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THE FUTURE OF OBSERVATIONAL RESEARCH AND RANDOMIZED CONTROLLED TRIALS IN RED BLOOD CELL TRANSFUSION MEDICINE

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ABSTRACT—Red blood cell (RBC) transfusions are commonplace in the intensive care unit (ICU) with at least 30% of ICU patients receiving a RBC transfusion at some point during their ICU stay. However, which patients should be transfused and what transfusion trigger(s) should be used remains unclear. RBC transfusion can be associated with adverse effects, but anemia is also associated with worse outcomes. Observational studies and randomized controlled trials (RCTs) have been conducted to try and answer some of the questions surrounding blood transfusion in critically ill patients. The need for blood transfusion and the benefit/risk ratio vary according to individual patient characteristics, including age and comorbidities, so large-scale RCTs in heterogeneous groups of patients may not be the most appropriate tool to investigate these issues; smaller RCTs in carefully defined patient groups may provide more useful information. Rigorous statistical analysis of large, carefully conducted observational studies will also help enhance our evidence-base in this field.

KEYWORDS—Critically ill, ICU, mortality, randomized controlled trial

INTRODUCTION

Red blood cell (RBC) transfusions are commonplace in the intensive care unit (ICU) with at least 30% of ICU patients receiving an RBC transfusion at some point during their ICU stay (1–3). Nevertheless, there is still considerable debate as to which patients should be transfused and what transfusion trigger(s) should be implemented. Despite improved blood transfusion practice in recent years, RBC transfusion can still be associated with adverse effects, including transmission of certain infectious diseases and development of immunosuppression. There are also concerns about limited availability of blood products and the costs of transfusion. However, the detrimental effects of anemia on outcome are also well established (4), such that the risks and benefits of transfusion versus anemia need to be carefully evaluated. Over the years, observational studies and randomized controlled trials (RCTs) have been conducted to try and clarify the relationship between RBC transfusion and outcomes in critically ill patients and to define optimal transfusion triggers. Here we discuss some of this evidence, concentrating on the adult population, and highlight the limitations of these two study types, before briefly discussing the likely future direction of research in this field.

Observational research

Over the last decade or so, several large, multicenter observational studies have investigated the epidemiology of RBC transfusion in ICU patients. In the Anemia and Blood Transfusion in Critically Ill Patients study (1), conducted in 1999, 37% of the 3,534 patients from western European ICUs received an RBC transfusion during their ICU stay. Transfused patients were older than those who did not receive a transfusion (64 vs. 59 years; $P < 0.001$) and had longer hospital lengths of stay (18.5 vs. 10.9 days; $P < 0.001$). Patients who received an RBC transfusion had higher ICU (18.5% vs. 10.1%; $P < 0.001$) and 28-day (29.0% vs. 14.9%; $P < 0.001$) mortality rates than did those who did not. In a logistic regression analysis adjusting for age, admitting hemoglobin level, Acute Physiology and Chronic Health Evaluation II score, and Sequential Organ Failure Assessment (SOFA) score, receipt of a transfusion was independently associated with an increased risk of dying (odds ratio [OR], 1.37; 95% confidence interval [CI], 1.02–1.84; $P = 0.04$). Similarly, in 516 propensity score–matched pairs, mortality rates were higher in transfused than in nontransfused patients (22.7% vs. 17.1%; $P = 0.02$).

In the CRIT study conducted in 2000/2001 (2), 44% of the 4,892 patients from 284 ICUs in the United States received at least 1 transfusion during their ICU stay. Again, RBC transfusion was associated with higher mortality rates than no transfusion, a difference that remained statistically significant in a matched propensity analysis in which characteristics including patient demographics, baseline Acute Physiology and Chronic Health Evaluation II and SOFA scores, origin of admission, admitting diagnoses, medical history, and hospital length of stay were used to match patients (adjusted mortality ratio, 1.65; 95% CI, 1.35–2.03; $P < 0.001$).

In the European Sepsis Occurrence in Acutely ill Patients (SOAP) study conducted in 2002 (3), 33% of the 3,147 patients had an RBC transfusion. Patients who had a transfusion were older (62 vs. 60 years; $P = 0.035$) and more likely to have liver cirrhosis or hematologic cancer, to be a surgical admission, and to have sepsis. Interestingly, unlike the two earlier studies, RBC transfusions were not associated with increased mortality in multivariate analysis after adjusting for possible confounders, including age, sex, comorbid diseases, Simplified Acute Physiology Score II and SOFA score on admission, the

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type of admission (medical or surgical), the presence of sepsis during the ICU stay, and the country of origin (relative hazard, 0.89; 95% CI, 0.76–1.05; $P = 0.159$). Moreover, in 821 pairs of patients matched according to a propensity score, 30-day survival was higher in transfused patients than in those who did not receive a transfusion (hazard ratio [HR], 0.73; 95% CI, 0.59–0.90; $P = 0.004$). The authors suggested this different finding compared with earlier studies may have been because of the greater use of leukoreduction in the SOAP study.

More recent observational data and retrospective analyses have also given conflicting results. Several studies have shown that RBC transfusions are associated with worse outcomes. In a retrospective analysis of data from 941,496 surgical patients in the United States, intraoperative RBC transfusion was associated with increased mortality (6.3 vs. 1.1%; $P < 0.001$), composite morbidity (34.6 vs. 11.8%; $P < 0.001$), and postoperative length of stay (12.0 vs. 3.54 days; $P < 0.001$) compared with no intraoperative transfusion (5); these differences remained significant after propensity-matched analysis. In retrospective analyses of 666 patients with severe burns (6), 1,150 patients with traumatic brain injury (7) and 4,546 cardiac surgery patients (8), transfusion during the ICU or hospital stay was also associated with worse outcomes. Others, however, have demonstrated improved outcomes associated with transfusion. In a retrospective analysis of prospectively collected data from 5,925 critically ill surgical patients, Sakr et al. (9) reported that RBC transfusion was associated with a lower risk of hospital death after multivariable analysis (relative risk [RR], 0.96; 95% CI, 0.92–0.99; $P = 0.031$), and in 1,054 patients with community-acquired sepsis, RBC transfusion was associated with a lower risk of 7-day (HR, 0.42; 95% CI, 0.19–0.50; $P = 0.26$), 28-day (HR, 0.43; 95% CI, 0.29–0.62; $P < 0.001$), and in-hospital (HR, 0.51; 95% CI, 0.39–0.69; $P < 0.001$) mortality (10).

The apparent differences in the results of these studies in relation to the association of transfusion with outcome are likely to be largely due to the number of variables collected and thus available for inclusion in the statistical models assessing the associations. Many of the often very large studies that reported worse mortality rates actually collected relatively few data on potential confounders. For example, patients who require an RBC transfusion are likely to be more severely ill; thus, if a study shows increased mortality rates in transfused patients is this actually because of the transfusion, or is it because these patients are anyway more ill and have a greater risk of dying? If sufficient data about risk factors for death at and after admission are not collected and adjusted for in multivariate or propensity analysis, the impact of transfusion on outcome may be overestimated. Rüttinger and colleagues (11) illustrated this point well in a retrospective analysis of 3,037 surgical ICU patients who required ICU admission. In univariate analysis, the number of RBC transfusions was associated with ICU mortality. In multivariate analysis accounting for limited confounders, those present only on admission, RBC transfusion was still found to be associated with worse outcomes (OR, 1.847; 95% CI, 1.263–2.701; $P = 0.002$). However, when a second more complex multivariate analysis was performed adjusting for additional potential confounders present during the ICU stay, RBC transfusion was no longer associated with mortality (OR, 0.898; 95% CI, 0.532–1.516; $P = 0.688$).

Randomized controlled research

Many claim that the best way of demonstrating the potential benefits of any intervention is the RCT. The most cited and best known of the RCTs within this field is the Transfusion Requirements in Critical Care (TRICC) study by Hebert et al. (12) published more than 10 years ago. This study indicated that a restrictive strategy (RBC transfusion only when hemoglobin level decreased <7 g/dL) was at least as good as a liberal strategy (RBC transfusion when hemoglobin concentration decreased <10 g/dL) with hospital mortality rates of 22.2% and. 28.1%, respectively ($P = 0.05$). The results from Hebert et al., combined with increasing concerns about infectious and immunosuppressive risks of RBC transfusions, led to a general change in attitudes to RBC transfusion, and guidelines now recommend lower transfusion triggers than previously practiced (13). In a subanalysis of the TRICC data from 203 trauma patients, 30-day mortality rates, development of multiple organ dysfunction, and length of ICU stay were all similar in restrictive and liberal groups, suggesting a restrictive approach may be safe in these patients (14). Indeed, recent European guidelines for management of bleeding following major trauma (15) recommend a target hemoglobin of 7 to 9 g/dL (grade 1C), based largely on the results of this study. However, in a reanalysis of the data from the TRICC study, Deans et al. (16) showed a higher mortality rate in patients with ischemic heart disease who were in the restrictive strategy group compared with those in the liberal group, in contrast to the global results of the study (12), suggesting that in patients with ischemic heart disease a more liberal approach to transfusion may be warranted.

There have been no other large randomized studies on transfusion strategies in general ICU populations since the TRICC study (12), largely for logistical reasons. Indeed, already in the TRICC study, only 13% of the 6,451 patients screened were randomized, limiting considerably the generalizability of these results (17). The European SOAP group of investigators started a randomized study to compare hemoglobin thresholds but abandoned it because enrollment was very slow, and too many patients were being excluded because physicians found it difficult to randomly assign certain types of patients to one or other transfusion strategy (18).

Other RCTs have been conducted in more specific groups of patients and given conflicting results. An RCT in 502 cardiac surgery patients demonstrated the noninferiority of a restrictive strategy of RBC transfusion, using a hematocrit of 24% as threshold, compared with a more liberal strategy using a hematocrit of 30% as threshold (19); regardless of the strategy, the number of transfused RBC units was an independent risk factor for death in these patients (HR for each additional unit transfused 1.2; 95% CI, 1.1–1.4; $P = 0.002$). In 2016 patients with cardiovascular disease, a liberal RBC transfusion strategy (hemoglobin threshold of 10 g/dL) had no beneficial effects, as assessed by survival or ability to walk across a room without human assistance, on 60-day follow-up, compared with a

restrictive approach (symptoms of anemia or at physician discretion for a hemoglobin level of <8 g/dL) after hip surgery (35.2% vs. 34.7%; not statistically significant) (20). However, this study included a population with very few risk factors, especially after an amendment was implemented because recruitment was very slow. A recent pilot study in 100 elderly, mechanically ventilated ICU patients showed a trend to reduced 180-day mortality in patients managed using a restrictive (hemoglobin trigger, 7.0 g/dL) compared with a more liberal (9.0 g/dL) RBC transfusion strategy (RR, 0.68; 95% CI, 0.44–1.05; $P = 0.073$) (21).

Results may be different in certain diseases. As an example, in a small study in 44 neurosurgical patients, Naidech et al. (22) showed that targeting a higher hemoglobin level (11.5 g/dL) in patients with subarachnoid hemorrhage was as safe as targeting a lower hemoglobin level (10 g/dL) and may have reduced the incidence of cortical cerebral infarction (30% vs. 41%; not statistically significant). In addition, in patients undergoing major cancer surgery, a liberal RBC transfusion strategy (hemoglobin trigger, 9 g/dL) was associated with fewer major postoperative complications compared with a restrictive strategy (hemoglobin trigger, 7 g/dL) (Pinheiro de Almeida et al., unpublished data). A study comparing restrictive (RBC transfusion at hemoglobin ≤7 g/dL) versus liberal (RBC transfusion at hemoglobin ≤9 g/dL) transfusion practice in patients with septic shock is ongoing (Transfusion Requirements in Septic Shock trial, NCT 01485315).

The future for research

Overall, the evidence for or against RBC transfusions is in fact relatively limited. In a meta-analysis conducted using a literature search until February 2011, 19 RCTs in which patients were randomized to treatment according to a clear transfusion "trigger" were identified (23). The results showed that restrictive strategies were associated with a statistically significant reduction in hospital mortality (RR, 0.77; 95% CI, 0.62–0.95; $P = 0.018$) but not 30-day mortality (RR, 0.85; 95% CI, 0.70–1.03; $P = 0.097$) or hospital length of stay (mean difference, 0.11; 95% CI, −0.16 to 0.38; $P = 0.42$). Moreover, although there was little heterogeneity among studies for the mortality outcome variable, two trials (12, 20) dominated the analysis, providing 75% of the statistical information. As these two studies were performed in specific populations, i.e., elderly patients undergoing hip replacement surgery (20) and ICU patients (12), the results of this meta-analysis may not apply to other groups of patients (23).

So how can we improve our evidence base? What should the next steps be in terms of future observational studies or RCTs? We do not think we need a repeat RCT on lower versus higher hemoglobin thresholds for RBC transfusion in *all* ICU patients. It is difficult to demonstrate an effect on outcome in interventional studies that are conducted in heterogeneous populations because, regardless of the effectiveness of the randomization strategy, almost inevitably some patients will benefit from the intervention being tested, whereas others will have no response, and some will have an adverse reaction (17). Moreover, it would be very difficult to conduct a truly randomized study of transfusion triggers in a nonspecific general population of ICU patients. As demonstrated in the discontinued SOAP transfusion study, physicians are reluctant to randomize certain patients to one or other group, e.g., randomizing an elderly patient with heart disease to a restrictive strategy or a young previously healthy trauma patient to a liberal strategy would be seen as unacceptable by many physicians (18). As such, protocol deviations would rapidly become the norm in such a study, if indeed such patients were included in the first place, and the results would therefore be difficult to generalize. In contrast, observational studies have *no* exclusion criteria, and *all* patients are included, making the results much more globally applicable and relevant. In addition, informed consent is generally not needed for an observational study, enabling all patients to be included at an earlier stage than if consent has to be obtained and again maximizing the potential patient population that can be included.

The randomization process has been promoted as being the best way to limit the influence of confounders by ensuring that the study groups are comparable at baseline. Indeed, the RCT is placed at the top of most of the hierarchical systems used to grade evidence, raised to such a status that other study types have been neglected or are distrusted. But observational studies have advantages over RCTs in terms of clinical relevance and generalizability and when well conducted and carefully analyzed and interpreted can provide important and useful information regarding ICU practice. Importantly, to reduce the effects of confounders and bias as much as possible in future observational studies, rigorous statistical techniques should be applied. Various approaches can be used to adjust for confounding, both at the study design phase (e.g., restriction or matching) and at the analytical phase (e.g., stratification, propensity scores, and multivariable adjustment). Each of these strategies has advantages and limitations, and the most appropriate statistical test will vary according to the type of population included, the study design, and the outcome of interest (11, 24, 25).

No study type is perfect for every clinical situation or research question, and this factor must be taken into account when assessing the available evidence. As Prof Rawlins (26) stated in his 2008 Harveian Oration, "Experiment, observation, and mathematics, individually and collectively, have a crucial role in providing the evidential basis for modern therapeutics…. Hierarchies of evidence should be replaced by accepting—indeed embracing—a diversity of approaches."

CONCLUSIONS

As for many other therapeutic interventions, the RBC transfusion "pendulum" has swung from fairly liberal use through restricted use and is perhaps beginning to swing back again with the realization that restricted approaches may perhaps be too restrictive in some groups of patients. To further evaluate the optimal approach to RBC transfusion, gaps in our knowledge of the risks and benefits of RBC transfusions in specific clinical situations must be filled, using a combination of observational and randomized controlled research techniques. Importantly, the point at which patients should be transfused will not be identical for all patients; hence, large-scale

RCTs in heterogeneous groups of patients are unlikely to provide valid answers for application in general clinical practice, but smaller RCTs in carefully defined patient groups will help define optimal RBC transfusion strategies in these patients. Other answers will be revealed by carefully conducted, rigorous statistical analysis of large, carefully conducted observational studies. Data from well-conducted observational studies and RCTs will also provide answers to other critical transfusion-related questions that are beyond the scope of the current article, including the ideal ratio between packed RBCs, fresh frozen plasma and platelet transfusions in the field of damage control resuscitation, the benefits of fresh versus stored RBCs, and the exact role of leukoreduction, among others. Decisions to transfuse must be made on an individual patient level, taking into account factors such as age, comorbid cardiac disease, hemodynamic measurements and tissue perfusion markers, and carefully weighing up the pros and cons. Red blood cell transfusions should not be guided only by an arbitrarily defined hemoglobin level "trigger."

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