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Blood Conservation in the Critically Ill Patient

Howard L. Corwin, MD^{a,b,*}

^a*Dartmouth Medical School, HB 7999, Hanover, NH 03755, USA*

^b*Critical Care Medicine, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA*

Red blood cell (RBC) transfusion began to come under scrutiny in the early 1980s when concerns about transfusion-related infections, particularly those caused by hepatitis C and HIV. Although advances in transfusion medicine have greatly decreased the risk of viral transmission during RBC transfusion, other concerns now drive the debate over transfusion practice and have led to a re-examination of the approach to RBC transfusion. This debate and the re-examination of transfusion approach have been particularly intense in relation to the care of the critically ill. This review focuses on transfusion practice in the critically ill.

Red blood cell transfusion in the critically ill

Anemia is common in critically ill patients and appears early in their ICU course. By day 3 after ICU admission, almost 95% of patients are anemic [1–3]. The anemia in these critically ill patients persists throughout the duration of their ICU and hospital stay, with or without RBC transfusion [3]. As a consequence of the anemia, critically ill patients receive a large number of RBC transfusions.

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* Critical Care Medicine, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756.

E-mail address: Howard.L.Corwin@Hitchcock.org

Studies conducted a decade ago [4] found that 50% of all patients admitted to the ICU are transfused during their ICU admission. In addition, 85% of patients with a prolonged ICU length of stay (≥ 1 week) received transfusions [5]. On average, these latter patients receive transfusions of 9.5 units of RBCs during their ICU admission. These transfusions are not restricted to the early ICU course; rather, patients are transfused at a rate of 2 to 3 units per week. Groeger et al [6], in a descriptive study of critical care units in the United States in the early 1990s, noted that on a single day almost 14% of patients in critical care units were transfused (ranging from 4% in cardiac care units to 27% in surgical ICUs).

Has the scrutiny of transfusion practice in the critically ill over the last decade resulted in a change in the approach to RBC transfusion in the ICU? There have been two large trials addressing this question over the last several years [3,7]. An observational study [3] of 4892 patients admitted to ICUs in the United States throughout 2000 and 2001 (the CRIT study) found that 45% of patients are still transfused and on average receive almost 5 units of RBCs. The results also showed that the initial RBC transfusion tends to occur early in the ICU stay, with ongoing RBC transfusions throughout their ICU stay. The mean pretransfusion hemoglobin level observed, that is, the “transfusion trigger,” was 8.6 ± 1.7 g/dL, a value comparable to that described in earlier reports [4,5]. A similar observational study [7] of transfusion practice in ICUs was performed across Western Europe (the ABC study). Data were collected on 3534 patients admitted to the ICU during a 2-week period in late 1999. Thirty-seven % of patients received a mean of 4.8 units of RBCs while in the ICU. The mean pretransfusion hemoglobin level was 8.4 g/dL.

The similarity in results between these two large observational trials is striking. These studies suggest that transfusion practice in response to the anemia of critical illness has changed little over the last decade and is consistent across the critical care community. This is particularly surprising, given the scrutiny to which transfusion practice has been subjected over the last decade and the data available regarding transfusion risks and efficacy. In particular, in a prospective randomized study of critically ill patients, Hebert et al [8] demonstrated that maintaining hemoglobin levels in the range of 7 to 9 g/dL is at least equivalent and in some patients (according to the acute physiology and chronic health evaluation [APACHE] II ≤ 20 or age ≤ 55 years) superior to maintaining hemoglobin levels greater than 10 g/dL with RBC transfusion. Both observational studies were conducted after the publication of the Hebert trial [8].

Red blood cell transfusion efficacy and risks

Red blood cell transfusions are commonly used in the critical care setting in an attempt to increase oxygen delivery to the tissues and in turn improve tissue oxygenation, especially in shock states. The rationale for this therapeutic

approach is that an increase in hemoglobin will increase the oxygen-carrying capacity of blood and thus provide more oxygen delivery to delivery-dependent tissue. Studies regarding the efficacy of RBC transfusions to increase tissue oxygen consumption and to improve clinical have not consistently demonstrated that this therapeutic maneuver is accompanied by an increase in oxygen use at either the whole-body level or at the level of the individual organs [9,10].

Transfused RBCs, especially during the time period immediately following transfusion, are not “normal.” Stored RBCs have a low p50 that increases the affinity of hemoglobin for oxygen and thereby reduces oxygen release to tissues. Furthermore, standard citrate phosphate dextrose-stored blood is rapidly depleted of 2,3-diphosphoglycerate and ATP, with resultant inadequacy of the red cell oxygen transport function. The duration of storage may also be an important determinant of the efficacy of RBCs. In a study [11] of septic patients, patients receiving RBC units stored for greater than 15 days developed more evidence of splanchnic ischemia than those receiving blood stored for less than 15 days. A follow-up study [12] using a rat sepsis model demonstrated that a transfusion of “fresh” RBCs acutely increased systemic oxygen uptake, whereas a transfusion of RBCs stored for 28 days failed to improve tissue oxygenation. The CRIT study [3] has found that the average age of RBCs transfused in the US is 21 days.

The best evidence available regarding the efficacy of blood transfusion among critically ill patients is the randomized controlled trial by Hebert et al [8]. As noted above, these investigators compared a liberal transfusion strategy (hemoglobin level of 10–12 g/dL with a transfusion trigger of 10 g/dL) with a restrictive transfusion strategy (hemoglobin level of 7–9 g/dL with a transfusion trigger of 7 g/dL). Patients in the liberal transfusion arm received significantly more RBC transfusions. Overall in-hospital mortality was significantly lower in the restrictive strategy group, although the 30-day mortality rate was not significantly different. However, in those patients who were less ill (APACHE ≤ 20) or younger (≤ 55 years of age), the 30-day mortality rates were significantly lower for the patients in the restrictive transfusion group. Therefore, a restrictive strategy is at least equivalent and possibly superior in some patients to a more liberal transfusion strategy.

RBC transfusion is not without risk. Both the ABC and CRIT studies [3,7] found that RBC transfusion was independently associated with worse clinical outcomes. These observational studies, as well as the studies by Hebert et al and other investigators [8,9,13] have raised questions regarding the validity of the historic assumption that RBC transfusion was beneficial for critically ill patients with anemia.

A significant association between the number of RBC transfusions and risk of subsequent infection has been reported in patients after trauma, burns, and a variety of both elective and emergency surgical procedures [14–17]. A recent meta-analysis [18] has demonstrated the relationship between allogeneic blood transfusion and postoperative bacterial infection using 20 peer-reviewed studies published from 1986 to 2000. The total number of subjects included in this meta-

analysis was 13,152 (5215 in the transfused group and 7937 in the nontransfused group). The common odds ratio for the risk for infection associated with RBC transfusion in this meta-analysis was 3.45 (range, 1.43–15.15), with 17 of the 20 studies demonstrating a value of $P \leq 0.05$. These results provide overwhelming evidence that RBC transfusion is associated with a significantly increased risk of postoperative bacterial infection in the surgical patient. Similarly, in critically ill patients, Taylor et al [19] have also demonstrated an association between RBC transfusion and both nosocomial infection and mortality.

This increase in infection risk is believed to be predominantly a result of leukocytes present in the transfused RBCs. These data have in turn led to the hypothesis that transfusing patients with leukoreduced blood should result in reduced morbidity and mortality compared with patients who receive non-leukoreduced RBC transfusions. However, most of the studies bearing on these questions have been flawed by retrospective design and inadequate consideration of the effects of comorbidities, whereas the few prospective studies in specific patient populations have reached contradictory conclusions. Meta-analyses of this literature have failed to identify a statistically significant effect of leukoreduction [20–22] on outcomes associated with RBC transfusions. A recent study [23] evaluating clinical outcomes following the institution of a universal prestorage leukoreduction program in Canada noted a reduction in in-hospital patient mortality after the introduction of this program. On the other hand, a randomized prospective study [24] comparing outcomes in patients receiving either leukoreduced or non-leukoreduced RBCs failed to demonstrate any beneficial effect of leukoreduction on clinical outcome, including in-hospital mortality, ICU length of stay or readmission rates, and antibiotic usage.

Red blood cell conservation

What determines whether a patient receives a blood transfusion? There are widespread deficiencies in the knowledge of transfusion risks and indications among physicians [25]. Therefore it is not surprising that the variability in transfusion practice between individual physicians and institutions is striking. Variation has been documented in the coronary artery bypass graft surgery (CABG) population. Among elective primary CABG operations at 24 academic centers, institutional RBC transfusion rates varied widely from 27% to 92% of patients [26,27]. Goodnough et al [28] also observed variation in institutional RBC transfusion rates, from 17% to 100% of patients at 18 centers performing CABG surgery. Mean RBC transfusion ranged from 0.4 to 6.3 units per patient in this study. The observed variation was not explained by patient or process characteristics. Furthermore, it was determined that 15% of the RBCs transfusions in this study were inappropriate [28]. Variation in transfusion practice is not restricted to cardiac surgical patients. In critically ill patients, almost half of all transfusions and almost two thirds of those for nonacute blood loss were

performed for either no identifiable indication or low hematocrit level alone [4]. Among non-ICU medical patients, 35% of RBC transfusions were judged either nonjustified or equivocal [29]. Similarly, other investigators have found the number of inappropriate transfusions ranging from 4% to as high as 57% [30,31].

Transfusion may in large part be driven by individual “transfusion triggers” rather than specific physiologic indication. In a study [4] of critically ill patients, the pretransfusion hematocrit level was similar regardless of transfusion indication. In the CRIT study [3], a low hemoglobin level was cited as the transfusion indication in 90% of RBC transfusions. The transfusion trigger used, either consciously or more likely unconsciously, was a hematocrit level of approximately 27%. The similarity of pretransfusion hemoglobin concentration in the CRIT and ABC studies tends to support the concept of transfusion trigger [3,7].

Recent recommendations have advocated that empirical automatic transfusion thresholds be abandoned in favor of a practice of RBC transfusion only for defined physiologic need [32,33]. However, the suggestion for a more conservative approach to RBC transfusion does not as yet appear to have resulted in any major alteration in practice patterns. It is clear that if a more conservative transfusion practice (lower transfusion trigger) were adopted, in the range of 7 to 9 g/dL for most critical care patients as suggested by Hebert et al [8], there would be a significant reduction in the number of RBC units received by critically ill patients.

Phlebotomy is an important factor contributing to anemia and the need for blood transfusions in the critically ill patient. Smoller and Kruskall [34] found that almost half of their ICU patients receiving blood transfusions were phlebotomized more than the equivalent of 1 unit of blood. The ICU patients described in this study, on average, were phlebotomized 65 mL per day. Phlebotomy blood losses in this range are consistent with other reports of critically ill patients over the last 2 decades and are often associated with the development of anemia [5,35,36]. In a more recent study [37] of patients treated in an ICU for more than 3 days, diagnostic phlebotomy accounted for approximately 17% of total blood loss. Similarly, the ABC study [7] documented an average daily phlebotomy volume of 41 mL, which had a significant, positive correlation to organ dysfunction.

Given the strong association between phlebotomy and blood transfusion, a reduction of this daily blood loss should have a positive impact on blood use in the ICU. The importance of blood conservation in the critical care setting has been stressed by Chernow et al [38] and Chernow [39]. Approaches directed toward reducing phlebotomy blood loss include the use of small volume (pediatric sized) tubes, elimination of arterial line blood discard, elimination of standing orders for laboratory tests, altering test ordering behavior, and daily feedback [40–44]. The use of small volume (pediatric) tubes has been shown to result in a decrease in phlebotomy blood loss in the range of 33% to 47% [41,42]. Foulke and Harlow [41] noted that a significant reduction in the number of patients transfused coincided with a reduction in the daily phlebotomy blood

loss. The finding that patients who are not transfused have significantly lower daily phlebotomy blood loss is consistent with this [5], although other factors may also be responsible for the lack of blood transfusion in these patients. Blood conservation systems have also been designed to eliminate blood discards [40,45]. Such systems in combination with advances in inline monitoring of laboratory parameters [46,47] (ie, arterial blood gases) could greatly reduce phlebotomy blood loss. Clearly, the appropriateness of the laboratory tests ordered is also an important issue. The pattern of test ordering by multiple physicians, seen in most ICUs, has clearly been demonstrated to increase unnecessary laboratory tests [48].

How much blood could potentially be saved in these patients by changing transfusion practice? Current transfusion guidelines stress the importance of abandoning specific “transfusion triggers” in making transfusion decisions, particularly in patients with hemoglobin levels above 7 g/dL [8,32,33]. It has been estimated that RBC transfusions given in the ICU without a clinical indication account for 28% of all RBCs transfused and therefore can potentially be saved [5]. The real savings could be higher if some RBC transfusions given for “clinical indications” actually reflect a “transfusion trigger” effect rather than a real transfusion indication. Transfusions associated with acute blood loss are less likely to be eliminated; however, to the extent that these transfusion decisions are also driven by arbitrary “triggers,” they could also be decreased. Clearly, combining decreased phlebotomy blood loss with more conservative transfusion practice would act synergistically to decrease the number of RBCs transfused in the ICU.

Over the last several years it has become clear that the view of anemia in the critically ill as simply the result of excessive phlebotomy by “Medical Vampires” is not completely accurate [49]. The RBC production in critically ill patients is not normal, and decreased levels of RBC production are also involved in the development and maintenance of the anemia observed in the critically ill. Over 90% of ICU patients have low serum iron (Fe), total iron binding capacity (TIBC), and Fe/TIBC ratio but have a normal or, more usually, an elevated serum ferritin level [2,50]. Similarly, low iron parameters and elevated ferritin levels are observed in patients with multiple organ dysfunction [51]. At a time when the iron studies are abnormal, serum erythropoietin (EPO) levels are only mildly elevated, with little evidence of reticulocyte response to endogenous EPO [2]. This blunted EPO response observed in the critically ill appears to result from inhibition of the EPO gene by inflammatory mediators [52,53]. It has also been shown that these same inflammatory cytokines directly inhibit RBC production by the bone marrow and may produce the distinct abnormalities of iron metabolism [54,55].

Anemia of critical illness, therefore, is a distinct clinical entity characterized by blunted EPO production and abnormalities in iron metabolism similar to what is commonly referred to as the anemia of chronic disease. As such, the bone marrow in many of these patients may respond to the administration of exogenous EPO, despite their critical illness. This may represent a therapeutic

option for the treatment of the anemia of critical illness and an additional way to conserve RBCs in the ICU.

In a small, randomized, placebo-controlled trial of 160 patients [1], therapy with recombinant human (rHu) EPO resulted in a reduction of almost 50% in RBC transfusions compared with placebo. In this trial, patients with hematocrit levels less than 38% on ICU day 3 were given rHuEPO at a dose of 300 units/kg daily for 5 days followed by every other day until ICU discharge. Despite receiving fewer RBC transfusions, patients in the rHuEPO group had a significantly greater increase in hematocrit levels.

The efficacy of rHuEPO demonstrated in the small trial cited above [1] was the basis for a recently completed randomized controlled trial of 1302 patients [56]. In this later trial, rHuEPO was given weekly at a dose of 40,000 units. All patients received three weekly doses, and patients who remained in the ICU on study day 21 received a fourth dose. Treatment with rHuEPO resulted in a 10% reduction in the number of patients receiving any RBC transfusion and a 20% reduction in the total number of RBC units transfused. Similar to the earlier study [1], the increase in hemoglobin from baseline to final level was greater in the rHuEPO group. Clinical outcomes were similar in the rHuEPO and placebo groups.

Taken together, these studies [1,56] demonstrate that rHuEPO therapy in “acute” critically ill patients will result in a decrease in RBC transfusion and an increase in hemoglobin level. This is consistent with the hypothesis that the critically ill patient has an anemia similar to anemia of chronic disease, which is characterized in part by a relative erythropoietin deficiency [57]. Further study is needed to determine whether the reduction in RBC transfusion with rHuEPO is associated with improvements in clinical outcome.

Summary

The condition of anemia and RBC transfusion remains a major clinical problem in the critically ill. If RBC transfusion were “risk free,” the debate over RBC transfusion practice would not be taking place. The data available suggest that RBC transfusion is associated with worse clinical outcomes [3,7]. Key to conserving RBCs in the ICU is modifying transfusion practice. The decision to transfuse involves balancing the risks of anemia and the risks of RBC transfusion. The risks of RBC transfusion, although they are clearly less than in the past, are still real. Other measures such as universal leukoreduction may reduce RBC risks even further; however, RBC transfusion will never be risk free [58,59]. The optimal hematocrit level for the ICU patient remains to be determined. However, it seems clear that for most critically ill patients a restrictive transfusion strategy, tolerating hemoglobin levels as low as 7 mg/dL, is acceptable [8]. In addition to changing transfusion practice, strategies to minimize phlebotomy blood loss and to increase the endogenous RBC production are also important in the blood management of the critically ill patient.

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