Red Blood Cell Storage: How Long Is Too Long?

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Red blood cells (RBCs) undergo biochemical and structural changes during storage, commonly referred to as the "storage lesion." Evidence suggests that the longer the RBC product is stored, the less effective is the transfused blood. Many studies linking morbidity to transfusion have not considered duration of RBC storage as a variable that may modulate the effect. In addition, the effects of supply and demand and RBC inventory management strategies have been incompletely investigated. It is possible to envision a blood management system based on modern inventory management strategies that could greatly reduce storage duration.

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Although there are well-described risks associated with red blood cell (RBC) transfusion [1–7], suitability of transfusion in relation to RBC shelf life has not been well established. Currently, it is determined by in vitro RBC structural integrity and in vivo recovery [8–10], but standards addressing in vivo RBC functionality after transfusion are lacking [11], in part because of the technical challenges of measuring tissue oxygen delivery in a clinically useful manner. What is indisputable is that RBCs undergo biochemical and morphologic changes during storage, and evidence suggests that the longer the RBC product is stored, the less effective is the transfused blood.

Most studies linking morbidity to RBC transfusion have not considered duration of RBC storage as a variable that may modulate the effect. This is not surprising because if multiple units are transfused, each may have been stored for a different length of time. Thus, we define storage duration and its determinants and review experimental studies detailing changes in RBCs during storage that limit their shelf life, clinical evidence of adverse effects of RBC transfusion without regard to storage duration, and more limited and conflicting evidence of an association between storage duration and adverse events. Finally, we suggest strategies that could be used to substantially shorten RBC storage duration.

Definition and Determinants of RBC Storage Duration

Storage duration is the time between blood donation and transfusion. The maximum US Food and Drug Administration (FDA)-approved storage duration is dependent on the storage system, but for most RBC products, the FDA limits storage duration to 42 days. The limit for storage duration is primarily related to the degree of in vitro hemolysis at the end of storage and the related percentage of transfused RBCs remaining in the circulation 24 hours after transfusion [8–10]. Duration of storage is dependent on blood type, how inventory is managed, and dynamics of supply and demand. Thus, units of less common blood types, such as AB negative, tend to be stored longer than more common types, particularly type O, because of less demand [12]. Currently, blood banks dispense blood on a first-in first-out basis, with the oldest unit selected first. This strategy guarantees a preponderance of transfusions with blood that has been stored longer. In one study, one-third of transfused units were stored longer than 21 days [12].

What Happens to RBCs During Storage?

Time-dependent change, known as the "storage lesion," reflect deterioration of RBCs with storage (Table 1) [13–21]. These changes mean that transfusion may result in delivery of high concentrations of RBC constituents, such as hemoglobin and free iron. Shedding of RBC microvesicles, whose surfaces have been found to be both procoagulant and proinflammatory, increases concentrations of biologically active lipids[13, 14, 22–25]. These constituents, along with biochemical and morphologic changes, may contribute to adverse clinical events.

Effects of Extracellular Hemoglobin

Baek and colleagues [26] hypothesized that pathophysiologic processes among patients with hemolytic anemia results in part from elevated concentrations of extracellular hemoglobin thought to drive the negative effects of vascular dysfunction and heme-driven oxidative reactions. Using a guinea pig exchange transfusion model, they found that transfusing older RBCs resulted in significantly more abnormal necrotic regions of the aortic root 24 hours after transfusion and higher amounts of collagen deposition 48 hours after transfusion, along with

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Table 1. Characteristics of the Storage Lesion

Storage Effect	Consequences
Changes to red cell structure and function	
Cellular membrane changes	Erythrocyte shape change Decreased survivability
Decreased 2,3-diphosphoglycerate	Increased oxygen affinity Decreased oxygen delivery
Decreased adenosine triphosphate	Erythrocyte shape change Increased cell fragility Less resistance to oxidative stress
Changes in red cell storage medium	
Accumulation of bioactive substances (cytokines, histamines, lipids, enzymes)	Increased oxidative environment Febrile transfusion reactions Immunologic activation/suppression

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nephrosis and renal tubular degeneration. Coinfusion of haptoglobin, a free hemoglobin binder, with older stored blood attenuated these effects (Fig 1).

Effects of Iron

One unit of RBCs contains approximately 200 mg of iron; if 25% of each unit is cleared by 24 hours, as is acceptable by current standards, this constitutes a substantial iron load to the monocyte/macrophage system [27]. Using a murine model, Hod and colleagues [27] found that prolonged RBC storage was associated with increased plasma nontransferrin-bound iron, leading to acute tissue iron deposition and inflammation. This nontransferrin-bound iron enhanced bacterial growth in vitro.

In a recent clinical investigation, extravascular hemolysis and circulating nontransferrin-bound iron were measured in relationship to duration of RBC storage (fresh, 3–7 days and 40–42 days, respectively) using autologous cells from 14 healthy volunteers [28]. Older stored units were associated with increased concentrations of nontransferrin-bound iron from rapid clearance of older blood, and this correlated with enhanced proliferation of an in vitro pathogenic strain of *Escherichia coli*. The investigators hypothesized that increased infectious risk, cytotoxicity, and thrombosis from transfusion may be related, in part, to production of circulating nontransferrin-bound iron.

Patients with transfusion iron overload, as well as those with hereditary forms of hemochromatosis, may have circulating nontransferrin-bound iron levels similar to those measured in healthy volunteers 4 hours after RBC transfusion; these patients are known to be at an increased risk for acute and chronic infections [28, 29].

Effects of Biochemical Changes

Stored RBCs accumulate lactic acid and potassium, and pH progressively decreases (Fig 2) [15, 18]. Routine storage of RBCs results in an early loss (within hours) of nitric oxide bioactivity, which may lead to impaired vasodilation in response to hypoxia and subsequent compromised blood flow. Repletion of S-nitrosohemoglobin may improve transfusion efficacy [19].

Effects of Morphologic and Functional Changes

In an animal model, RBCs stored for 5 to 6 weeks had reduced oxygen-delivering capacity compared with RBCs stored for 2 to 3 weeks when a low hematocrit value was present [30]. In a study examining the effect of storage duration of strain-specific rat blood on tissue oxygen delivery, Rigamonti and colleagues [31] found that fresh blood resulted in higher tissue oxygen tension and increased regional cerebral blood flow.

With longer storage, RBCs change shape from a normal biconcave disk to echinocytes and spheroechinocytes (Figs 2, 3) [32, 33]. These changes reduce their deformability and increase their likelihood of occluding the microcirculation (Fig 4) [32, 33]. The resulting decrease in tissue blood flow may explain why stored blood does not fully correct anemia-associated deficits in tissue oxygen delivery [19]. The cause of decreased deformability is thought to be, in part, oxidative-induced membrane changes or depletion of adenosine triphosphate and 2,3-diphosphoglycerate [16].
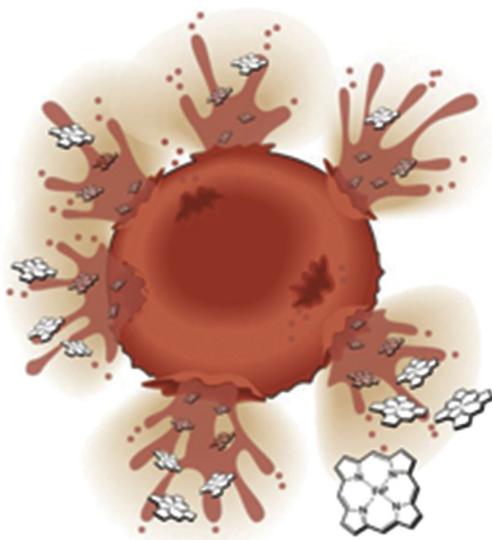

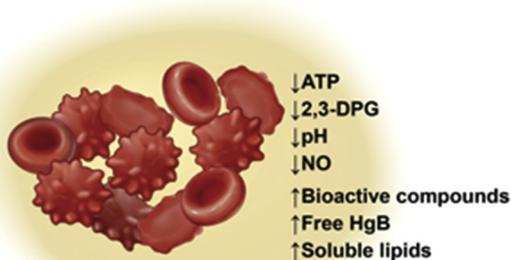*Fig 1. Senescent red blood cell lysis with release of free hemoglobin, shown as biochemical structures.*

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Fig 2. Older stored blood with a large number of abnormally shaped red blood cells (echinocytes and spheroechinocytes). Shape changes are accompanied by biochemical changes within the cells and byproduct accumulation in the storage medium. (ATP = adenosine triphosphate; 2,3-DPG = diphosphoglycerate; HgB = hemoglobin B; NO = nitric oxide.)

Fig 4. Implications of the storage lesion: reduced red blood cell deformability and impaired microvascular tissue flow. (A) Normal capillary. (B) Capillary blocked by abnormally shaped red blood cells.

At 2 weeks of storage, RBCs demonstrate enhanced aggregability [17]. Longer RBC storage and white blood cell burden increase the number of RBCs adhering to vascular endothelium and the strength of this adhesion. Leukocyte reduction results in less adhesion [34].

Effects of Microvesicles

As RBC storage duration increases, concentration of microvesicles increases [25]. Many of these microvesicles express phosphatidylserine, which facilitates thrombin generation in vitro. This is a possible mechanism by which stored RBCs contribute to thrombotic and other complications associated with transfusion (Table 1; Fig 5) [25, 35, 36].

RBC Transfusion and Adverse Clinical Outcomes

The morbidity associated with RBC transfusion is likely multifactorial, and separating out the incremental effect of storage duration is difficult. Thus, before presenting
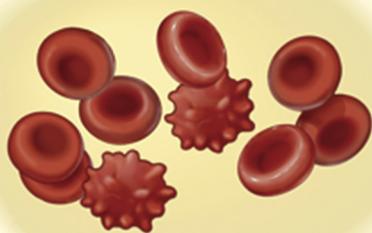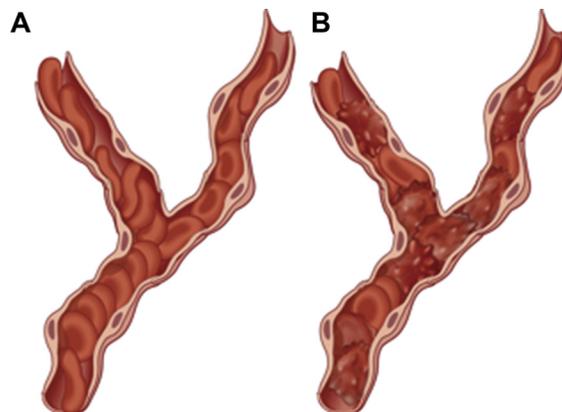
the limited and conflicting information about clinical adverse effects of RBC storage duration, we present evidence that transfusion, irrespective of storage duration, is associated with risks for complications.

Most investigations reporting morbidity risks associated with transfusion are cohort studies rather than more definitive randomized trials. Nonetheless, they reveal complications associated with transfusion—infection, transfusion-related acute lung injury (TRALI), febrile nonhemolytic reactions, and transfusion-associated circulatory overload —for which there is general consensus of a causal link.

Immunomodulation, with downregulation of the immune system, is associated with RBC transfusion and may increase susceptibility to infections [37]. Risk for bacteremia/septicemia and superficial and deep sternal wound infections appears to increase in a dose-related manner as the number of RBC units received increases [38]. Variables related to specifics of storage and processing, such as degree of leukocyte reduction, are implicated in transfusion-related immunomodulation, which may lead to infection [13, 39]; however, the relationship between leukocyte reduction and infectious complications is unclear. For example, a recent double-
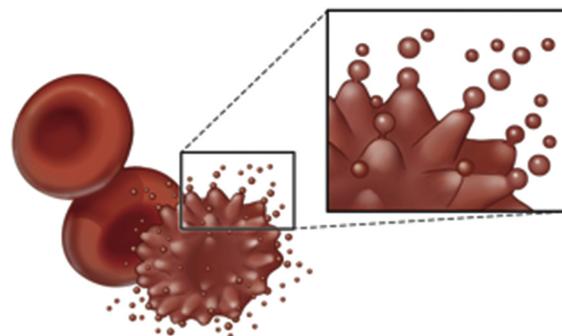

Fig 3. Fresh blood with normally shaped biconcave diskocytes and few abnormally shaped red blood cells.

Fig 5. Red blood cell phospholipid vesicles (microvesicles, insert), which accumulate in the storage medium.

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blinded randomized trial in patients undergoing colorectal operations reported that leukocyte depletion did not reduce infectious complications associated with transfusion. Infections were higher in patients who underwent RBC transfusions compared with those who did not; however, infectious complications were similar when RBCs depleted of leukocytes were used and when RBCs that were not depleted of leukocytes were used [40].

Transfusions during and after cardiac operations are associated with higher prevalence of respiratory complications, acute respiratory distress syndrome, and longer intensive care unit and hospital stays [1]. It is unclear whether pulmonary morbidity associated with transfusion is related to TRALI or transfusion-associated circulatory overload, or both, or lung damage from cardiopulmonary bypass [1, 41–45]. Special efforts to reduce TRALI-related pulmonary morbidity have been the subject of consensus statements, with management strategies recommended to identify and reduce risk in the transfused population.

A number of investigators report an increase in early and late mortality after surgical interventions in patients who receive perioperative RBC transfusions [2, 4, 46–48]. Both Hajjar and colleagues [49] and Van Straten and associates [50] observed that the number of RBC units transfused was an independent risk factor for early death after cardiac operations.

In contrast, others have not found associations of transfusion with adverse outcomes; a randomized trial of liberal versus restrictive transfusion strategies for high-risk patients undergoing hip operations demonstrated similar postoperative complications and functional outcomes, including comparable inability to walk independently at 60 days. These authors took length of RBC storage and leukocyte reduction status into consideration [51]. Nevertheless, study investigators suggested that in the absence of anemia symptoms, it is appropriate to withhold transfusion in the elderly, just as others have suggested for critically ill patients [52].

How Long Is Too Long?

Clinical investigations in trauma and cardiac surgical procedures suggest an association between longer RBC storage and adverse outcomes. Increased storage duration has been reported to be an independent risk factor for postinjury multiple organ failure [53], infection [54], deep vein thrombosis [55], and hospital mortality [55]; the latter 2 are particularly associated with blood stored 28 days or longer. In an acute care facility setting of 4,933 patients admitted with the diagnosis of cardiovascular disease, Eikelboom and colleagues [56] found a modest graded association between longer RBC storage and mortality. In patients undergoing cardiac operations, longer RBC storage is associated with increased postoperative length of stay and renal complications [57]. Leal-Noval and colleagues [58] reported that transfusion of RBCs increased cerebral oxygenation in patients with severe traumatic brain injury, except in those who

received RBCs stored longer than 19 days. In critically ill trauma patients, Kiraly and colleagues [59] noted a decrease in peripheral tissue oxygenation in patients who received blood stored longer than 21 days. Blood stored longer has been associated with increased risk in other settings: Pettila and associates [60] reported that exposure to older RBCs was associated with increased risk of death in the critical care setting. In pediatric cardiac operations, Ranucci and colleagues [61] found a risk-adjusted association between older RBCs used for priming the cardiopulmonary bypass machine and postoperative morbidity in pediatric patients. In the percutaneous coronary intervention population, Robinson and coworkers [62] reported an increase in postprocedure mortality at 30 days after coronary interventions. The authors noted that use of older RBCs may have contributed to the increased hazard for death.

Weinberg and colleagues [63] found that larger volumes of transfusion—especially with RBCs stored longer than 2 weeks—were associated with higher mortality. In a large study of cardiac surgical procedures, patients who received blood stored longer than 2 weeks experienced more postoperative complications as a composite end point than did those receiving blood stored less than 2 weeks [64]. Both short- and long-term survival were reduced. These studies suggest that the shelf life of stored RBCs should be limited to about 2 weeks.

However, other studies report no apparent relation of storage duration to clinical outcomes. Walsh and colleagues [65] studied 22 critically ill euvolemic patients and reported no clinically significant adverse effects of longer RBC storage on gastric tonometry or global indices of tissue oxygenation. Edgren and colleagues [66] reported a similar 7-day risk of death among transfused patients for all durations of storage except RBCs stored 30 to 42 days. The authors surmised that these findings may have been due to "weak" confounding. In a cohort of 9 healthy volunteers, Weiskopf and colleagues [67] found that fresh and stored blood were similarly effective in reducing brain oxygenation deficits. Yap and colleagues [68] studied 670 patients undergoing cardiac operations who received an admixture of RBC units of varying storage duration and reported that the total amount of RBCs transfused, rather than storage duration, was associated with early postoperative morbidity and mortality. Thus, controversy continues and may or may not be resolved by ongoing randomized trials for RBC storage duration. For example, CT.gov lists current storage duration studies—NCT00458783, NCT00991341, and NCT01319552—that are under way in the United States. Certainly, conservation programs can manage modifiable factors that place patients at increased risk for receiving an RBC transfusion or experiencing its adverse effects.

Can Storage Duration Be Decreased?

Current first-in first-out RBC inventory optimization is focused on minimizing the number of expired, ie, wasted, products. To avoid product expiration, hospitals reduce

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the number of new shipments they receive, and blood distribution centers export excess, usually older, products to locations with greater demand. In recent years, however, new models of inventory management have emerged in the retail sector to reduce inventory shelf time in favor of just-in-time delivery of products. Might these more dynamic strategies work in blood banking to further reduce storage duration? A model already exists. Platelets expire 5 days after donation. Managing platelet inventory requires hourly monitoring and more frequent deliveries from the blood collection agency. With this infrastructure in place, it is attractive to contemplate an RBC distribution system that works the same way to reduce RBC storage duration to 14 days or less.

The effect of supply versus demand has been incompletely investigated. Atkinson and colleagues [69] simulated a last-in first-out management strategy in a large tertiary care–based blood collection center and transfusion service. They found that mean storage duration and blood availability were highly sensitive to supply and demand. When the supply-to-demand ratio was less than 0.98, mean age of RBCs transfused was less than 1 week. However, when supply exceeded demand by 6% or more, a last-in first-out strategy resulted in a mean RBC storage duration of 35 days or more.

Conclusions

Evidence that deterioration of RBC units contributes to the adverse effects of transfusion is difficult to separate from the apparent dose-dependent effect of multiple transfusions. This is in part related to the different storage durations among transfused units. Thus, limits on effective shelf life of RBCs have yet to be established. In theory, it is possible to envision a blood management system based on modern inventory management strategies that could greatly reduce storage duration.

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