Risks Associated With the Transfusion of Various Blood Products in Aortic Valve Replacement

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Background. Patients undergoing cardiac operations often require transfusions of red blood cells, plasma, and platelets. From a statistical point of view, there is a significant collinearity between the components, but they differ in indications for use and composition. This study explores the relationship between the transfusion of different blood components and long-term mortality in patients undergoing aortic valve replacement alone or combined with revascularization.

Methods. A retrospective single-center study was performed including 1,311 patients undergoing aortic valve replacement. Patients who received more than 7 units of red blood cells, those who died early (7 days), and emergency cases were excluded. Patients were monitored for up to 9.5 years. A broad selection of potential risk factors were analyzed using Cox proportional hazards regression, where transfusion of red blood cells, plasma, and platelets were forced to remain in the model.

Results. The transfusion of red blood cells was not associated with decreased long-term survival (hazard ratio [HR], 1.01; \( p = 0.520 \)) nor was the transfusion of platelets (HR, 0.946; \( p = 0.124 \)); however, the transfusion of plasma was (HR, 1.041; \( p < 0.001 \)). All HRs are per unit of blood product transfused. No increased risk was found for patients undergoing a combined procedure.

Conclusions. No significant risk for long-term mortality was associated with transfusion of red blood cells during the study period. However, the transfusion of plasma was associated with increased mortality.

Blood transfusions after coronary artery bypass grafting (CABG) have commonly been associated with increased long-term mortality \([1–8]\), as has CABG combined with aortic valve replacement (AVR) \([9]\). We reached different results in a CABG population, where we extended the number of risk factors entered in the survival analysis, and did not find any association between transfusion of red blood cells (RBC) and long-term survival in patients only undergoing CABG \([10]\). Instead, preoperative hemoglobin and renal function were strong predictors for survival, both of which also are strongly associated with receiving blood transfusions. In a later analysis, we included all types of transfusions and found that the transfusion of plasma was significantly associated with decreased long-term mortality \([11]\).

Whereas the CABG population has a high degree of vascular disease, diabetes, and chronic obstructive pulmonary disease, patients who require valve operations present a different spectrum of risk factors. As previously shown by our group, the risk factors seem to determine the need for transfusion and also long-term prognosis \([10, 11]\). Therefore, studying the relation between transfusion and outcome in AVR patients with a different composition of risk factors is needed. Accordingly, the present investigation evaluated the relationship between transfusion of different components and long-term mortality in patients undergoing AVR alone or together with CABG.

Material and Methods

The local ethics committee approved the study protocol. The patients included in this study underwent cardiac operations at the Cardiothoracic Department at the University Hospital in Lund, Sweden, from January 1, 2002, to December 31, 2008.

Study Design

Data were collected from four principal sources. Clinical data were retrieved from the in-house quality database, which continuously collects relevant clinical information from the perioperative care during the patients' hospital...
**Abbreviations and Acronyms**

- ALT = alanine aminotransferase
- AVR = aortic valve replacement
- BMI = body mass index
- CABG = coronary artery bypass grafting
- CCS = Canadian Cardiovascular Society
- CI = confidence interval
- COPD = chronic obstructive pulmonary disease
- CPB = cardiopulmonary bypass
- CRP = C-reactive protein
- eGFR = estimated glomerular filtration rate
- HR = hazard ratio
- IABP = intraaortic balloon pump
- ICU = intensive care unit
- LVEF = left ventricular ejection fraction
- MDRD = Modified Diet in Renal Disease
- NYHA = New York Heart Association
- PCI = percutaneous coronary intervention
- PLA = plasma
- PVD = peripheral vascular disease
- RBC = red blood cell
- RIFLE = risk-injury-failure-loss-end stage
- TRALI = transfusion-related acute lung injury
- TRC = platelets

stay. Extracts from the databases of the hospital clinical chemistry laboratory and hospital blood bank served as the second and third sources of data.

Survival and time of death for each patient were checked against the national tax registry in 2011, defining the follow-up period from 2.5 to 9.5 years. Where data were missing or extreme outliers were identified, patient records were read to complete the database as a first step. Imputation was used when no data could be retrieved and was considered proper [8].

**Patient Inclusion and Exclusion**

All patients who underwent AVR alone or AVR together with CABG were included in the study (n = 1,334). The study excluded 6 patients who underwent emergent operations, defined as an operation within 1 hour of the decision to operate, and 17 patients who died during the first 7 days. A total of 1,311 patients were finally included in the analysis.

In a subgroup analysis, we also excluded 200 patients who received 8 or more units of RBCs. The cutoff of 8 units was chosen because 8 units of RBC clinically represents, together with plasma, more than half the blood volume in most patients and indicates a massive bleeding where the transfusion is life-saving.

**Database Management**

The construction of the database has been described in detail previously [10, 11]. To summarize, the database has a 100% completion rate on perioperative information, 100% on transfusion, 99.9% on mortality, and 95% to 99% on laboratory data.

Postoperatively, renal function for the patients was categorized using RIFLE (Risk-Injury-Failure-Loss-End Stage) criteria based on preoperative creatinine and the maximum creatinine during the hospital stay [11]. Renal function was also expressed as estimated glomerular filtration rate (eGFR) and calculated according to the Modified Diet in Renal Disease formula [11].

**Selection of Outcomes and Statistical Analysis**

Selection of variables for the survival analysis was based on frequently found predictors for decreased survival in recent survival studies focusing on renal function or RBC transfusion in cardiac operations [11]. In addition, we added other potential risk factors and preoperative laboratory variables that could reflect a preoperative morbidity of importance for long-term survival.

Entered as dichotomous variables were sex, diabetes, COPD, history of cerebrovascular disease, peripheral vascular disease, left ventricular ejection fraction (LVEF) 0.30 to 0.50, LVEF of less than 0.30, recent myocardial infarction, known pulmonary hypertension (systolic pressure > 60 mm Hg), acute coronary symptoms, previous CABG, previous percutaneous coronary intervention, sole AVR or combined AVR and CABG, preoperative or postoperative intraaortic balloon pump, postoperative sepsis, postoperative stroke, postoperative atrial fibrillation, postoperative myocardial infarction, and reoperation for bleeding or mediastinitis.

Perfusion time, age, time on ventilator in the intensive care unit, and body mass index were entered as continuous variables. Renal function (expressed as preoperative eGFR), hemoglobin, plasma C-reactive protein (CRP), plasma alanine aminotransferase, plasma leukocyte count, and platelet count were entered as continuous variables. Transfusion of blood products was defined as a transfusion during the operation or the hospital stay and was entered as a continuous variable representing units of blood products transfused.

A Student t test was used for group comparisons where numbers were large and not strongly skewed; otherwise, a Wilcoxon–Mann-Whitney test was performed. Unless otherwise stated, numbers are presented as mean ± 1 standard deviation.

The Cox proportional hazard model was used for determining the factors that had an effect on long-term survival, and Wald statistics was used to determine the strength of the relation. In the Cox analysis, a stepwise removal of nonsignificant variables was performed where we forced transfusions of blood products to remain in the analysis. The interaction between different types of transfusion was evaluated by creating eight variables: RBC transfusion (yes/no), plasma transfusion (yes/no), and platelet transfusion (yes/no) in all combinations. These variables were entered in the final model if they had more than 10 cases in a group. For missing data, a mean substitution was used. The R-project 2.13.0 software (The R Project for Statistical Computing http://www.r-project.org/) with the survival package was used to test the proportional hazards assumption for a Cox regression model fit. All other statistical analysis was performed using Statistica 8 software (StatSoft Inc, Tulsa, OK).
In the study group, 938 patients (71.5%) received a RBC transfusion, 669 (51.0%) received a plasma transfusion, and 214 (16.3%) received platelets (Fig 1). Patient characteristics and outcome are described in Appendix Tables 1 and 4 based on whether they received plasma. Characteristics and outcome based on RBC and platelet transfusion are presented in Appendix Tables 2, 3, 5, and 6.

Cox Analysis on the Entire Cohort
A stepwise elimination of nonsignificant variables in the Cox proportional hazard ratio (HR) analysis left the following variables in the model: age per year, COPD, diabetes, peripheral vascular disease, LVEF less than 0.30, LVEF 0.30 to 0.50, preoperative CRP per mg/L, preoperative eGFR per mL/min/1.73 m², reoperation for mediastinitis, transfusion of RBC per unit, transfusion of plasma per unit, and transfusion of platelet per unit (Table 1). In this model, transfusion of RBC had a HR of 1.010 (95% CI, 0.98 to 1.04, $p = 0.520$), transfusion of plasma had a HR of 1.041 (95% CI, 1.03 to 1.06, $p < 0.001$), and transfusion of platelets had a HR of 0.946 (95% CI, 0.88 to 1.02, $p = 0.124$) for each unit transfused (Table 1 and Fig 2). The result of the interaction analysis did not find any significant interactions (Table 2).

Subgroup Analysis
We excluded from the cohort 200 patients who received more than 7 units of RBC to form a subgroup that was used to further study the effect of plasma transfusion on survival. When stepwise elimination was performed on the remaining 1,111 patients, the following factors remained in the model: age per year, COPD, diabetes, LVEF 0.30, LVEF 0.30 to 0.50, preoperative CRP per mg/L, preoperative leukocytes per 10⁹/L, postoperative stroke, transfusion of RBC per unit, transfusion of plasma per unit, and transfusion of platelets per unit. Transfusion of RBC had a HR of 1.047 (95% CI, 0.98 to 1.12, $p = 0.186$), transfusion of plasma had a HR 1.075 (95% CI, 1.05 to 1.10, $p < 0.001$), and

Table 1. Cox Proportional Hazard Modela

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n = 1311)</th>
<th>Patients Receiving &lt; 8 Units of RBC (n = 1111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>HR (95% CI)</td>
<td>Wald</td>
</tr>
<tr>
<td>1.055 (1.04–1.07)</td>
<td>49.4</td>
<td>&lt;0.0001$^b$</td>
</tr>
<tr>
<td>1.844 (1.41–2.41)</td>
<td>20.1</td>
<td>&lt;0.0001$^b$</td>
</tr>
<tr>
<td>1.697 (1.30–2.21)</td>
<td>15.3</td>
<td>0.001$^b$</td>
</tr>
<tr>
<td>1.462 (1.10–1.94)</td>
<td>6.9</td>
<td>0.0086$^b$</td>
</tr>
<tr>
<td>1.488 (1.17–1.90)</td>
<td>10.2</td>
<td>0.0014$^b$</td>
</tr>
<tr>
<td>1.971 (1.43–2.71)</td>
<td>17.4</td>
<td>&lt;0.0001$^b$</td>
</tr>
<tr>
<td>Pre-op CRP</td>
<td>1.005 (1.00–1.01)</td>
<td>9.9</td>
</tr>
<tr>
<td>Pre-op eGFR</td>
<td>0.995 (0.99–1.00)</td>
<td>4.4</td>
</tr>
<tr>
<td>Pre-op leukocytes</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Transfusion of Red blood cells</td>
<td>0.453 (0.21–0.99)</td>
<td>4.0</td>
</tr>
<tr>
<td>Plasma</td>
<td>1.014 (1.03–1.06)</td>
<td>34.1</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.946 (0.88–1.02)</td>
<td>2.4</td>
</tr>
</tbody>
</table>

aCox proportional hazard analysis of the entire population and for the subgroup of patients who received < 8 units of blood. Nonsignificant correlations are left blank. $^b$Significant $p$ values.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; HR = hazard ratio; LVEF = left ventricular ejection fraction; PVD = peripheral vascular disease.
transfusion of platelets had a HR of 0.921 (95% CI, 0.75 to 1.13, \( p = 0.124 \)) for each unit transfused (Table 1).

**Analysis of Plasma Transfusions**

Patients who received plasma had more preoperative comorbidities (Appendix Table 1) and more postoperative complications (Appendix Table 4) than patients who did not receive plasma. Patients who received plasma received an average of 8.0 ± 10.8 units (median, 4; interquartile range, 2 to 9 units), and 90.3% also received RBC transfusion, with an average of 6.1 ± 2.1 units (median, 4, interquartile range, 2 to 8 units).

**Analysis of Patients With Elevated CRP**

Patients who had an elevated CRP (>5 mg/L) preoperatively had more comorbidities in general but did not differ in age, sex, body mass index, frequency of diabetes or peripheral vascular disease compared with patients with normal CRP (Appendix Table 7). Patients with elevated CRP had worse renal outcome, required more transfusion, and had more heart failure and sepsis (Appendix Table 8).

**Comment**

The present study revealed that plasma instead of RBCs is associated with increased long-term mortality after aortic valve operations. This finding contrasts previous studies in cardiac surgery where plasma has not been entered in the analysis [1–3, 12]. In a study focusing on AVR, Engoren and colleagues [12] found that RBC transfusion was associated with adverse outcome only if valve

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**Table 2. Interaction Analysis**

<table>
<thead>
<tr>
<th>Interaction</th>
<th>No.</th>
<th>HR (95% CI)</th>
<th>Wald</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC yes / PLA yes / TRC yes</td>
<td>190</td>
<td>1.247 (0.75–2.08)</td>
<td>0.7</td>
<td>0.3980</td>
</tr>
<tr>
<td>RBC yes / PLA yes / TRC no</td>
<td>414</td>
<td>1.348 (0.91–2.00)</td>
<td>2.2</td>
<td>0.1400</td>
</tr>
<tr>
<td>RBC yes / PLA no / TRC yes</td>
<td>16</td>
<td>2.048 (0.71–5.88)</td>
<td>1.8</td>
<td>0.1825</td>
</tr>
<tr>
<td>RBC no / PLA yes / TRC yes</td>
<td>6</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>RBC no / PLA yes / TRC no</td>
<td>59</td>
<td>0.973 (0.51–1.84)</td>
<td>0.0</td>
<td>0.9320</td>
</tr>
<tr>
<td>RBC no / PLA no / TRC yes</td>
<td>2</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>RBC yes / PLA no / TRC no</td>
<td>318</td>
<td>1.076 (0.71–1.64)</td>
<td>0.1</td>
<td>0.7323</td>
</tr>
</tbody>
</table>

*Interaction between different types of transfusion when the variables were added to the final Cox model. Number of patients in each group is also presented.

CI = confidence interval; HR = hazard ratio; PLA = plasma; RBC = red blood cells; TRC = platelets.
replacement was combined with a coronary operation. The present analysis could not find that valve replacements or combined procedures differed in long-term survival. To our knowledge, the study by Engoren and colleagues [12] and the present study are the only studies focusing on valve patients. Therefore, it is fair to assume that RBC transfusion is not associated with increased long-term mortality in AVR patients.

We previously performed an analysis including all types of blood products in coronary artery operations and found that RBC transfusion was not associated with adverse outcome, whereas plasma transfusion was [11]. Only a few studies have included plasma in a study on long-term mortality. However, those that examined short-term outcome found a negative effect associated with plasma [13–15]. Plasma transfusions have several well-documented adverse effects, such as allergic reactions, transfusion-related acute lung injury, and other immunologic responses [16], which could explain the adverse short-term outcome.

The adverse long-term outcome associated with plasma transfusion found in this study could be explained by other mechanisms than those described above. The present study does not offer any insight to the underlying mechanisms. The most important question is, however, whether plasma transfusion is a surrogate marker for a comorbidity that we cannot control for in our model. Presently, we cannot conclude whether the plasma is the problem or the poor condition of the patient who requires it.

The rate of plasma transfusion was high and the indication multifactorial. The tradition at our department during the study interval was to mainly use plasma as colloid volume substitution after the operation to keep intravascular volume at an adequate level. Another indication for plasma transfusion alone is postoperative coagulopathy. Still, 90.3% of the patients who received a plasma transfusion also received a RBC transfusion (Fig 1), leaving only 59 patients (4.5%) who received only plasma transfusions. Therefore, the most common indication for plasma transfusion in this study was postoperative bleeding, and in the few who had plasma but no RBC, plasma was used a volume expander. However, patients who received a plasma transfusion were older and had significantly more preoperative morbidity than nonreceivers. Thus, plasma transfusion could be a marker for postoperative bleeding and also for comorbidity, as presented in Appendix Table 1.

The present study found a weak association between preoperative renal function and long-term outcome. Several studies, including CABG alone or combined with AVR, have shown this association is much stronger [10, 17–19]. For instance, in a similar model including only CABG patients, we found that preoperative eGFR was one of the strongest predictors in the survival analysis, whereas in the present study, it was one of the weaker [11]. The findings in this study offer no explanation for this. It could be argued, however, that an important cause for renal dysfunction in this patient population is low cardiac output due to the aortic stenosis, which is reversed once the valve has been replaced, thereby eliminating a risk factor. In the CABG population, nonreversible atherosclerosis could be the main cause for renal dysfunction. This should serve only as an observation and be used to form a hypothesis for future studies.

The analysis also revealed another unexpected risk factor, preoperative CRP. In a similar analysis of 5,261 CABG patients, our group could not find that preoperative CRP affected long-term survival [11]. However, Cappabianci and colleagues [20] and Kangasniemi and colleagues [21] associated increased preoperative CRP with increased long-term mortality. Both studies, however, included small patient cohorts and a limited number of risk factors as well as a mixed population of cardiac surgical patients. Increased CRP levels have been associated with adverse long-term outcome in patients with coronary artery disease in general [22].

In patients with aortic valve disease not scheduled for surgical intervention, CRP has shown conflicting results as a predictor for outcome. Imai and colleagues [23] found an association between aortic valve area and progression rate, Solberg and colleagues [24] found it was predictive for survival, but Novaro and colleagues [25] could not find any association between CRP and disease severity in much larger cohorts.

In a post hoc analysis, we could conclude that patients with elevated CRP had more comorbidities but did not differ in age, sex, or body mass index. Moreover they had slightly worse renal outcome, needed more transfusions, and had more heart failure and sepsis. They did not, however, have more neurologic complications, more atrial fibrillation, or more reoperations for bleeding. From these observations, it is hard to deduce any mechanisms for the observation that preoperative CRP level is associated with adverse long-term outcome. To conclude, the association between CRP and outcome in AVR patients offers possibilities for further research on its validity as a prognostic marker as well as the underlying mechanisms.

The present analysis has a few shortcomings. It would have been desirable to have a larger number of individuals in the analysis. In a multivariate analysis of this type, slightly more than 1,300 individuals could be considered too low for sufficient power, and a larger population would be desired. However, we studied more than 5,000 patients in a similar study describing a CABG population and made similar findings [11].

The analysis was made with the presumption that the risk associated with blood products is linear. At the same time, the number of plasma units transfused is a highly skewed variable. In an effort to control for this, a post hoc analysis was made where the square root of units of plasma was used. However, the Wald decreased from 34 to 32 by this change. A linear approach to the risk associated with blood products therefore seems reasonable.

The sex of the donors and the age of blood products have both been suggested as risk factors in similar analyses [6, 26]. We did not have access to data for these two variables and could not adjust for them. However, because our analysis did not find any association between RBC transfusion and outcome, the age of the RBCs would probably not affect the analysis.
Despite our effort to increase the number of potential risk factors in our analysis, there were several factors that we could not control for. For instance, genetic predisposition, coronary artery disease severity, and intraoperative complications could be factors affecting long-term outcome and were not included in this analysis.

In conclusion, the salient finding of this study is the absence of any association between RBC transfusion and long-term mortality in patients undergoing AVR alone or combined with CABG. Instead, an association was found between plasma transfusion and long-term mortality. Given that more than half of the patients undergoing cardiac operations receive a transfusion of any sort, the importance of the findings in this and similar studies should not be underestimated. Instead, better models to control for confounding risk factors are needed to further clarify this topic and thereby improve transfusion guidelines.

We would like to express our gratitude to Associate Professor Peter Höglund for his invaluable help with survival statistics, Professor Martin L. Olsson for providing transfusion data, and Jan Karlsson for building and maintaining our primary database.

References