Review

Age of blood: does it make a difference?

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Abstract

During the past 20 years, the perceived value of blood transfusions has changed as it has become appreciated that transfusions are not without risk. Red blood cell transfusion has been associated with disease transmission and immunosuppression for some time. More recently, proinflammatory consequences of red blood cell transfusion have also been documented. Moreover, it has become increasingly evident that stored red blood cells undergo time-dependent metabolic, biochemical, and molecular changes. This 'storage lesion' may be responsible for many of the adverse effects of red blood cell transfusion. Clinically, the age of blood has been associated with multiple organ failure, postoperative pneumonia, and wound infection. The relationship between age of blood and clinical adverse effects needs further study.

Keywords blood, blood transfusion, multiple organ failure

Introduction

The use of blood transfusion dates back to the mid-17th century. By the early 1900s blood transfusion emerged as a standard of clinical practice that was perceived as relatively free of risk. The value of blood transfusion was largely unchallenged until the early 1980s, when transfusion-related disease transmission, particularly HIV transmission, became a huge public health concern. Intense scrutiny and evaluation of transfusion practice and its risk/benefit balance followed.

Adverse effects of allogeneic blood transfusion

Clearly, the view of blood transfusion as risk free is no longer valid. Adverse consequences of red blood cell (RBC) transfusion include the following: hemolytic and non-hemolytic transfusion reactions, transmission of infectious agents, transfusion of contaminated RBCs, and transfusion-mediated immunomodulation.

The first indication that immune modulation secondary to allogeneic blood transfusion existed in humans was reported more than 25 years ago, when Opelz and colleagues [1] observed improved renal allograft survival with pretransplant allogeneic RBC transfusions. More recently, Opelz and coworkers [2] reported a clear improvement in renal allograft survival with allogeneic blood transfusion in addition to modern immunosuppressive therapy. Moreover, allogeneic blood transfusion-associated immunosuppression has been associated with a decreased recurrence rate of spontaneous abortion in affected women [3] and a reduced clinical relapse rate in patients with chronic inflammatory bowel disease [4]. It has also been argued that immunosuppressive effects of allogeneic blood transfusion might adversely affect the outcome of patients undergoing curative operation for malignancy [5]. In addition, several clinical studies demonstrated that allogeneic transfusion is an independent risk factor for postoperative bacterial infections [6,7].

Although most emphasis has been placed on immune suppression following transfusion, it has become evident that proinflammatory effects may be important as well. Cytokines and other inflammatory mediators have been shown to accumulate during storage of blood products [8,9]. Plasma from stored RBCs has been demonstrated to prime the oxidase system in neutrophils (even if leukoreduced), delay apoptosis, and activate endothelial cells [10,11], setting the stage for neutrophil-mediated tissue destruction and organ failure. Indeed, several investigators have identified blood transfusion as an independent risk factor for postinjury multiple organ failure (MOF) [12,13].

 MOF = multiple organ failure; RBC = red blood cell.

Table 1

Red blood cell storage lesion

Storage effects	Consequences
Decreased 2,3-diphosphoglycerate	Increased oxygen affinity and decreased oxygen unloading by hemoglobin
ATP depletion	Erythrocyte shape changes Increased osmotic fragility Decreased deformability
Microvesiculation and loss of lipid membrane	Decreased erythrocyte viability
Lipid peroxidation	Cellular injury and death
Bioactive substance generation: histamine, cytokines, lipids	Febrile transfusion reactions Neutrophil priming/endothelial activation Cellular injury Transfusion-related acute lung injury Multiple organ failure (?)

Red blood cell storage lesion

The advancement of transfusion medicine as a specialty has paralleled our ability to store blood *ex vivo* in its liquid state. As storage techniques have improved and extended the storage period up to 42 days, there has been a shift from focusing on maintaining RBC viability to including the quality of transfused RBCs as well.

The 'storage lesion' has been defined as the constellation of changes to the RBC that occur during storage, including metabolic, biochemical, and molecular changes, which eventually result in irreversible damage and ultimately limit the storage period [14]. Although the term traditionally has been restricted to corpuscular damage, recent evidence shows that a number of bioreactive substances accumulate in the medium during storage [8,9,11]. Selected changes characteristic of the storage lesion and their potential consequences are listed in Table 1.

We have been particularly interested in the relationship between blood transfusion and neutrophil priming. Silliman and coworkers [10] demonstrated that, during routine storage of whole blood and packed RBCs, agents were generated that significantly primed the NADPH (nicotinamide adenine dinucleotide phosphate, reduced form) oxidase system. This effect was not significant until after 2 weeks of storage and was maximal by by the time all of the components were out of date. Those authors subsequently showed that this effect was largely due to accumulation of proinflammatory lipids, in particular lysophosphatidylcholines [15].

Evidence of clinical relevance

Despite the relative wealth of data regarding the changes related to storage of blood products, evidence of clinical significance has been sparse. As noted earlier, multiple studies now document adverse effects of allogeneic blood transfusion. The relationship between these adverse effects and the age of transfused blood, however, has not been adequately studied.

RBC transfusions are frequently advocated to increase oxygen delivery in critically ill patients. The immediate effectiveness of this therapy in increasing systemic oxygen uptake is questionable because storage depresses the ability of RBCs to deform as well as unload oxygen peripherally. Because 2,3-diphosphoglycerate and deformability recover *in vivo* following transfusion, one would expect to see a delayed increase in systemic oxygen consumption after RBC transfusion. Marik and Sibbald [16], however, noted no improvement in systemic oxygen consumption for up to 6 hours after transfusion. Moreover, those authors noted an unexpected decrease in gastric intramucosal pH (measured by gastric tonometry) following transfusion with blood stored for longer than 15 days. They suggested that transfusion of old, poorly deformable RBCs leads to microcapillary sludging and obstruction, resulting in gut ischemia.

In light of the potential for stored RBC transfusion to adversely affect oxygen delivery and uptake, Purdy and colleagues [17] studied the relationship between the age of transfused blood and survival in critically ill septic patients. The authors retrospectively studied 31 patients admitted to their intensive care unit with severe sepsis. The number of units of packed RBCs transfused and the age of each unit was determined using blood bank records. There was no difference between survivors ($n = 12$) and nonsurvivors ($n = 19$) in age, sex, intensive care unit length of stay, incidence of septic shock, Acute Physiology and Chronic Health Evaluation II score, or total number of packed RBCs transfused. Nonsurvivors, however, were transfused with significantly older RBCs (median 24 days versus 21 days in survivors; $P < 0.0001$). Survivors were transfused with a greater proportion of RBCs that were less than 10 days old (85%), whereas nonsurvivors received a greater proportion of RBCs that were greater than 20 days old (76%).

Vamvakas and Carven [18] investigated the association between the duration of storage of transfused RBCs and postoperative infection following coronary artery bypass graft surgery. They observed that the mean duration of storage of all transfused RBCs was a significant predictor of postoperative pneumonia and wound infection. The risk for pneumonia increased by 1% per day of mean RBC storage time. Age of transfused RBCs remained a significant predictor of postoperative infection after controlling for other known risk factors.

Blood transfusion has consistently been shown to be a major risk factor for postinjury MOF. Initially, transfusion requirement was thought to be a surrogate for injury severity, but multiple studies have demonstrated it to be a robust and independent predictor of postinjury MOF [12,13].

We previously demonstrated that old, but not outdated, packed RBC plasma primes neutrophils for superoxide production [15]. Furthermore, old blood plasma activates endothelial cells in a dose- and age-dependent fashion [11]. The concordant activation of endothelial cells and priming followed by activation of neutrophils is crucial to the development of postinjury MOF.

To investigate the clinical relevance of these laboratory data, we performed a multivariate analysis of trauma patients who received transfusions to examine the effects of the age of stored blood on the development of postinjury MOF [19]. We observed that patients who developed MOF received significantly older packed RBC units and, furthermore, that the age of the units was an independent predictor of MOF.

Conclusion

Current evidence shows that metabolic, biomechanical, and molecular changes occur during the storage of blood products. Data are accumulating that these changes may lead to harmful consequences in the recipient. Further studies are necessary to clarify this relationship. Changes in blood banking practice (i.e. leukocyte reduction), clinical practice (i.e. lower transfusion 'trigger', recombinant erythropoietin), and continued development of blood substitutes may facilitate avoidance of the adverse effects of allogeneic blood transfusion.

Competing interests

PJO has received honoraria for consultancy services to Ortho Biotech Products, L.P.

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