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Should red cell transfusion be individualized? Yes

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Introduction

Anemia is common in critically ill patients admitted to the intensive care unit (ICU) and is associated with a poorer outcome [1, 2]. However, red blood cell (RBC) transfusion can have complications and its availability is limited. Hence, one has to find a balance between the risks of anemia and the risks of transfusion. This decision process should be individualized and based on more than a hemoglobin level.

What is the evidence?

The landmark Transfusion Requirements In Critical Care (TRICC) trial [3] showed similar mortality rates in 838 critically ill patients randomized to a liberal transfusion strategy (hemoglobin levels 10–12 g/dl) or a restrictive strategy (hemoglobin levels 7–9 g/dl). The study was

stopped prematurely because of difficulties in recruitment [3]; indeed, only 15 % of the screened patients were enrolled. Importantly, mortality rates were higher in patients in the liberal than in the restrictive arm of the study in the subgroups of younger (age <55 years) and less sick (APACHE II score ≤ 20) patients. A post hoc review indicated that patients with ischemic heart disease and those with higher APACHE II scores in the liberal transfusion group had lower mortality rates [4]. Hence, although at first sight it seems that there were no differences in outcome, this is not true when the results are examined further.

Moving to the most recent large randomized controlled trial (RCT) on transfusions after cardiac surgery [5], the global composite outcome, including primarily infectious complications, was similar in the liberal (hemoglobin levels >9 g/dl) and the restrictive (hemoglobin levels 7.5–9 g/dl) treatment arms, but mortality was higher in patients randomized to restrictive transfusion (4.2 vs. 2.6 %, $p = 0.045$). This raises serious concerns about the safety of restrictive transfusion in these patients. A recent RCT in cancer patients undergoing major surgery [6] showed that a liberal transfusion strategy with a hemoglobin trigger of 9 g/dl was associated with fewer major postoperative complications compared with a restrictive strategy.

Another recent RCT, the Transfusion Requirements In Septic Shock (TRISS) trial, investigated the impact of liberal versus restrictive transfusion strategies on outcome in 1005 patients with septic shock [7]: 90-day survival rates were similar between groups. Transfusion rates were very high in the liberal arm (98.8 vs. 63.9 % in the restrictive arm). The presence of a strict protocol to achieve certain hemoglobin levels irrespective of the patient's general condition may lead to inappropriately high rates of transfusion. Accordingly, whether the results of this study are applicable in current practice is debatable.

Observational trials have the advantage, compared to randomized studies, that all patients are included, but it is difficult to separate the harmful effects of transfusion per se from the harmful effects of the complication for which the transfusion was indicated. This was nicely illustrated in a study of patients after cardiac surgery, in which the authors convincingly showed that the increased mortality was due to bleeding, which required more transfusions, rather than to the transfusions [8]. It was also well illustrated in a study by Ruttinger et al. [9], in which a simple analysis including only a few variables showed that transfusions were associated with a worse outcome, but this difference disappeared when more variables were included in the analysis. Likewise, in a study of more than 5000 patients after CABG surgery [10], transfusions were associated with reduced long-term survival, but this difference disappeared when the preoperative hemoglobin and estimated glomerular filtration rate were taken into account.

Earlier observational trials raised more concerns than more recent ones about the association between RBC transfusion and poor outcome in critical illness. In an early epidemiological survey of 3534 patients admitted to 146 western European ICUs [2], RBC transfusion was found to be an independent risk factor for death after adjusting for possible confounding factors and in a

propensity score-matched analysis [2]. Similar results were reported in trauma patients [11], in patients with burns [12], in patients undergoing cardiac surgery [13], and in patients with acute coronary syndromes [14]. More recent observational studies [1, 15] gave different results. In a post hoc analysis of the Sepsis Occurrence in Acutely ill Patients (SOAP) database, including 3147 ICU patients from 24 European countries, blood transfusion was not associated with a higher risk of death in a multivariable analysis and, in 821 pairs matched according to a propensity score, 30-day survival was higher in patients who received blood transfusions than in those who did not [15]. This finding does not support the view that blood transfusions, as currently administered, are associated with increased mortality rates in acutely ill patients. Another study in 5925 postoperative patients admitted to a surgical ICU in Germany reported that blood transfusion was independently associated with a lower risk of in-hospital death, especially in patients aged from 66 to 80 years, in patients admitted to the ICU after non-cardiovascular surgery, in patients with higher severity scores, and in patients with severe sepsis [1] (Fig. 1). Likewise, Park and colleagues [16] reported that RBC transfusion was associated with a lower risk of mortality in patients with severe sepsis.

Fig. 1 Relative risk (RR) of in-hospital death due to blood transfusion in selected subgroups of ICU patients. Reproduced from [1]. CI confidence interval, SAPS Simplified Acute Physiology Score, SOFA Sequential Organ Failure Assessment

These differences between the results of earlier and more recent observational studies may be explained by changes in transfusion practice, especially the implementation of leukoreduction with subsequent reduction in the rate of transfusion-related immunosuppression. In addition, the more restrictive transfusion strategies applied after the publication of the TRICC trial [3] may have become too restrictive in severely ill patients who are most likely to benefit from this therapy.

The case against using hemoglobin levels to trigger transfusion

The ultimate goal of RBC transfusion is to improve oxygen delivery to the tissues. Hemoglobin levels are readily available at the bedside but are not a surrogate for oxygen delivery and may not be sufficient to reflect

adequate tissue perfusion or cellular metabolic needs. In a study of the sublingual microcirculation in patients with severe sepsis [17], we showed that blood transfusion differentially improved microvascular perfusion in patients with impaired baseline perfusion, suggesting that transfusions may be particularly useful in this subset of patients. The clinical decision concerning blood transfusion should be based on a global assessment of the patient's condition, including measures of tissue oxygenation, when available, and comorbidities [18]. Future research on the subject should consider patient diversity and develop more individualized approaches for blood transfusion that are more likely to decrease the risk-to-benefit ratio.

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