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The Decision to Transfuse: One Size Might Not Fit All

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Although the transfusion of red blood cells (RBCs) has been a mainstay of clinical practice for over 60 years, we still do not have clear evidence for which patients benefit from transfusion and under what circumstances. Since 1999, when the results of the landmark Transfusion Requirements in Critical Care study were published [1], more than 20 randomized, controlled trials have been performed comparing outcomes among patients assigned to different transfusion strategies.[2, 3 and citations therein] In most of these studies, the ‘liberal’ transfusion strategy targeted a transfusion threshold at 9–10g/dL, while the more ‘restrictive’ transfusion strategy specified a transfusion threshold at 7–8g/dL. In general, these studies found relatively few differences in the outcomes of the patients in the two transfusion arms. Some outcome differences were seen, but the specific endpoints which appeared to be affected by the transfusion strategy was not consistent between studies, possibly due to differences in the patient populations studied. Two meta-analyses have addressed this point by grouping these trials by patient category. One meta-analysis found no differences in mortality between subjects in the liberal and restrictive arms over several categories.[2] A second meta-analysis observed differences in the composite outcome measure constructed for the meta-analysis, which included 30-day mortality and 7 other ischemic and adverse events. Better outcomes were observed for the subjects in the liberal transfusion arm for both cardiovascular and orthopedic patients, but this was not the case for ICU patients. Thus, there continues to be an unmet need for more evidence to help guide clinicians on appropriate transfusion strategies.

Few studies of this nature have been conducted in patients with solid organ malignancies[4], or those with hematologic malignancies and myelodysplastic syndromes.[5, 6] These patients often require extensive transfusion support.[7] A study reported in this issue of *Critical Care Medicine* takes a much-needed step to address this gap.[8] The Transfusion Requirements in Critically Ill Oncologic Patients (TRICOP) Study is a single center,

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randomized, double-blind, controlled trial comparing outcomes among subjects assigned to a liberal (< 9 g/dL) or restrictive (< 7 g/dL) RBC transfusion strategy. Adult patients with solid organ malignancies who developed septic shock within 6 hours of admission to the ICU were included. The number of units of RBC transfused to subjects in the restrictive arm was lower than in the liberal arm as was the proportion of patients receiving RBC. There was no statistically significant difference between the two arms of the study for the primary outcome measure (28-day mortality) although there was a trend toward increased mortality in the restrictive arm (45.0% vs. 55.6%, $p=0.08$). There were also no differences in most of the secondary outcomes including 60-day mortality, the need for various interventions, occurrence of several ischemic events or other severe adverse events, hospital and ICU length-of-stay, or hospital re-admission rate. There was however, a statistically significant difference in mortality at 90 days again favoring the liberal arm (59.1% v. 70.2%, $p=0.03$).

This study was well-designed and achieved a high degree of internal validity. The patients in the two arms of the study were well-balanced for baseline characteristics, and compliance with the protocol was excellent with 95% of subjects being transfused as assigned with no indication that protocol deviations were significantly more frequent in one of the arms. Good separation between the mean hemoglobin levels of the two arms was achieved over the 7-day observation period (approximately 0.5–2.0 g/dL among transfused patients). The study was powered to detect an absolute difference of 16% in the 28-day mortality rate based on an anticipated mortality rate of 50%, (which was observed) and analyzing 300 subjects (which was achieved). This study illustrates the value of anticipating the unexpected and performing the sample size calculation based on a two-sided test. Indeed in this trial, the result was the opposite of what had been expected and mortality was found to be increased in the restrictive arm, not decreased as hypothesized. Consistent with most previous trials, clinicians caring for the patients were not blinded to the study arm assignment, which introduces a risk of bias, especially for outcome measures which are interventions deployed based on clinician judgment. The study population was highly selected and very specific with a large number of exclusion criteria. Although this created a relatively homogenous study population, caution is warranted in extrapolating these results to other categories of patients.

There are no studies in the same patient population as TRICOP (i.e. patients with solid organ malignancies and septic shock). One multicenter study randomized 1005 ICU patients with septic shock to transfusion for hemoglobin levels of either 7g/dL or 9g/dL with leukoreduced RBC.[9] This trial, which included only a small number of subjects with hematologic malignancies and an unreported number with solid organ tumors, found no differences in any of the outcome measures including 28- or 90-day mortality and the occurrence of ischemic events, unlike TRICOP. In another study, patients with solid organ malignancies (but not septic shock) who were admitted to the ICU following major abdominal surgery were randomized to receive leukoreduced RBC for a hemoglobin level of either 7g/dL or 9g/dL.[4] Among 31 outcome measures, the only differences seen were for the composite outcome, 30-day mortality, cardiovascular complications (the latter two were elements of the composite outcome and contributed most of the events) and abdominal infection, all of which favored the liberal arm of the study. These results resemble those from the TRICOP patients, which also showed a trend for increased mortality at 28 days

although with a much greater effect size. However, these two studies differed in that ischemic events were elevated in the restrictive arm of the larger study,[4] an outcome which was not seen in the TRICOP cohort.

Stepping back, the value of the TRICOP study is not only the insight it provides into managing RBC transfusions in this particular group of patients, but its indirect conclusion that RBC transfusion needs may vary among patient groups. Although the authors suggest that “expert opinion” recommends restrictive RBC transfusion strategies, it is notable that such practice guidelines are more nuanced. For example, the Clinical Practice Guidelines from the AABB published in *JAMA* in 2016 recommend a hemoglobin threshold of 7 g/dL for “hospitalized adult patients who are hemodynamically stable, including critically ill patients” and of 8 g/dL for “patients undergoing orthopedic surgery or cardiac surgery and those with pre-existing cardiovascular disease”. [10] But even more importantly, these recommendations are preceded by the statement: “When deciding to transfuse an individual patient, it is good practice to consider not only the hemoglobin level, but the overall clinical context and alternative therapies to transfusion” and lists a number of variables that may influence this decision. The accumulating evidence that patient requirements for and responses to RBC transfusion are variable supports the clinical intuition that care must be tailored to the patient.

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