EDITORIAL

Blood Transfusion — When Is More Really Less?

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Blood transfusion has for years been considered to have obvious clinical benefits and to be a relatively low-risk procedure. Not until the early 1980s did transfusion practices begin to come under systematic scrutiny. Initially, this trend was driven by concern about transfusion-related infection, particularly by human immunodeficiency virus, but advances in transfusion medicine have greatly decreased the risk of transmission of viruses by transfused blood. Now, other concerns — the effects of transfusion on the immune system, transfusion-related acute lung injury, and the age of transfused blood — drive the debate over transfusion practice and have led to methodical examinations of the benefits of transfusion. These new considerations are particularly important for critically ill patients.

Anemia is prevalent in critically ill adults, who as a group receive a large number of red-cell transfusions.[1,2] By the third day in the intensive care unit (ICU), 95% of critically ill patients have anemia, and 40 to 50% of them will receive on average almost 5 units of red cells during their stay in the ICU. Despite the frequency of transfusion among the critically ill, the optimal treatment of anemia in euvolemic, critically ill patients remains controversial. Red-cell transfusion is commonly used in the critical care setting to increase oxygen delivery to tissues, especially in patients in shock.[3] However, several studies have raised questions regarding the validity of the assumption that red-cell transfusion is beneficial for critically ill patients with anemia.[1-4] Two plausible hypotheses could explain the apparent lack of benefit from such transfusions: immunomodulation[5] and the "storage lesion,"[6] which consists of biochemical and molecular changes and an accumulation of inflammatory mediators that develop over time in stored red cells.

The best evidence concerning the efficacy of red-cell transfusion in critically ill patients is from the Transfusion Requirements in Critical Care (TRICC) trial.[4] In this randomized, controlled study involving adults in critical care, a liberal transfusion strategy (target hemoglobin level, 10.0 to 12.0 g per deciliter, with a transfusion trigger of 10.0 g per deciliter) was compared with a restrictive transfusion strategy (target hemoglobin level, 7.0 to 9.0 g per deciliter, with a transfusion trigger of 7.0 g per deciliter) in a general medical and surgical setting. The restrictive group received 54% fewer red-cell units than did the liberal group, and the restrictive strategy was found to be at least as effective as the liberal strategy with respect to mortality. In patients who were less acutely ill (with a score of <20 on the Acute Physiology and Chronic Health Evaluation [APACHE II]) or under 55 years of age, the restrictive strategy was actually superior, since it was associated with a decrease in mortality, as compared with the liberal strategy.

Most of the information on red-cell transfusion in critically ill patients has come from studies in adults, but such transfusions are also frequently used in critically ill infants and children. A recent observational study found that 14% of children who were admitted to a pediatric intensive care unit (PICU) received at least one red-cell transfusion during their stay in the PICU.[7] Determinants for transfusion were similar to those that have been reported in adults (anemia, cardiac disease, severity of illness, and multiple organ dysfunction), suggesting that the use of red-cell transfusion in children is similar to that in adults.

In this issue of the *Journal*, a study by Lacroix et al., called the Transfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) trial,[8] is a notable advance in the study of red-cell transfusion in children and has implications for understanding the role of such transfusions in all critically ill patients. The transfusion thresholds adopted by the investigators (7 g per deciliter vs. 9.5 g per deciliter) were similar to those used in the TRICC trial and produced a mean difference of 2.1 g per deciliter in hemoglobin level between the two study groups. Low death rates among patients in PICUs precluded the use of death as an end point, but multiple organ dysfunction was an appropriate and clinically meaningful primary outcome. Similar to the results in the TRICC trial, the restrictive strategy used in the TRIPICU trial was at least equivalent to the liberal strategy in the outcome of multiple organ dysfunction and was associated with a 44% reduction in the number of red-cell transfusions. Even with a conservative transfusion threshold (7 g per deciliter), nearly 50% of the children in the TRIPICU trial received a transfusion, which highlights the frequency of anemia in critical illnesses. Although the numbers of temporary protocol suspensions were relatively low, we wonder whether the suspensions were actually necessary or whether they were, as the authors suggest, a reflection of physicians' discomfort in withholding transfusion rather than of a physiological need for more oxygen delivery.

The study by Lacroix et al. is consistent with recent data from the Premature Infants in Need of Transfusion (PINT) trial, in which 451 infants weighing less than 1000 g, who had a gestational age of less than 31 weeks and were less than 48 hours old, were randomly assigned to either a low-threshold group or a high-threshold group as a transfusion strategy.[9] The primary outcome was a composite of in-hospital death, severe retinopathy, bronchopulmonary dysplasia, and brain injury as detected by cranial ultrasonography. There was no difference between the two groups in the composite outcome and no suggestion of a difference between them in the incidence of brain injury. However, Bell et al.,[10] in their single-center trial of restrictive versus liberal transfusion strategies in 100 hospitalized preterm infants (weight, 500 to 1300 g), found no differences in most outcomes, including survival, patent ductus arteriosus, retinopathy, and bronchopulmonary dysplasia. However, the investigators noted that infants in the restrictive group had more apneic and neurologic events, including combined parenchymal brain hemorrhage and periventricular leukomalacia. These differences in outcomes should be considered as hypothesis-generating because the composite neurologic outcomes were not designated a priori[11] and were not confirmed by the PINT trial.

Are there any patients in whom red-cell transfusion is beneficial? Clearly, such transfusions can be lifesaving in the setting of acute bleeding, but most transfusions in critically ill patients are not given for acute bleeding.[2] A large body of experimental and clinical evidence suggests that patients with cardiovascular disease do not tolerate anemia well. Among patients who decline to undergo blood transfusion, the odds of death are greater in patients with anemia who have cardiovascular disease than in such patients without cardiovascular disease.[12] But results from observational studies of transfusion in patients with acute coronary syndromes or underlying cardiovascular disease are conflicting.[13-15]

In addition to death, many other clinically relevant end points — including myocardial infarction, infection, and functional recovery — require evaluation. An ongoing clinical trial, called Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) (chaired by Dr. Carson), will compare an aggressive transfusion strategy with a strategy based on symptoms in patients with cardiovascular disease or other risk factors.[16] Until such patients and those with other conditions are evaluated in clinical trials, uncertainty among clinicians will remain, along with variations in transfusion practice.

Where does this leave us now? Red-cell transfusion has always made sense to physicians when the hemoglobin concentration is low, particularly in a sick patient. The face validity of this idea has driven transfusion practice for much of the past century and frequently still does today. The weight of evidence, however, does not support the unrestricted use of red-cell transfusion in critically ill patients. Instead, a transfusion trigger of 7.0 g per deciliter for most critically ill adults and children appears to be appropriate. A higher threshold might be indicated for patients with cardiovascular disease, pending the completion of further

clinical trials. Red-cell transfusion should no longer be regarded as "may help, will not hurt" but, rather, should be approached as "first, do no harm."

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