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.**

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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

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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 $\pm$ 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).