Transfusion Thresholds in FOCUS

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Even though red-cell transfusion is an accepted and widely used intervention, questions regarding which patients should receive transfusions and under what circumstances continue to spark debate. There has been limited evidence from clinical trials to inform policy. Meanwhile, concern about potential risks of blood transfusion and the costs of maintaining an adequate and safe blood supply\(^1\) have heightened interest in strategies to reduce the use of red-cell transfusion. These strategies include preoperative optimization of hemoglobin levels, the use of cell salvage during and after surgery, and pharmacologic interventions to reduce blood loss.

In the Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS),\(^2\) Carson et al. describe another strategy: the use of lower hemoglobin thresholds to initiate transfusion. A recent Cochrane review\(^4\) of 17 trials comparing variously defined transfusion triggers, including a lower hemoglobin threshold (range, 7 to 9 g per deciliter) and a higher hemoglobin threshold (range, 9 to 12 g per deciliter), concluded that although there was good evidence that lower thresholds reduced blood use, available data were inadequate to determine whether lower thresholds had adverse effects on functional status or other major outcomes.

Although the review suggested that it was likely that a restrictive hemoglobin threshold for transfusion was as safe as a liberal strategy, the results were heavily weighted by the Transfusion Requirements in Critical Care (TRICC) trial.\(^3\) The TRICC trial compared a threshold of 10 g per deciliter with a threshold of 7 g per deciliter in patients in the intensive care unit (ICU). Overall, 30-day rates of death were similar in the two groups, but in the predefined subgroups of patients under the age of 55 years and those who were less critically ill, rates of death were significantly lower in the restrictive-strategy group. Complications occurring in the ICU were also similar overall, with the notable exception of a significantly higher number of cardiac events in the restrictive-strategy group. Thus, the overall results suggesting similar outcomes with a lower versus higher transfusion threshold might not be broadly generalizable beyond the ICU setting and particularly to patients with cardiac disease.

The FOCUS trial was designed to address this question among patients who had a history of or risk factors for ischemic heart disease and were undergoing surgical repair of a fractured hip.\(^2,4\) This study population is an important one in which to pose this question, since such patients are likely to be transfused because of surgical blood loss and their age, and it is plausible that they may be compromised at lower hemoglobin levels.\(^5-7\)

In this study, 2016 patients over the age of 50 years (mean, 81.6) were randomly assigned to two study groups once their postoperative hemoglobin level fell below 10 g per deciliter. In the liberal-strategy group, single-unit transfusions were given to restore and maintain a hemoglobin level above 10 g per deciliter. In the restrictive-strategy group, transfusions were given when the hemoglobin level fell below 8 g per deciliter. Transfusion for symptoms of anemia was permitted in both groups. The trial had good statistical power to detect a difference in the primary outcome (death or an inability to walk 10 ft without human assistance) at 60 days after randomization, which was ascertained through telephone calls by assessors who were unaware of study-group assignments in all but 17 participants.

Although the restrictive-strategy group received
only half the number of transfusions administered in the liberal-strategy group, rates of the primary outcome did not differ significantly between the two groups, with 35% of patients in each group unable to walk unassisted, including 142 patients (76 of whom were in the liberal-strategy group) who had died. However, the average hemoglobin level in both groups was low by World Health Organization standards and could have limited functional recovery regardless of the transfusion strategy. There were no significant differences between groups among predefined secondary and tertiary outcomes, including in-hospital myocardial events, other coexisting illnesses, and final discharge destination, but the study was not adequately powered to assess these outcomes.

Although a significant between-group separation in hemoglobin levels was obtained, the absolute difference was on average only 1 g per deciliter. This difference may not have been clinically significant in this group of elderly patients and therefore may have contributed to the lack of detectable difference in the primary outcome between the two groups.

Although the interpretation that the transfusion strategy makes no difference in functional outcome in patients without symptoms of anemia is likely to be correct, the same cannot be said with confidence of the lack of adverse effects, given the study’s insufficient power to assess these events. Nevertheless, the absolute numbers of adverse events in this high-risk group was relatively low; cardiovascular events, including myocardial ischemia, heart failure, transient ischemic attack, and stroke, each occurred in no more than 6% of patients in either group. This low event rate is reassuring and supports the authors’ conclusion that a postoperative hemoglobin threshold of 8 g per deciliter in the absence of symptomatic anemia appears to be acceptable in elderly patients with or at risk of ischemic heart disease.

In using lower hemoglobin thresholds to guide transfusion, the risks of undertransfusion should not be overlooked. The decision to transfuse should be guided by an assessment of individual patients on the basis of a combination of signs, symptoms, and laboratory measures, and not by a single hemoglobin level. In the FOCUS trial, transfusion for symptoms occurred more often in the restrictive-strategy group, and protocol violations resulting in additional transfusions (a total of 56) in this group may have reduced this frequency.

Despite these caveats, the FOCUS trial provides new evidence to support the view that a more restrictive transfusion threshold in the absence of symptoms of anemia may be reasonable, including in elderly patients at risk for cardiovascular events. Such a policy would reduce exposure to allogeneic blood transfusion with its attendant risks and costs.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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