 | 0.94-1.06 | 0.84 | 1.05 | 0.98-1.12 | 0.15 | 0.93 | 0.84-1.02 | 0.11 |
| Randomization arm (BCD/LD) | 1.80 | 1.04-3.13 | 0.04 | 2.12 | 1.01-4.58 | 0.05 | 1.36 | 0.70-2.77 | 0.40 |
| Number of platelet transfusions | 1.37 | 1.12-1.68 | 0.002 | 1.29 | 1.03-1.61 | 0.03 | 1.14 | 0.93-1.41 | 0.22 |
| Number of plasma transfusions | 1.14 | 1.06-1.23 | <0.001 | 1.11 | 1.01-1.21 | 0.02 | 1.10 | 1.01-1.21 | 0.04 |

RBC=Red blood cells, BCD=Buffy-coat depleted, LR=Leukocyte-depleted

## DISCUSSION

In this retrospective analysis of data from two randomized controlled trials [5,6], the number of transfused plasma units was independently associated with all-cause mortality. Although leukocyte-containing RBCs were associated with mortality, the number of transfused RBC units was not. The number of transfused RBC units, but not the number of transfused plasma units or the receipt of platelet transfusion, was associated with the development of postoperative infections and with the stay in the ICU for at least 4 days. Transfusion of platelet units was associated with mortality with postoperative infections developed during the hospital-stay. Because patients who receive RBC transfusions, receive also plasma and platelet transfusions, it is difficult to determine whether plasma and platelet transfusions could be independently associated with postoperative complications.

Our results are consistent with those of several previous studies which reported that infections after cardiac surgery are associated (in a dose-dependent manner) with the number of RBC transfusions [1-4]. We previously reported that the excess mortality secondary to leukocyte-containing RBC transfusions was due to higher mortality associated with postoperative infections [15]. To identify other risk factors (or confounders) than RBCs, in the current analysis we distinguished between deaths occurring in the presence or absence of infections in the postoperative period. Because in our first RCT [5] organ failure was not recorded, in this analysis we used ICU-stay for at least 4 days as parameter for prolonged mechanical ventilation (and thus for respiratory failure). In practice, after extubation almost all patients were transferred from the ICU to the ward within 24 hours. In agreement with other studies [16,17], we found in the multivariate analysis that the most important predictors of longer ICU-stay were the number of transfused RBCs and the patient's age. However, in contrast to others [18-21], we found no association between prolonged mechanical ventilation and plasma or platelet transfusions.

The finding that plasma transfusions are associated with all-cause mortality, while leukocyte-containing RBC transfusions and platelet transfusions are associated only with deaths with postoperative infections in the postoperative period, were unanticipated. A predominant role of plasma transfusions on outcome after cardiac surgery is consistent with the results of Ranucci et al [22]. Other studies that focused on plasma transfusions reported contradictory findings [7-9]. Similarly platelet transfusions were reported not to be associated with mortality [10,11], except in two studies that found an association with platelet transfusions and mortality in cardiac surgery; however, these studies applied no corrections for concomitant RBC or plasma transfusions [12,13].

Plasma-containing blood products have been implicated in the pathogenesis of transfusion-related acute lung injury (TRALI). Patients undergoing cardiac surgery are at higher risk to develop TRALI, even if leukocyte-reactive antibodies in transfused plasma are absent [23,24]. However, TRALI seems unlikely as a cause of enhanced mortality because parameter for respiratory failure (prolonged ICU-stay) was not associated with plasma transfusion in our study. On the other hand, in a laboratory analysis we found in patients with low mannose-binding lectin (MBL) levels is a risk factor in the development of multiple-organ-dysfunction-syndrome (MODS), which may contribute to mortality [25]. Besides allogeneic leukocytes in RBC products inducing higher pro-inflammatory cytokine levels after cardiac surgery associated with more postoperative infections and mortality [26], platelet units also contain bioactive mediators. Increased CD40 ligand (CD40L or CD154) present in platelet units can induce production and release of proinflammatory markers [27,28]. Both leukocyte-containing RBCs and platelet transfusions could thus aggravate an existing inflammatory reaction impairing the outcome after cardiac surgery. More investigations are needed on the possible causal roles of transfusion of different blood components.

This study has several limitations. First, this is an observational analysis, despite the fact that the data were extracted from two RCTs. Second, the combined studies had not been designed to investigate the effects of plasma and platelet transfusions. Evidence-based transfusion triggers for platelet and plasma transfusions had not been used in either of our RCTs. Instead, plasma and platelet transfusions were administered based on institutional habits and the preferences of the clinicians. In both studies, also information on blood loss was not adequately documented. Aprotinin to reduce the risk of bleeding was administered only in the second study and only for selected patients (16% of the current population). In an earlier study we found no effect of aprotinin in the development of postoperative complications [26]. Therefore, the effects of aprotinin were not considered in this analysis. Finally, our two RCTs had been performed 7 years apart. Between the time periods that the two studies were conducted, surgical procedures and transfusion practices has changed, as reflected in the difference in length of ICU-stay between the two studies.

Nowadays, more restrictive criteria for RBC transfusion are used. In the periods when our studies were performed no clear consensus on the indications for plasma and platelet transfusions in these patient populations was present. Nevertheless despite guidelines for blood transfusions, the patients that receive perioperative blood transfusions in cardiac surgery is still high [29]. As the use of antiplatelet agents increases, we expect that more patients will receive blood transfusions in the future. In conclusion, we found that the number of RBC transfusions was not associated with postoperative mortality, whereas plasma transfusions

were dose-dependently associated with all-cause mortality. The transfusion of platelets was associated with mortality in the presence of (leukocyte-containing) RBCs. However, only few retrospective studies have considered the effects of plasma and platelet transfusions, which predominantly are transfused to patients who also received RBC transfusions. Our findings underscore the need for further studies to investigate the aggregate effects of all the various blood components transfused in cardiac surgery.

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