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CRITICAL CARE

Aged erythrocytes: a fine wine or sour grapes?

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Editor's key points

- Transfusion of older stored erythrocytes might be associated with increased morbidity and mortality.
- Storage can result in functional erythrocyte defects ('storage lesion').
- Some clinical studies suggest that transfusion of older erythrocytes is associated with worsened outcomes.
- The quality of available evidence is too poor to recommend changes in transfusion practice.

Summary. Blood transfusion saves many lives but carries significant risk of injury. Currently, red blood cell (RBC) concentrates can be stored up to 42 days. Concerns have recently been raised about the safety and efficacy of transfusing stored RBCs. Refrigerated storage results in a 'storage lesion' that is reflected by metabolic derangements, RBC shape modification, rheological changes, oxidative injury to lipids and proteins, alterations in oxygen affinity and delivery, increased adhesion of RBCs to endothelial cells, and accumulation of bioactive substances in storage media. In animal models, transfusion of aged, but not fresh, RBCs induces organ injury, inflammation, coagulopathy, and impaired oxygen delivery. A number of clinical studies, mostly observational or retrospective and from a single centre, have reported an association between transfusion of older RBCs and increased clinically significant outcomes, such as increased morbidity and mortality in certain patient populations, including trauma, critical care, and cardiac surgery. Others, however, have failed to indicate an influence of RBC age on outcome. The quality of evidence is currently too poor to make recommendations to change current transfusion practice; however, the transfusion community looks forward to the results of randomized trials currently addressing the long-standing question regarding the effects of RBC storage on clinically significant outcomes.

Keywords: blood erythrocytes; blood transfusion; erythrocyte storage; outcome

Red blood cell (RBC) transfusion is considered one of the most important and common medical interventions in many clinical situations. It is indicated for improvement of oxygen-carrying capacity of blood to tissues. RBC units are refrigerated and stored for increasing periods of time in order to optimize availability and minimize wastage. Storage is limited mainly by US FDA standards[1] that require $<1\%$ haemolysis at the end of storage and at least 75% of allogeneic erythrocytes still circulating in the recipient's blood 24 h after transfusion. The current upper limit of storage conforming to these requirements is 42 days, and optimization of storage time mandates the principle of transfusing the oldest compatible unit that is available when an order is made from the blood bank.[2 3]

Stored RBC units experience biochemical and structural changes involving intracellular, membranous and extracellular medium components. These alterations, referred to as the 'storage lesion', probably influence erythrocyte oxygen affinity, ability to change shape, membrane stability, and other factors affecting RBC function and transfusion efficacy. The efficacy of transfusing stored, refrigerated erythrocytes in improving oxygen-carrying capacity and delivery to the tissues has not been very well studied in the past. Recent data question the efficacy, and more worrisome, the safety of this prevalent treatment, which according to several researchers should be reserved to specific extreme clinical situations of increased, unmet oxygen demand, such as major trauma and haemorrhage or to supply-dependent patients such as those with acute coronary syndrome.[4]

This article reviews the scientific data available to date regarding the RBC 'storage lesion', experimental data regarding the efficacy and possible side-effects of stored RBC transfusion, and the contradictory clinical data addressing these issues. If available data and ongoing studies confirm current concerns regarding clinical risks associated with transfusion of older blood, it will entail major operational and financial impact on national blood supplies and the organization of blood banks would be anticipated.

The storage lesion

Many biochemical, morphological, and molecular changes are known to occur during storage that affect RBC function and possibly safety despite improvements in preservation methods. These are collectively referred to as the 'storage lesion', the significance of which is discussed below and

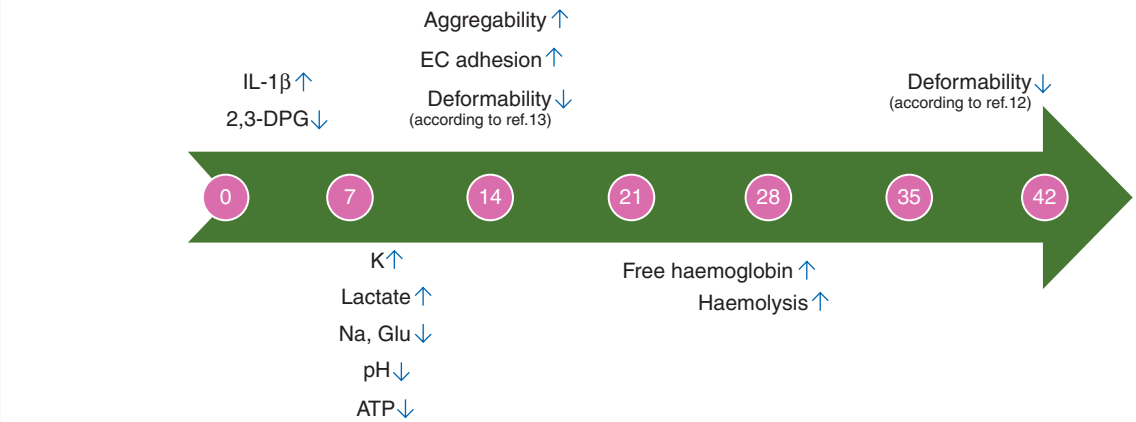

Fig 1 'Storage lesion' timeline, days.

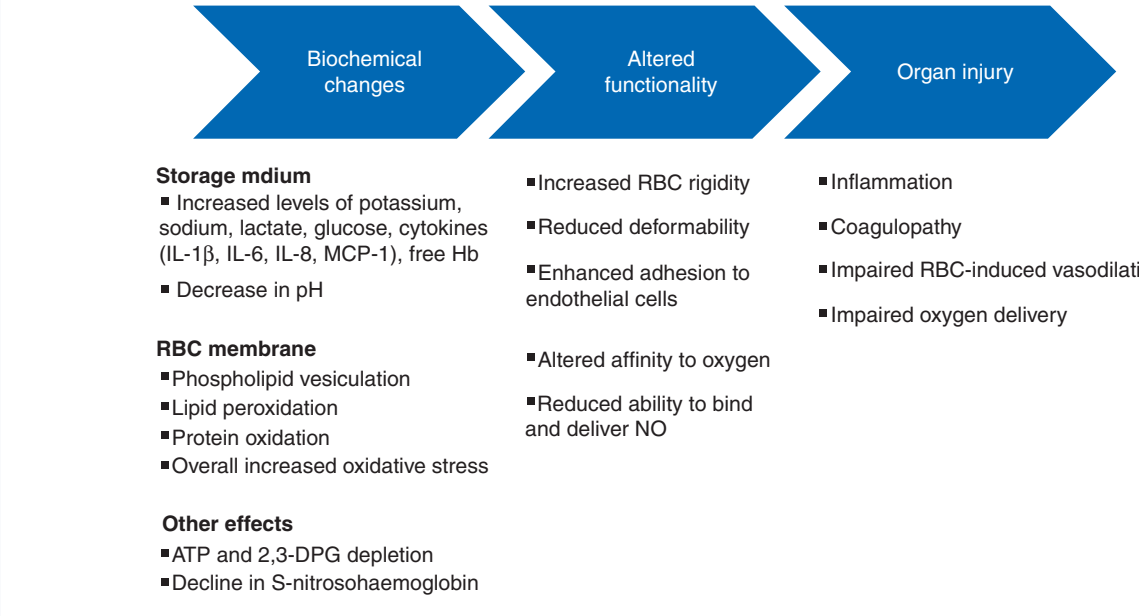

Fig 2 Effect of storage time on storage medium and RBC structure and function. IL, interleukin; MCP-1, monocyte chemoattractant protein-1; Hb, haemoglobin; ATP, adenosine triphosphate; 2,3-DPG, 2,3-diphosphoglycerate; RBC, red blood cell; NO, nitric oxide.

described in Figures 1 (as a proposed timeline) and 2 (as a process).

Concentrations of potassium and lactate in the RBC storage medium more than double within a week of storage, and reach 10 times their baseline level within 42 days. Sodium and glucose concentrations, and also pH, decrease considerably over the first 14 days of storage.[5] Haemolysis also occurs and increases with time. Free haemoglobin levels in the supernatant and haemolysis rates are greater after 28 days of refrigeration compared with 7 days.[6] Bioreactive substances also accumulate in the storage medium. These include various proinflammatory cytokines such as interleukin-1β (the levels of which are increased already on day 1 of rat RBC storage),[7] monocyte chemoattractant protein-1 (MCP-1) (the levels of which increase considerably from collection to 28 days of storage), and lysophosphatidylcholine, that some researchers,[8 9] but not all,[5] have implicated in transfusion-related lung injury and neutrophil activation. Additional alterations include membrane phospholipid vesiculation, protein oxidation, and lipid peroxidation of the cell membrane, all leading to structural changes.[10 11]

Deformability is the ability of erythrocytes to change shape. It is crucial for flow through small capillaries and to avoid stasis, as some capillaries are narrower than the erythrocyte width. Many researchers have attributed reduced deformability for the negative effects seen after RBC transfusions. In rats, RBC deformability is reduced at 7 days of storage, inducing a