Transfusion Threshold Trials: The Need to Establish a Clear Difference in Transfusion Practice between Study Groups

To the Editor:

Thresholds for erythrocyte transfusion are currently under much scrutiny, with increasing evidence to support more restrictive transfusion practice,1–5 and we read with interest the study by Pinheiro de Almeida et al.6 There is little dispute that patients with cancer who are anemic have poorer outcomes than those who are not anemic,7 but prospective data to support benefit from transfusion are lacking. Increasing concerns regarding risks such as transfusion-associated circulatory overload, transfusion-related acute lung injury, and alloimmunization have led to a number of randomized control trials addressing transfusion thresholds in well-defined patient groups such as patients treated in the intensive care unit (ICU): Transfusion Requirements in Critical Care (TRICC),4 following hip (Functional Outcomes in Cardiovascular patients Undergoing Surgical hip fracture repair [FOCUS])3 and cardiac surgery (Transfusion Requirements After Cardiac Surgery [TRACS]).2 and patients with acute upper gastrointestinal bleeding4 and sepsis (Transfusion Requirements In Septic Shock [TRISS]).3

There are no previous prospective randomized data examining transfusion thresholds in oncology patients; in their article entitled “Transfusion requirements in surgical oncology patients” published in the January edition of Anesthesiology, Pinheiro de Almeida et al.6 randomize 198 critically ill patients following surgery for abdominal malignancy to restrictive (threshold 7 g/dl) and liberal (threshold 9 g/dl) strategies. They demonstrate an impressive and unexpected almost two-fold increase in their composite 30-day outcome (all-cause mortality, cardiovascular complications, acute respiratory distress syndrome, acute kidney injury requiring renal replacement therapy, septic shock, or reoperation) in the restrictive group. The outcome was reached in 35.6% in the restrictive group versus 19.6% in the liberal group (P = 0.012).

Thirty-day mortality was 8.2% (liberal) versus 22.8% (restrictive) (P = 0.005); this difference persisted at 60 days. The most common causes of death were septic shock and multisystem organ failure. Cardiovascular events and intraabdominal sepsis were more frequent in the restrictive group.

We question whether the differences observed are related to differences in transfusion practice or other confounding variables. A considerable 57.7% of those even in the liberal group were not transfused during their ICU stay, that is, were not subject to the intervention of interest. Although the authors state that differences in hemoglobin were statistically significant, this only relates to the hemoglobin concentration of 8.0 g/dl may be associated with postoperative complications in abdominal surgery. They also refer to a Korean propensity-matched study suggesting that transfused patients with septic shock have better outcomes8; this was not corroborated by the recent randomized controlled TRISS trial.

The authors go on to suggest that cancer patients may be more susceptible to impaired tissue oxygenation and that impaired microvascular flow below a hemoglobin concentration of 8.0 g/dl may be associated with postoperative complications in abdominal surgery. They also refer to the study suggesting that transfused patients with septic shock have better outcomes; this was not corroborated by the recent randomized controlled TRISS trial.

We note a small excess in major operations such as esophagectomy and gastroduodenopancreatectomy, as compared to cystectomy and hysterectomy, in the restrictive group. This may explain the excess of abdominal sepsis in this group as well as their excess mortality and increase in the composite 30-day outcome. There was also a small (albeit
nonsignificant) excess of patients with diabetes, chronic obstructive pulmonary disease, and congestive heart failure in the restrictive group. Adequate blinding is challenging for this patient group, and treating physicians were not blinded to the randomization. It is therefore possible that the rest of the care delivered was different between the groups. These confounding factors may have contributed toward the worse outcomes in the patients in the restrictive transfusion group.

The implications of this study could be substantial, and although the numbers of patients are small compared with other similar studies, the outcomes are apparently significant. However, the evidence that true differences in hemoglobin between the two groups was achieved is lacking, and furthermore, less than half of the patients even in the liberal group required transfusion and less than a third of patients in the study received any blood. This makes it difficult to assign differences in outcomes between the groups to transfusion.

Given the unexpected findings of this study, we would advise caution in interpreting the results. We feel differences in outcome cannot be attributed to the transfusion strategy alone. Further randomized studies are needed prior to altering the care delivered was different between the groups. These concerns with the interpretation of data and conclusions that can be drawn from these results.

Competing Interests

The authors declare no competing interests.


References


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Liberal Transfusion Practice or Perioperative Treatment of Anemia to Avoid Transfusion?

To the Editor:

With great interest we read the article by Pinheiro de Almeida et al.1 on “Transfusion Requirements in Surgical Oncology Patients” that addresses a clinical problem of utmost importance and ongoing debate. However, there remain some concerns with the interpretation of data and conclusions that can be drawn from these results.

1. Patients were included in this study if their hemoglobin level was more than or equal to 9 g/dl before admission to the intensive care unit (ICU). A hemoglobin level of 9 to 10 g/dl represents a state of severe anemia that occurred in a certain number of patients despite transfusion before randomization (fig. 3). Unfortunately, the incidence and severity of anemia according to the World Health Organization definition in the study groups is not reported. Regarding the further comorbidity profile of patients included, the number of patients with emergency operations (n = 13 vs. 9), congestive heart failure (n = 6 vs. 3), chronic obstructive pulmonary disease (n = 9 vs. 5), diabetes mellitus (n = 26 vs. 20), metastatic cancer disease (n = 39 vs. 32), and cerebrovascular disease (n = 8 vs. 2) were, at least numerically, higher in the restrictive group. It would be interesting whether the composite of these comorbidities was equally distributed between groups to better understand the interaction of anemia and perioperative