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

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Abstract

Background:

Patients undergoing cardiac surgery 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 together with revascularization.

Methods:

A retrospective single-centre study was performed including 1311 patients undergoing aortic valve replacement. Patients receiving more than seven units of red blood cells, those suffering early death (7 days) and emergency cases were excluded. Patients were followed for a period of up to 9.5 years. A broad selection of potential risk factors were analysed 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 (HR=1.01, $p=0.520$), whereas the transfusion of plasma was (HR=1.041, $p<0.001$). Transfusion of platelets was not associated with decreased long-term survival (HR=0.946, $p=0.124$). All hazard ratios 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.

Introduction

Blood transfusions after CABG have commonly been associated with increased long-term mortality (1-8) as has CABG combined with 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 RBC and long-term survival in patients only undergoing CABG (10). Instead pre-operative hemoglobin and renal function were found to be 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 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 COPD, the population of patients requiring valve surgery present a different spectrum of risk factors. As previously shown by our group, it seems as if the risk factors determine both the need for transfusion and long-term prognosis (10, 11). Therefore, studying the relation between transfusion of outcome in valve patients with a different composition of risk-factors is needed. Accordingly, the aim of the present investigation is to evaluate the relationship between transfusion of different components and long-term mortality in patients undergoing AVR alone or together with CABG.

Methods

Study design

The study protocol was approved by the local ethics committee. The patients included in this study underwent cardiac surgery at the Cardiothoracic Department at the University Hospital in Lund, Sweden, from January 1, 2002 to December 31, 2008. Data was collected from four principal sources. The clinical data was retrieved from the in-house quality database, which continuously collects relevant clinical information from the perioperative care during the patients' hospital stay. Extracts from the databases of the hospital clinical chemistry laboratory and hospital blood bank served as the second and third source of data. Survival and time of death for each patient was checked against the national tax registry in 2011 defining the follow-up period from 2.5 to 9.5 years. Where data was 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=1334). Patients who underwent emergent surgery, defined as surgery within one hour of the decision to operate, were excluded (n=6). Patients who died during the first seven days also were excluded (n=17). A total of 1311 patients were finally included in the analysis.

In a subgroup analysis, we also excluded patients who received 8 or more units of RBC (n=200). The cut-off of 8 units was chosen since 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 95-99% on laboratory data.

Postoperatively, renal function for the patients was categorized using RIFLE-criteria based on preoperative creatinine and the maximum creatinine during the hospital stay(11). Renal function was also expressed as eGFR and calculated according to the MDRD 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 surgery(11). In addition, we added other potential risk factors and pre-operative laboratory parameters that could reflect a pre-operative morbidity of importance for long-term survival. The following variables were entered as dichotomous variables: gender, diabetes, COPD, history of cerebrovascular disease, peripheral vascular disease, LVEF 30-50%, LVEF<30%, recent myocardial infarction, known pulmonary hypertension (systolic pressure>60 mmHg), acute coronary symptoms, previous CABG, previous PCI, sole AVR or combined AVR and CABG, IABP before surgery, IABP after surgery, post-operative sepsis, post-operative stroke, post-operative atrial fibrillation, post-operative myocardial infarction and reoperation for bleeding or mediastinitis. Perfusion time, age, time on ventilator in the ICU and BMI were entered as continuous variables. Renal function (expressed as preoperative eGFR), hemoglobin, plasma CRP, plasma ALT, plasma leukocyte and platelet count were entered as continuous variables. Transfusion of blood products was defined as a transfusion during surgery or the hospital stay, and was entered as a continuous variable representing units of blood products transfused.

A student's 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 \pm 1 standard deviation.

The Cox proportional hazard model was used for determining which factors had an impact on long-term survival, and Wald-statistics was used to determine the strength of the relation. In the Cox analysis a stepwise removal of non-significant variables were 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 then 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 (version 2.13.0) software with the survival package was used to test the proportional hazards assumption for a Cox regression model fit. All other statistics was performed using Statistica version 8 (StatSoft inc, Tulsa, OK, USA)

Results

Study population

In the study group, 938 patients (71.5%) received a RBC transfusion, 669 patients (51.0%) received plasma transfusion and 214 patients (16.3%) received platelets (figure 1). Patient characteristics and outcome are described in table E1 and E4 based on whether they received plasma or not.

Characteristics and outcome based on RBC and platelet transfusion are presented in tables E2, E3, E5, and E6.

Cox analysis on the entire cohort

A stepwise elimination of non-significant variables in the Cox proportional hazard ratio analysis left the following variables in the model: age per year, COPD, diabetes, peripheral vascular disease, LVEF <30%, LVEF 30-50%, pre-operative CRP per mg/L, Pre-operative eGFR per ml/min/1.73m², reoperation for mediastinitis, transfusion of RBC per unit, transfusion of plasma per unit and transfusion of platelets per unit (Table 1). In this model, transfusion of RBC gave a hazard ratio of 1.010 (95% C.I. 0.98-1.04, p=0.520), transfusion of plasma gave a hazard ratio 1.041 (95% C.I. 1.03-1.06, p<0.001) and transfusion of platelets gave a hazard ratio of 0.946 (95% C.I. 0.88-1.02, p=0.124) for each unit transfused (Table 1 and Figure 2). The result of the interaction analysis did not find any significant interactions (Table 2).

Subgroup analysis

Patients that received more than 7 units of RBC (n=200) were excluded from the cohort to form a subgroup that was used to further study the impact of plasma transfusion on survival. When stepwise elimination was performed on the remaining 1111 patients, the following factors remained in the model: age per year, COPD, diabetes, LVEF <30%, LVEF 30-50%, pre-operative CRP per mg/L, pre-operative 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 gave a hazard ratio of 1.047

(95% C.I. 0.98-1.12, $p=0.186$), transfusion of plasma gave a hazard ratio 1.075 (95% C.I. 1.05-1.10, $p<0.001$), and transfusion of platelets gave a hazard ratio of 0.921 (95% C.I. 0.75-1.13, $p=0.124$) for each unit transfused (Table 1).

Analysis of plasma transfusions

Patients that received plasma had more pre-operative comorbidities (Table E1) and more post-operative complications (Table E4) as compared to patients not receiving plasma. The patients that received plasma received on average 8.0 ± 10.8 (median 4, IQR 2-9) units of plasma, and 90.3% also received RBC transfusion with an average of 6.1 ± 2.1 (median 4, IQR 2-8) units.

Analysis of patient with elevated CRP

The patients who had an elevated CRP ($> 5\text{mg/L}$) preoperatively had more co-morbidities in general, but did not differ in age, sex, BMI, frequency of diabetes or peripheral vascular compared to patients with normal CRP (Table E7). In terms of outcome, the patients with elevated CRP had worse renal outcome, required more transfusion, had more heart failure and sepsis (Table E8).

Discussion

The present study revealed that plasma instead of RBCs is associated with increased long-term mortality after aortic valve surgery. This finding contrasts previous studies in cardiac surgery where plasma has not been entered in the analysis (1, 2, 3, 12). In a study focusing on AVR, Engoren et al found that RBC transfusion was associated with adverse outcome only if valve replacement was combined with coronary surgery (12). The present analysis could not find that valve replacements or combined procedures differed in terms of long-term survival. As to our knowledge, the study by Engoren 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 surgery and found that RBC transfusion was not associated with adverse outcome whereas plasma transfusion was (11). To our knowledge, 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, TRALI, and other immunological 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 co-morbidity that we cannot control for in our model.

Presently, we cannot conclude whether it is the plasma that is the problem or the poor condition of the patient who requires it.

The rate of plasma transfusion is high and the indication was multifactorial. During the study time, the tradition at our department was to mainly use plasma as colloid volume substitution after surgery in

order to keep intravascular volume at an adequate level. Another indication for plasma transfusion alone is postoperative coagulopathy. Still, 90.3 % of the patients receiving plasma transfusion also received RBC transfusion (Fig 1), leaving only 59 (4,5%) patients who received only plasma transfusions. Therefore, the most common indication for plasma transfusion in this study is postoperative bleeding, and in the few who had plasma but no RBC, plasma was used a volume expander. However, patients receiving plasma transfusion were older and had significantly more preoperative morbidity than non-receivers. Thus, plasma transfusion could be a marker both for post-operative bleeding and for comorbidity as presented in table E1.

The present study found a weak association between pre-operative renal function and long-term outcome. In several studies including both CABG alone or in combination with AVR this association has been shown to be much stronger (10, 17-19). For instance, in a similar model including only CABG patients, we found that pre-operative GFR was one of the strongest predictors in the survival analysis, whereas in the present study it is 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, non-reversible atherosclerosis could be the main cause for renal dysfunction. This should serve only as an observation and be used to form a hypotheses for future studies.

The analysis also revealed another unexpected risk factor, preoperative C-reactive protein. In a similar analysis including 5261 CABG patients, our group could not find that pre-operative CRP affected long-term survival (11). On the other hand, Kangasniemi et al and Cappabianci associated increased pre-operative CRP with increased long-term mortality(20, 21). Both of these studies, however, included small patient cohorts and a limited number of risk-factors as well as a mixed population of cardiac surgery patients. Increased CRP levels have been associated with adverse long-term outcome

in coronary artery disease patients in general (22). In patients with aortic valve disease not scheduled for surgery, CRP has shown conflicting results as a predictor for outcome. Imai et al found an association between aortic valve area and progression rate and Solberg found it to be predictive for survival, whereas Novaro et al could not find any association between CRP and disease severity in much larger cohorts (23-25). In a post-hoc analysis we could conclude that the patients with elevated CRP had more co-morbidities but did not differ in age, gender or BMI. Moreover they had slightly worse renal outcome, needed more transfusions, had more heart failure and sepsis. They did, however not, have more neurological complications, more atrial fibrillation, or 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 1300 individuals could be considered too low for sufficient power, and a larger population would be desired. However, in a similar study describing a CABG population we studied more than 5000 patients, 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. Therefore, a linear approach to the risk associated with blood products seems reasonable. Moreover, both the sex of the donors and the age of blood products have been suggested as risk-factors in similar analyses (6, 26). We did not have access to either one of these two variables, and could not adjust for them. However, since our analysis did not find any association between RBC transfusion and outcome, the age of RBC would probably not affect the analysis. Despite our effort to increase the number of potential risk factors in our analysis, there are 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.

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 surgery receive transfusion of any sort, the importance of 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.

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Disclosures:

Henrik Bjursten has vested interests in ErySave AB (a start-up company working on autologous blood salvage). Lars Algotsson lectures for Orion Pharma AB and Abbott Scandinavia AB. The other authors have no conflict of interest to report.

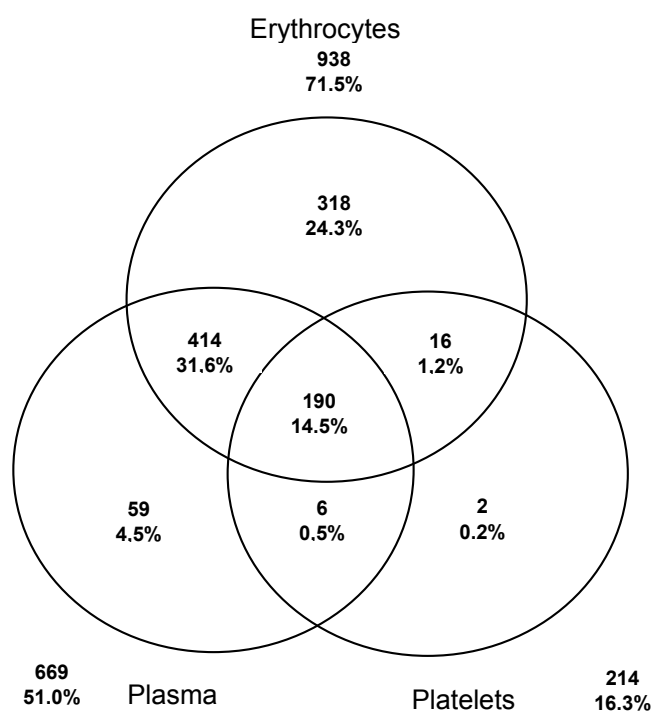
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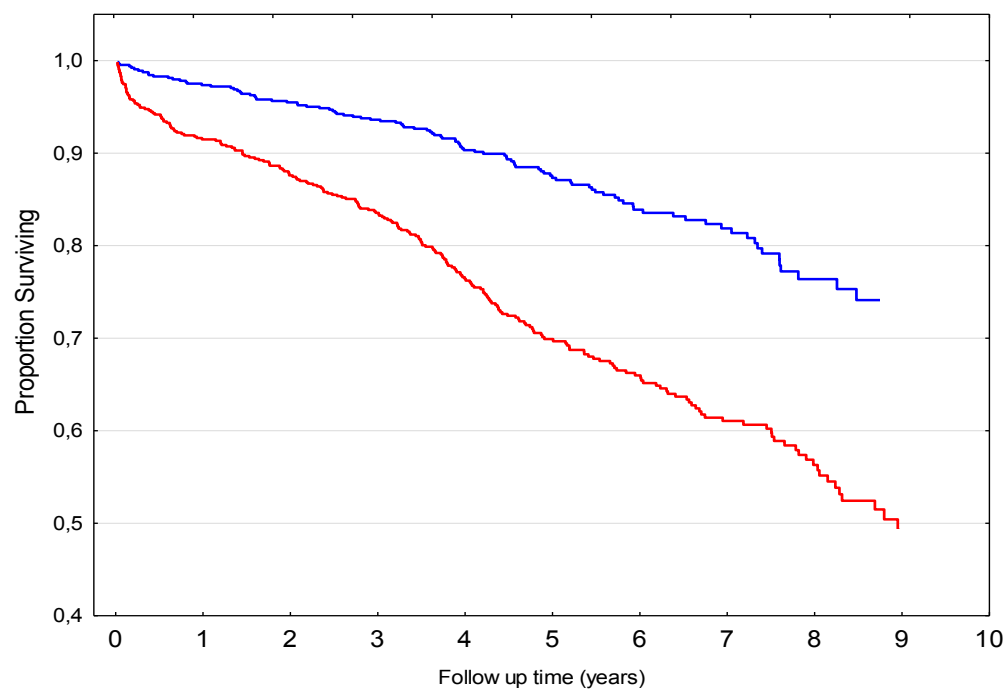
Figure 1

Venn diagram of the covariance of transfusion of different blood products in the study population number and percentage (of entire population of 1311 patients) receiving products.

Figure 2

Unadjusted Kaplan-Meier plot for the entire study group, where the group is divided between patients receiving plasma transfusion (red line) and patients not receiving plasma transfusion (blue line).





No transfusion	642	625	613	589	489	366	241	167	77	38
Transfusion	669	612	586	549	423	308	242	166	99	39
All	1311	1237	1199	1138	912	674	483	333	176	77

Abbreviations

ALT = Alanine Aminotransferase

AVR = Aortic Valve Replacemant

CABG = Coronary Artery Bypass Grafting

CCS = Canadian Cardiovascular Society

CPB = Cardiopulmonary Bypass

COPD = Chronic Obstructive Pulmonary Disease

CRP = C-Reactive Protein

eGFR = estimated Glomerular Filtration Rate

ICU = Intensive Care Unit

IABP = Intraortic Balloon Pump

LVEF = Left Ventricular Function

MDRD = Modified Diet in Renal Disease

NYHA = New York Heart Association

PCI = Percutaneous Coronary Intervention

RBC = Red Blood Cell

RIFLE = Risk-Injury-Failure-Loss-End Stage

TRALI = Transfusion Related Acute Lung Injury

Table 1. Cox Proportional hazard model

	All patients n=1311				Patients receiving <8 units of RBC n=1111			
	HR	95% C.I.	Wald	p	HR	95% C.I.	Wald	p
Age	1.055	1.04-1.07	49.4	0.0000	1.060	1.04-1.08	50.5	0.000
COPD	1.844	1.41-2.41	20.1	0.0000	1.976	1.42-2.74	16.6	0.000
Diabetes	1.697	1.30-2.21	15.3	0.0001	1.663	1.20-2.31	9.3	0.002
Peripheral vascular disease	1.462	1.10-1.94	6.9	0.0086				
LVEF 30-50%	1.488	1.17-1.90	10.2	0.0014	1.687	1.26-2.26	12.4	0.000
LVEF <30%	1.971	1.43-2.71	17.4	0.0000	2.370	1.59-3.53	18.1	0.000
Pre-operative CRP	1.005	1.00-1.01	9.9	0.0017	1.006	1.00-1.01	10.1	0.002
Pre-operative GFR	0.995	0.99-1.00	4.4	0.0363				
Pre-operative leucocytes					1.018	1.00-1.03	4.2	0.040
Postoperative stroke					2.325	1.01-5.36	3.9	0.048
Reop for mediastinitis	0.453	0.21-0.99	4.0	0.0459				
Transfusion of RBC	1.010	0.98-1.04	0.4	0.5200	1.047	0.98-1.12	1.7	0.186
Transfusion of Plasma	1.041	1.03-1.06	34.1	0.0000	1.075	1.05-1.10	34.9	0.000
Transfusion of Platelets	0.946	0.88-1.02	2.4	0.1240	0.921	0.75-1.13	0.6	0.440

Legend: Cox proportional hazard analysis of the entire population and for the subgroup of patients receiving less than 8 units of blood. Non-significant correlations are left blank. COPD = Chronic Obstructive Pulmonary Disease. LVEF = Left Ventricular Ejection Fraction. CRP = C-Reactive Protein. eGFR = estimated Glomerular Filtration Rate. RBC=Red Blood Cells. n/a = not applicable Significant p-levels in italics.

Table 2. Interaction analysis

	<i>n</i>	<i>HR</i>	<i>95% C.I.</i>	<i>Wald</i>	<i>p</i>
RBC yes / PLA yes / TRC yes	190	1,247	0,75-2,08	0,7	0,3980
RBC yes / PLA yes / TRC no	414	1,348	0,91-2,00	2,2	0,1400
RBC yes / PLA no / TRC yes	16	2,048	0,71-5,88	1,8	0,1825
RBC no / PLA yes / TRC yes	6				
RBC no / PLA yes / TRC no	59	0,973	0,51-1,84	0,0	0,9320
RBC no / PLA no / TRC yes	2				
RBC yes / PLA no / TRC no	318	1,076	0,71-1,64	0,1	0,7323

Legend: Interaction between different types of transfusion (RBC red blood cells, PLA plasma, TRC platelets) when the variables were added to the final Cox model. Number of patients in each group is also presented.

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