

Complications after Cardiac Surgery due to Allogeneic Blood Transfusions

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Abstract

Cardiac surgery is worldwide a common procedure, which requires large numbers of red blood cells. Allogeneic blood transfusions are necessary for correction of anemia and bleeding disorders, although blood transfusions are associated with higher morbidity and mortality. Possible complications of blood transfusions contributing to increased risk for morbidity and mortality are transfusion-transmitted infections, transfusion-related acute lung injury (TRALI), and storage of blood products related complications and due to transfusion-related immunomodulation (TRIM). Probably complications due to TRIM are the most common cause of transfusion-related mortality after cardiac surgery. A possible cause for complications due to TRIM is that allogeneic blood transfusions given during cardiac surgery can aggravate a pre-existent inflammatory response after cardiac surgery. In this review we focus on these causes of complications of blood transfusions in cardiac surgery.

Keywords: Blood transfusions; Cardiac surgery; TRALI; TACO; TRIM; Infections; Mortality; SIRS

Introduction

Coronary artery bypass graft (CABG) surgery is frequently performed for re-vascularization of the myocardium. Worldwide approximately 1,000,000 patients are undergoing cardiac surgery annually. Nowadays more older patients with more comorbidities are operated, which is possible due to more advanced techniques. Herewith allogeneic blood transfusions play a crucial role in performing of these more complicated surgical procedures. Until the discovery of the ABO-bloodgroups in the early 1900s allogeneic blood transfusions were a high-risk procedure. However the high safety of allogeneic blood transfusions nowadays, there are still risks leading to higher morbidity and mortality associated with allogeneic blood transfusions.

Patients undergoing cardiac surgery consume a large numbers of red blood cells (RBC) transfusions; estimated approximately 20% of the total blood supply [1]. The transfusion rates for CABG show great variability between hospitals with a mean number of transfused units varying between 0.4 to 6.3 units per patient [2]. In this review we will discuss the effects of blood transfusions in cardiac surgery.

Anemia and Blood Transfusions in Cardiac Surgery

Preoperative anemia can be due to several reasons, such as iron-deficiency or gastrointestinal bleeding. The incidence of preoperative anemia in cardiac surgery ranges between 25-32% [3,4]. Several observational studies observed that preoperative anemia was associated with increased neurological and renal complications [5-7]. Anemic patients had a higher early and late mortality than non-anemic patients undergoing cardiac surgery and not only preoperative anemia also the nadir of the Hemoglobin (Hb) concentration during cardiac surgery is related with worse adverse outcome [8].

During cardiac surgery due to hemostatic abnormalities intra- and postoperative bleeding are commonly seen, which can result in postoperative anemia. In one study up to 44% of the patients had anemia after cardiac surgery [9]. In this study every 1 mg/dL decrease in Hb-concentration was associated with 13% increase in cardiovascular events and 22% increase in all-cause mortality. While massive blood loss is associated with an 8-fold increase in mortality [10].

The main goal of blood transfusions is to increase the oxygen delivery (DO₂) to tissues and oxygen utilization by cells (VO₂). It has

been observed that in cardiac surgery blood transfusions increases DO₂ while VO₂ remains stable. This is due to enhancement of erythrocyte rheology and thereby improvement of blood physiology as blood viscosity, perfusion and hemodynamic functions.

Although blood transfusions are necessary in cardiac surgery, several studies found that blood transfusions had also deleterious effects. In these studies transfusion of RBCs was dose-dependently associated with postoperative infections and higher mortality [11,12]. In a prospective study in cardiac surgery, 4.8% of patients who did not receive RBCs suffered from postoperative infections, contrasting with 29% in patients who received 6 or more RBC units [13]. In another study patient who received RBC transfusions had a lower heart output and cause more congestive heart failure [14]. These findings suggest that patients with cardiovascular dysfunction have less tolerance to anemia. Besides short-term (30-and 90-days) mortality, also long-term mortality (1-year, 5-and 10-years) was influenced by transfusion of RBCs negatively [15-18]. However all these studies were retrospectively designed and provide by no means proof of a causal role of allogeneic RBC transfusions on postoperative morbidity and mortality. Many factors, such as age and duration of surgery influence the outcome after cardiac surgery. Furthermore sicker and critically ill patients could receive more blood transfusions, therefore no causality between blood transfusions and complications could have proven.

For decades a Hb-level of 10 g/dL was considered as an appropriate trigger for red blood cell (RBC) transfusions. A randomized controlled trial (RCT) performed in the 1990s changed the classical transfusion policy for RBCs drastically [19]; resulting in a tendency for lowering the Hb trigger. In this large RCT in 838 patients, staying at an intensive care unit (ICU), patients were either transfused to maintain the Hb

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Received April 07, 2013; Accepted June 23, 2013; Published June 25, 2013

Citation: Bilgin YM, van de Watering LMG (2013) Complications after Cardiac Surgery due to Allogeneic Blood Transfusions. J Clin Exp Cardiol S7: 005. doi:10.4172/2155-9880.S7-005

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value between 7 and 9 g/dl (restrictive) or above 10 g/dl (liberal). Patients assigned to a restrictive trigger received an average of 2.6 units of RBCs compared with 5.6 units in the liberal group. Mortality at 30 days, the primary outcome measure, was not significantly different between the groups: 18.7% versus 23.3% ($p = 0.11$) in favor of the restrictive trigger arm. In subgroups of patients younger than 55 years of age and those with a lower APACHE (Acute Physiology And Chronic Health Evaluation) risk score, mortality was significantly lower in the restrictive group than in the liberal group: 5.7% versus 13% ($p = 0.02$) and 8.7% versus 16.1% ($p = 0.03$), respectively. This study investigated all ICU-patients which represents a heterogenous population. More recent in cardiac surgery one randomized controlled trial suggested that a more restrictive RBC strategy aiming for a hematocrit of 24% is as safe as a liberal RBC strategy aiming for a hematocrit of 30%; the 30-day mortality and severe complications rate was approximately 10% in both groups [20]. However since the implementation of universal leukodepletion of red blood cells in several countries, two observational studies showed that blood transfusions were not associated with higher mortality rates, instead higher Hb concentrations and receipt of blood transfusions were associated with lower hospital mortality [21,22].

Complications of Blood Transfusions During Cardiac Surgery

Several causes could explain for the adverse effects of blood transfusions in cardiac surgery. Most common transfusion-related adverse effects in cardiac surgery are due to transfusion-related acute lung injury (TRALI), blood product storage-related complications and transfusion-related immunomodulation (TRIM).

Transfusion-Related Acute Lung Injury (TRALI) and Transfusion-Associated Cardiac Overload (TACO)

A leading cause of transfusion-associated mortality is transfusion-related acute lung injury (TRALI), which is estimated to occur in general population in about, 1:1,000 to 5,000 blood transfusions and has an estimated mortality rate of 5-10% [23]. In cardiac surgery the incidence of TRALI is higher than in other clinical settings (2.4%) with a mortality rate of 13% [24]. According to an international agreed definition, the onset of TRALI is within 6 hours after blood transfusion [25]. The pathophysiology of TRALI has not been completely clarified [26]. One of the possible causes can be that passively transfused anti-leukocyte antibodies in the donor's plasma bind to antigens on patient's neutrophils and initiate priming and activation with release of cytokines, proteases and free oxygen radicals. Neutrophil sequestration in the lungs can finally leading to endothelial damage and capillary leakage. Besides leukocyte antibodies there is circumstantial evidence that other insults such as bio-active lipids accumulating in stored erythrocytes, CD40 ligand in platelet products and cytokines involved in infections can prime neutrophils to adhere to the vascular endothelium [27]. Consequently, TRALI occur more often in patients in whom leukocytes are already primed, such as blood transfusions in the past and immunization by pregnancy. In patients with TRALI who underwent cardiac surgery it has been found that these patients had an already systemic inflammation and activation of neutrophils before blood transfusion, which suggests that blood transfusions act as a second hit in the development of TRALI [28]. This could be the reason that TRALI has a higher incidence in cardiac surgery than in the general population. Transfusion-associated cardiac overload (TACO) refers to pulmonary edema after transfusion of blood products. Recipients with renal or cardiac diseases and older patients are more susceptible for TACO, which is a serious underreported complication of blood transfusions.

A retrospective analysis in elderly patients who underwent orthopedic surgery revealed an incidence of 2% after red blood cell transfusions and this could be up to 8% dependent on co-morbidity and age, with a fatality rate varying between 5 to 20% [29]. Due to the cardiac status and more blood transfusions and fluid are given, it is expected that in cardiac surgery the incidence of TACO is higher than in other clinical settings. The discrimination between TACO and transfusion-related acute lung injury (TRALI) can be difficult (Table 1). Patients with TACO have usually more cardiac failure than patients with TRALI [30]. The treatment of TACO consists of volume reduction with eventually ventilatory and/or circulatory support. More important is to prevent the risk of TACO by a restrictive transfusion strategy or the use of diuretics in patients with underlying cardiac and/or renal disease or in elderly patients.

Storage Time of Red Blood Cells

Blood collected from voluntary donors is stored according to the protocols of the blood banks. During storage red blood cells show a number of structural and functional alterations, referred to as storage lesions. Changes in shape, rigidity, depletion of 2,3-diphosphoglycerate (2,3 DPG) and nitric oxide scavenging are presumed to result in impaired perfusion and oxygen delivery [31]. The clinical effects of storage times have only been evaluated in observational studies with unequivocal conclusions in different clinical settings. In cardiac surgery several retrospective studies investigated the storage time of RBCs [32-34], although these studies revealed controversial conclusions. More recent an observational study suggests an association between RBCs stored longer than 14 days and postoperative infections [35], while in other two studies no association was found in postoperative length of stay in the hospital, infections and mortality [36,37]. Currently there are RCT's running, which could answer the questions of storage time of blood products in the future [38].

Transfusion-Related Immunomodulation (TRIM)

Allogeneic RBC transfusions have profound effects on the recipient's immune system. This immunomodulatory effect of blood transfusions, presumed to result from allogeneic leukocytes are referred to as transfusion-related immunomodulation (TRIM). Compared with other adverse effects, the effects of are excessive [39]. Because allogeneic leukocytes are the most important factor held responsible for the clinical effects of TRIM; RCTs investigating their role are indispensable [40]. To investigate the clinical effects of TRIM several studies were performed comparing leukocyte-containing with leukodepleted blood products in different clinical settings.

Six RCTs are performed in cardiac surgery investigating the effects

SYMPTOMS	TRALI	TACO
Onset of symptoms	< 6 hours	Mainly < 6 hours
Respiratory symptoms	Dyspnea	Dyspnea
Central venous pressure	Normal	Increased
Pulmonary wedge pressure	Normal	Increased
Fluid balance	Positive or negative	Positive
X-ray thorax	Bilateral infiltrates	Bilateral infiltrates with signs of fluid overload
Echocardiography	Normal ejection fraction	Decreased ejection fraction
B-type natriuretic peptide	Low or normal	High

Table 1: Possible Differences Between Transfusion Related Acute Lung Injury (Trali) And Transfusion Associated Cardiac Overload (TACO).

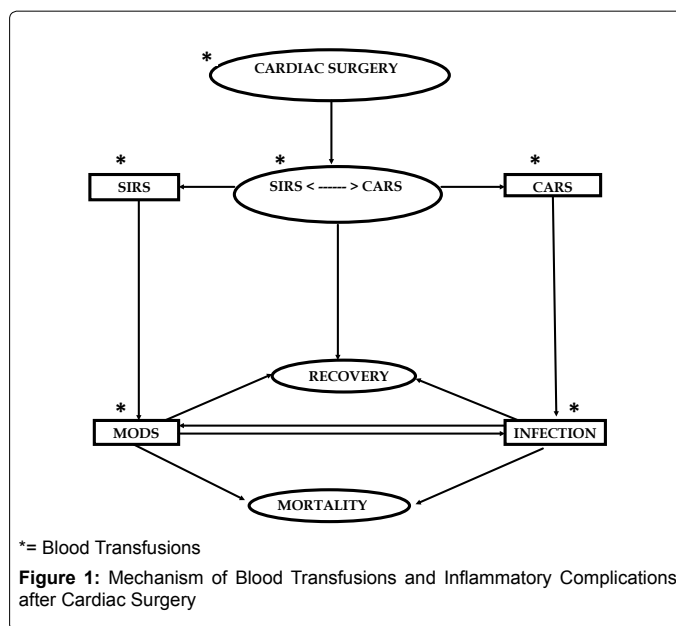
of leukocyte-containing blood transfusions: four of them are published as full articles [41-44]. Two other studies in cardiac surgery are still available only as abstracts, mentioning limited data [45,46]. When the results of RCTs conducted in cardiac surgery are combined in a meta-analysis, the mortality rate was increased with 72% in patients who received leukocyte-containing RBCs (OR = 1.72; 95% CI: 1.05-2.81, p = 0.01) [47]. For postoperative infections the RCT's revealed different outcomes. Two RCTs showed a transfusion-dose dependent beneficial effect of leukocyte-depleted RBCs [41,43]. Three RCTs did not show benefit of leukocyte-depleted RBCs [42,45,46] and one RCT only in the development of pneumonia [44].

Because in most of Western World universal leukodepletion is implemented, no new randomized controlled trials from these countries are expected. After this implementation several observational studies were performed, comparing the incidence of complications before and after the implementation of leukodepletion. One large multicenter study in critically ill patients from Canada (that included also cardiac surgery patients) reported reduced hospital mortality, decreased occurrence of fever and use of antibiotics after the implementation of universal leukoreduction [48]. Another "before-after study" observed a decrease in postoperative hospital-stay in patients who received leukoreduced blood transfusions [49]. Despite a lot of publications; the controversy on the clinical effects of leukocyte-containing RBCs remains. However there are sufficient data showing that transfusion of leukodepleted red blood cells in cardiac surgery has a beneficial effect.

Inflammatory Response and Blood Transfusions in Cardiac Surgery

During cardiac surgery blood is exposed to the extra-corporeal circuit, ischemia/reperfusion injury and many inflammatory responses are activated. These responses lead to post-perfusion systemic inflammatory response syndrome (SIRS), which can lead to organ failure and infections and subsequently to death. SIRS is defined by a body temperature less than 36°C or more than 38°C, heart rate more than 90/min, tachypnea with breaths more than 20/min or pCO₂ less than 4.4 kPa (32 mm Hg) and leukocyte count less than 4x10⁹/l or more than 12x10⁹/l. SIRS can be diagnosed when two or more criteria are present [50]. SIRS is a subset of cytokine storm with an abnormal regulation of cytokines and is immediately counteracted by a compensatory anti-inflammatory response syndrome (CARS) [51]. An overwhelming SIRS can dominate CARS resulting in multiple-organ dysfunction-syndrome (MODS). While when CARS dominates, this may lead to more enhanced susceptibility for postoperative infections (Figure 1). It has been hypothesized that leukocyte-containing RBC transfusions to patients with an activated inflammatory response (as after cardiac surgery) could further imbalances the postoperative SIRS-CARS equilibrium initially in favour of SIRS; this second-hit response induced by allogeneic leukocytes may be in combination with infections the cause of a more severe MODS [52]. This hypothesis is supported by an observational study, that showed that SIRS was associated with blood transfusions and patients with SIRS had a mortality rate 13-fold higher than in patients without SIRS [53].

The inflammatory response in cardiac surgery is reflected by an increase in several pro-and anti-inflammatory mediators. Several studies investigated the role of allogeneic blood transfusions in relation with inflammatory mediators. One study found in 114 patients who underwent cardiac surgery an association between perioperative allogeneic RBC transfusions and postoperative increase of concentrations of the inflammatory mediators bactericidal permeability



increasing protein (BPI), as a marker of neutrophil activation [54]. While another study found an increase in IL-6 in patients undergoing cardiac surgery who received blood transfusions [55]. Only one study investigated profiles of some inflammatory mediators in relation with leukocyte-containing blood products [56]. In patients who would develop infections, MODS or died had higher pro-inflammatory cytokine concentrations in the group that received leukocyte-containing RBC then in the group that received leukocyte-depleted RBC. These findings of this study support that leukocyte-containing blood transfusions amplify an inflammatory response in addition to an ongoing systemic inflammatory response induced by cardiac surgery.

Conclusions

For correction of anemia and bleeding disorders all blood components are transfused in large amounts in the setting of cardiac surgery. Allogeneic blood transfusions have not only beneficial, but also deleterious effects. Possible causes of complications of blood transfusions in cardiac surgery could be transfusion-related acute lung injury (TRALI), blood product storage-related complications and to transfusion-related immunomodulation (TRIM). Probably complications due to TRIM are the most common causes of transfusion-related mortality after cardiac surgery. It has been suggested that blood transfusions induce a second insult to the systemic inflammatory response that already after cardiac surgery exists. Reduction of the use of blood products in cardiac surgery can further decrease mortality; therefore more research is necessary in this field.

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This article was originally published in a special issue, [Advances in Cardiac Surgery and Therapeutics](#) handled by Editor(s). Dr. Wilbert S. Aronow, New York Medical College, USA