Clinical Studies of Erythrocyte Outcomes and Mortality

Size Really Counts

OVER the past years, an increasing number of studies report adverse outcomes associated with transfused blood components. Of this extensive and growing literature, outcomes after erythrocyte transfusions are the most numerous. Although erythrocytes are licensed for storage up to 42 days, reports suggest that units stored longer than 14–21 days may potentially be associated with a greater risk of morbidity and mortality, what is referred to as "the storage lesion."1,2

There are ongoing controversies relating storage duration of allogeneic erythrocytes with the risk of adverse patient outcomes. However, most of these reports are based on special patient populations, such as cardiac surgical patients, trauma patients, and intensive care unit patients. This patient selection is likely due to the fact these are easier groups to study because of their high incidence of bleeding and subsequent erythrocyte transfusion and their high relative mortality compared with other patients. However, this critically ill group is simultaneously at risk of multiorgan system dysfunction because of causes that may also reflect their underlying illness and confound interpretation of the postulated effects of stored erythrocytes on transfused patients.

Defining the adverse effects of transfusions has been based on clinical endpoints ranging from mortality to multiorgan system dysfunction, mechanical ventilation duration, infection rate, intensive care unit/hospital length of stay, and hospitalization cost, as examples.3,4 However, the molecular and mechanistic causes of the erythrocyte storage lesions are complex and extend beyond oxygen delivery and tissue oxygenation because they impact on patient outcomes. A diverse number of mechanisms are believed to be responsible for the "storage lesion," including increased nitric oxide scavenging from erythrocyte microparticles and/or cell-free hemoglobin in older blood5 and impaired nitric oxide production with reduced nitric oxide synthesis by dysfunctional endothelial cells, collectively reducing nitric oxide levels below a critical threshold in vascular beds causing vasoconstriction and impaired organ flow.1,2,6 However, multiple mechanisms have been implicated.4,7

Despite the extensive use of erythrocyte transfusions, many of our clinical practices have evolved out of recommendations and consensus evaluation that have not been consistently tested in robust clinical trials.1,8 Clinical studies attempting to provide evidence-based approaches to transfusion practices have only been recently published. This complex literature describing variable effects of erythrocyte storage on patient outcomes is largely observational and mostly retrospective and offers divergent conclusions.9 The few randomized pilot studies have not been powered to detect differences in clinical endpoints because of relatively small patient numbers.8,10 However, most of these studies have evaluated more critically ill patients. Furthermore, the erythrocyte storage effects on clinical outcomes remain in a state of equipoise and limited data exist outside of cardiac surgery and trauma.5,8

In this issue of Anesthesiology, Saager et al.11 retrospectively analyzed 6,994 patients from their data base of 86,483 adult general surgical patients. The information was obtained from 2005 to 2010 from the Cleveland Clinic Perioperative Health Documentation System registry and merged with blood product data from perioperative management. Of note is the current study used only leukocyte-reduced, allogeneic erythrocyte transfusions in the evaluation. The authors grouped patients who received
erythrocyte transfusions into three storage duration groups of ≤14 days, >14 days to ≤28 days, or >28 days. As the authors state in their methods, Kaplan–Meier survival density function estimates were obtained and plotted for each of the three groups. However, because it does not adjust for potential confounding factors, there was no testing for differences in their analysis. The authors used a multivariable Cox proportional hazards regression to characterize median erythrocyte storage duration and postoperative mortality rate. The authors also adjusted for characteristics influencing storage duration. Saager et al.11 report that 23% received 1 U, 44% received 2 U, 11% received 3 U, 9% received 5 U, and 13% received more than 5 U of erythrocytes. They concluded that in their population of noncardiac surgical patients, increasing median storage duration was not associated with an increased risk of postoperative mortality.

This study adds further insight into our ongoing investigations into the impact of erythrocyte storage duration on patient outcomes. It is important to note that a previous study by Koch et al.12 from the same institution reported that patients transfused with erythrocytes for cardiac surgery from 1998 to 2006 fared worse if older units were transfused. This study included 2,872 patients who received 8,802 units stored for less than 14 days and 3,130 patients who received 10,782 units stored for more than 14 days. The median storage age was 11 days compared with 20 days, and the older units had increased hospital mortality (2.8% vs. 1.7%, P = 0.004), intubation > 72 h (9.7% vs. 5.6%, P < 0.001), renal failure (2.7% vs. 1.6%, P = 0.003), and sepsis (4.0% vs. 2.8%, P = 0.01). Older erythrocytes were associated with an increase in the risk-adjusted rate of their composite adverse event outcome (P = 0.03).12 However, comparison of the study by Saager et al. with the study by Koch et al. has certain limitations. Not only are the primary diagnoses different, but patient accruals occurred over different time intervals. In addition, variable leukoreduction was used in the study by Koch et al. compared with universal leukoreduction used in the study by Saager et al. These differences may contribute to the disparate results from the same center and indicate the caution necessary in interpreting the literature.

One of the reasons most of the current data on the erythrocyte storage lesion effect are from trauma and cardiac surgery patients is again because these patients often have significant bleeding and receive multiple transfusions. However, in the current study, patients received a relatively small number of erythrocytes, and the authors note they did not examine transfusion criteria or appropriateness. Their sample size was not large enough to analyze massive transfusions or the impact of storage on massive transfusion outcomes. It is important to note, as the authors have identified, that postoperative morbidity and complications were not tabulated, findings that provide a more sensitive but certainly less crucial outcome than mortality.

Although multiple studies on outcomes associated with erythrocyte storage and transfusions have been reported, many of these studies have a multitude of limitations, including retrospective analysis, different methodological and analytical approaches insufficiently adjusting for confounding factors or disease severity, single- versus multiple-center populations, retrospective versus prospective evaluation, variable population sizes, accrual time range, divergent patient populations, and variable erythrocyte processing and storage methods. All of these confounding variables make it difficult to compare the results of a single study with another patient group; this is again highlighted in the differences between the two Cleveland Clinic reports.11,12 However, support for the results of the study by Saager et al. comes from another exceedingly large retrospective cohort study of more than 1 U erythrocyte transfusion in Sweden and Denmark between 1995 and 2002 that evaluated 404,959 transfusions.13 There were no differences in 7-day mortality, but nonsignificant trends for events associated with older erythrocytes more than 30 days likely due to confounding events.

The current study is an important addition to the literature because these surgical patients represent a less critically ill patient population compared with other age of erythrocyte storage studies. Whether the age of erythrocytes transfused has a significant effect on clinical outcomes still remains in a state of equipoise. We unfortunately cannot answer this question with the data available. Three randomized, controlled, clinical trials addressing this question are underway. Two trials are being conducted in Canada, one in low birth weight neonates (ARIPI)14 and another in intensive care unit patients, The Age of Blood Study (ABLE). Both the authors of this Editorial are on the steering committee for the Red Cell Storage Duration Study (RECESS), an National Heart Lung Blood Institute study designed to evaluate the age of erythrocytes in transfused complex cardiac surgery patients comparing transfusion of ≤10 days versus ≥21 days old erythrocytes on change in the composite multiple organ dysfunction score from the preoperative baseline and on mortality.‡ The observational and retrospective current study by Saager et al. reported in this journal did not find an association between storage duration of erythrocytes and mortality in noncardiac surgical patients. This article contributes one more important bit of information to help us understand the relative risks of transfusions. Large databases such as the one queried in the current investigation offer an important method to ask questions but require careful analysis, recognizing that potential shortcomings may be best answered by randomized studies. Unfortunately, large, adequately powered, prospective trials may not be feasible, and we may have to rely on proper analyses of large databases, such as the study by Saager et al., for guidance. We hope the current randomized trials will

help further resolve important aspects of the erythrocyte storage outcome question.

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