Restrictive red blood cell transfusion and alternatives to transfusion in the critically ill: a review of the clinical evidence

Anemia is a common problem in the critically ill. Its causes are multifactorial and include bleeding, iatrogenic blood loss through diagnostic phlebotomy and blunted erythropoiesis. Although red blood cell transfusions are a life-saving therapy in cases of severe anemia and in the acutely bleeding patient, the benefits in cases of mild and moderate anemia are still debated. Several blood conservation strategies may help to reduce blood loss, and hence mitigate against anemia in the critically ill. These strategies include the use of hemoglobin substitutes, hemostatic agents, blood salvage, erythropoietin and preventative strategies to minimize blood loss in the critically ill. This review article highlights and summarizes potential benefits and risks associated with red blood cell transfusion. It also summarizes current clinical evidence for a restrictive red blood cell transfusion strategy in critically ill adults, children and premature infants, and discusses evidence for different red blood cell conservation strategies in the critically ill setting.

KEYWORDS: red blood cell conservation strategies ■ red blood cell transfusion ■ transfusion ■ transfusion alternatives

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Anemia is a common problem in critically ill patients. Over 90% of patients admitted to an intensive care unit are anemic by the third day of their stay. The reasons for anemia are multifactorial and include bleeding, iatrogenic blood loss through diagnostic phlebotomy and blunted erythropoiesis. As a result, many critically ill patients are transfused. Indeed, two large multicenter cohort studies reported that 45% of US [1] and 37% of European [2] intensive care unit patients are transfused. The primary rationale for transfusing critically ill patients with red blood cells (RBCs) is to increase oxygen delivery, and subsequently improve tissue oxygenation. Although RBC transfusions are a life-saving therapy in cases of severe anemia and in the acutely bleeding patient, the benefits in cases of mild and moderate anemia are still debated [3,4]. Furthermore, a large body of literature documents several potential harms associated with RBC transfusions [5].

This review will discuss the potential benefits and risks of administering RBC transfusions in the critically ill. We will also summarize current clinical evidence for a restrictive RBC transfusion strategy in critically ill adults, children and premature infants, and discuss evidence for different RBC conservation strategies in the critically ill setting.

Rationale for red blood cell transfusions: potential benefits & risks

There are two main reasons for administering a RBC transfusion. RBCs are excellent volume expanders as they are maintained in the intravascular space for prolonged periods. More importantly, they are the main transport mechanism for oxygen, and are thus an essential component to ensure optimal delivery of oxygen to the tissues [6]. The amount of oxygen delivered, either to the whole body or to specific organs, is quantified by the product of cardiac output and the arterial oxygen content, which is almost entirely due to oxygen carried by RBCs. The relationship between oxygen delivery and oxygen consumption is biphasic [7]. In health, the amount of oxygen delivered (DO_2) to the whole body exceeds resting oxygen requirements by a factor of 2–4 [8]. Thus, oxygen consumption is independent of oxygen delivery. However, there is a point whereby oxygen consumption does become dependent upon oxygen delivery; this point is called the critical DO_2 and corresponds to the anaerobic threshold. Any further decrease in oxygen delivery may potentially render the tissues hypoxic and provide a setting for the development of multiple organ failure. Although RBC transfusions are often given to increase oxygen delivery and mitigate

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Table 1. Infectious and noninfectious risks associated with red blood cell transfusions.

Risks	Incidence (number of transfused units)
Infectious risks	
Viral infection	–
Hepatitis A	1:2,000,000
Hepatitis B	1:31,000*–81,000‡
Hepatitis C	1:1,935,000–3,100,000
HIV (AIDS)	1:2,135,000–4,700,000
HTLV I/II	1:1,900,000
Bacterial contamination	1:14,000–28,000
Parasitic infection	1:4,000,000
Prions	Rare
Noninfectious risks	
Febrile nonhemolytic reactions	1:500
Urticarial reactions	1:50–100
Anaphylactic reactions	1:23,000
Hemolytic transfusion reactions	1:9000
TRALI	1:1300 – 5000
TACO	1:17,000
Post-transfusion purpura	1:143,000

**Risk attributable to window period of Hepatitis B infection (before development of positive hepatitis B surface antigen [HBsAg]) and chronic HBV carriers with undetectable levels of HBsAg.*
‡Risk attributable to window period of Hepatitis B infection only.
HTLV: Human T-cell lymphotrophic virus;
TACO: Transfusion-associated circulatory overload;
TRALI: Transfusion-related acute lung injury.

tissue ischemia, the ability of RBC transfusions to increase oxygen consumption has not been consistently demonstrated [8].

Allogeneic RBC transfusions have well-described adverse consequences that can be divided into infectious [9–11] and noninfectious risks [12,13] (see Table 1). Infectious risks include the risk of transmission of HIV, hepatitis B and C, human T-cell lymphocyte virus (HTLV), West Nile virus and variant Jacob Creutzfeldt disease. However, with significant advancements in the screening of donors for transmittable diseases, these infections via blood components are rare. Noninfectious risks include febrile, urticarial and hemolytic transfusion reactions, as well as transfusion-related acute lung injury (TRALI) [12,13]. There are other potential mechanisms by which RBCs may exert additional adverse effects that impact mortality and morbidity. These include immunomodulation [14–17], as well as biomechanical and biochemical changes that occur as the stored RBC ages, and are referred to as the red cell storage lesion, that may further decrease the ability of the RBC to transport, release or deliver oxygen [13,18,19].

Clinical evidence for a restrictive red blood cell transfusion strategy in the critically ill

Several randomized controlled trials have examined the effects of restrictive RBC transfusion practices in nonacutely bleeding adult [20], pediatric [21] and neonatal patient populations [22,23].

In adult patients, Hebert *et al.* randomized 838 euvolemic critically ill patients with hemoglobin concentrations of less than 90 g/l to a restrictive transfusion strategy (target hemoglobin of 70–90 g/l with a hemoglobin transfusion threshold of 70 g/l), or a liberal transfusion strategy (target hemoglobin of 100–120 g/l with a hemoglobin transfusion threshold of 100 g/l) in the Transfusion Requirements in Critical Care (TRICC) trial [20]. Patients in the restrictive arm had lower hemoglobin levels (85 vs 107 g/l, $p < 0.01$), received fewer red cell transfusions (2.6 vs 5.6 units per patient, $p < 0.01$), and had a trend toward a lower mortality at 30 days (18.7 vs 23.3%, $p = 0.11$). In subgroup analyses, a restrictive RBC transfusion strategy was superior to a conservative strategy for younger patients (<55 years old, $p = 0.02$) and those who were less severely ill (Acute Physiology and Chronic Health Score [APACHE II] < 20, $p = 0.02$). The results from this seminal trial demonstrated that a restrictive RBC transfusion strategy reduces red cell transfusion requirements, and is at least as safe, and possibly superior, to a more liberal approach for critically ill adults [20]. We recently published a subgroup analysis of 203 trauma patients from the TRICC trial [24]. The 30-day all-cause mortality rates (10 vs 9% respectively, [$p = 0.81$]), as well as all morbidity measures, were similar between the restrictive and liberal transfusion groups.

A separate subgroup analysis of 67 trauma patients from the TRICC trial who had sustained a traumatic brain injury was also conducted by our group because of the concern that the injured brain may represent a particularly vulnerable organ susceptible to adverse consequences of decreased oxygen transport [25]. Despite these concerns, the 30-day all-cause mortality rates for the restrictive versus liberal transfusion groups (17 vs 13% [risk difference: 4.1 with 95% CI: 13.4–21.5]) and all measures of morbidity were similar. Although the

results of these two subgroup analyses of trauma patients from the TRICC trial may be interesting, caution is advised in their interpretation, as both were derived from subgroup analyses, and neither study was adequately powered to evaluate for clinically important benefit or harm.

Patients with cardiovascular disease (n = 357) represent another subgroup of patients who were analyzed separately in the TRICC trial. Overall, the 30-day mortality rate was similar for the restrictive and liberal transfusion groups (23 vs 23%, p = 1.00) [26]. However, in 257 patients who had severe ischemic heart disease, there was a trend toward an increase in 30-day mortality in the restrictive as compared with the liberal transfusion group (26 vs 21%, p = 0.38). The results of two additional large retrospective observational studies examining red cell transfusions in patients with acute myocardial infarction are contradictory, with one study suggesting that transfusion at higher hemoglobin thresholds may be beneficial [27], and the second study demonstrating an association between RBC transfusion and increased mortality [28]. Further large randomized, controlled trials are required in this patient group to determine whether a lower hemoglobin transfusion trigger is at least as safe as a more liberal trigger in patients with ischemic heart disease. A multicenter trial examining RBC transfusion triggers in high-risk patients with cardiovascular disease and who have sustained a hip fracture (the Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair [FOCUS] trial) is nearing completion and will further inform this issue [101].

Lacroix and colleagues recently published a randomized, controlled trial of 637 pediatric intensive care unit patients (age range: 3 days to 14-years-old) and found that a hemoglobin threshold of 70 g/l as compared with a more liberal transfusion threshold of 95 g/l reduced red cell transfusion by 44% (0.9 ± 2.6 vs 1.7 ± 2.2 units per patient, p < 0.001), without differences in mortality or in new or progressive multiorgan dysfunction between the two groups [21].

A single-center, randomized controlled trial of 100 preterm infants (birth weight 500–1300 g) found no differences in survival, patent ductus arteriosis, retinopathy or bronchopulmonary dysplasia between the study groups [23], but there was an significant increase in grade IV intraventricular hemorrhage (4 [14%] versus 0, p = 0.054), apneic episodes (>1 apnea episode per day: 21 [43%] versus 10 [20%], p = 0.017), and a trend toward greater periventricular leukomalacia (4 [14% vs 0], p = 0.115) in the restrictive as compared with the liberal transfusion group. A subsequent multicenter trial of 451 premature (<31 weeks) infants with extremely low birth weights (<1000 g), the Premature Infants in Need of Transfusion (PINT) trial, randomized the subjects to varying hemoglobin thresholds according to age (days), method of blood sampling (capillary vs central venous catheter sampling) and need for respiratory support [22]. The differences in the transfusion thresholds for the restrictive and liberal groups were between 9 and 20 g/l. Infants in the restrictive as compared with the liberal group had lower mean hemoglobin levels and a trend towards a decreased number of RBC transfusions (4.9 ± 4.2 vs 5.7 ± 5.0, p = 0.07). Infants in the restrictive transfusion arm were also exposed to fewer RBC donors (2.1 ± 2.0 vs 2.6 ± 2.7, p = 0.035). There were no significant differences in the primary composite outcome of death, survival with bronchopulmonary dysplasia, severe retinopathy of prematurity or brain injury (74 vs 69.7%, p = 0.25) between the restrictive versus liberal transfusion groups. When death was examined as a separate outcome, there was a trend toward an increase in mortality for the restrictive as compared with liberal transfusion group (21.5 vs 17.5%, respectively; risk difference: 2.6%; 95% CI: 3.5–8.8%, p = 0.21). These findings should be considered as hypothesis-generating, and require confirmation or refutation in future trials to understand whether a restrictive transfusion strategy is safe in the premature infant population.

Alternatives to red blood cell transfusions for patients with subacute anemia: blood conservation strategies

There are a number of alternatives to RBC transfusion that may be directly applicable to the critically ill patient [29,30] (TABLE 2). They include the use of artificial oxygen carriers (hemoglobin substitutes and perfluorocarbons) [31,32]; stimulation of endogenous production of RBCs with the use of erythropoietin [33,34]; reduction of blood loss through the use of antifibrinolytics [35], hemostatic agents [36] and cell salvage [37]; restrictive diagnostic phlebotomy with small-volume sample tubes [38–40]; minimization of routine daily phlebotomies; point-of-care microanalysis [41,42]; closed blood-sampling techniques [43,44]; and the use of audits, educational programs and reminders to help physicians comply to a lower RBC transfusion threshold [45–47].

Table 2. Potential benefits and risks of red blood cell transfusion alternatives in critically ill patients.

Strategy	Mechanism of action	Potential benefits	Potential risks
Strategies to reduce acute blood loss			
Artificial oxygen carrier (modified hemoglobin oxygen carriers, perfluorocarbons)	Increased oxygen transport without RBC transfusion	Prolonged shelf life Can be stored at room temperature No risk of disease transmission No immunologic effects Possible reduction in need for transfusion	Short half-life Interference with laboratory measures (hemoglobin substitutes) Vasoreactivity (hemoglobin substitutes) Need for 100% oxygen to provide effective oxygenation may cause lung injury (perfluorocarbons)
Antifibrinolytic agents: tranexamic acid or epsilon aminocaproic acid	Improved hemostasis results in reduction of acute blood loss	Reduced blood loss Reduced need for RBC transfusion Under investigation for use in trauma patients	Thrombosis
Antifibrinolytic agents: aprotinin	Improved hemostasis	Reduced risk of perioperative bleeding and need for reoperation in cardiac surgery patients	Thrombosis
Recombinant activated factor VIIa	Improved hemostasis results in reduction of acute blood loss	Possible benefit in selected cases refractory to standard surgical and medical treatment	Thrombosis
Postoperative cell salvage	Return of blood collected in surgical drains	Reduced need for RBC transfusion	Limited applicability to most critical care patients Quality of reinfused blood (hemolyzed, diluted, and cytokines)
Strategies to prevent subacute anemia			
Reducing blood loss associated with diagnostic testing		Increased hemoglobin level	
Closed blood-sampling techniques	Reduction of chronic blood loss through phlebotomy	Reduction of discard blood Reduced risk of bacterial colonization of catheter hubs and bloodstream infections	Retrograde arterial embolization
Small-volume sample tubes	Reduction of chronic blood loss through phlebotomy	Reduced blood loss	Potential for insufficient volume for analysis
Point-of-care microanalysis	Reduction of chronic blood loss through phlebotomy	Short turnaround time for results Less personnel time	Variable accuracy and precision Need for ongoing quality assurance/calibration
Erythropoeitin	Increased bone marrow production of RBCs	Reduced mortality reported in some subgroups Increase in hemoglobin level and possible reduced need for transfusion	Thrombosis
Restrictive RBC transfusion trigger	Lower threshold when RBCs are transfused	Reduce or avoid need for blood transfusions	Possible risk of increased complications in patients with cardiac disease not clear

RBC: Red blood cell.

Artificial oxygen carriers: hemoglobin oxygen substitutes & perfluorocarbons

Hemoglobin substitutes may delay and/or reduce exposure to allogeneic blood in the acutely bleeding trauma patient. There are two classes of hemoglobin substitutes. These include the hemoglobin oxygen-based carriers (HBOCs) and the perfluorocarbons [48,49]. HBOCs differ with respect to their molecular size, chemistry, viscosity and oxygen-binding affinity [49]. Advantages of HBOCs include their ready availability without the need for cross-matching, long shelf-life, ability to be stored at room temperature and reduced risk of disease transmission [31,50]. Disadvantages include their relatively short half-life (24–48 h), interference with laboratory measures, and vasoreactivity with increased vascular resistance [31]. Potential causes for increased vascular resistance include scavenging of nitric oxide, enhanced adrenergic receptor sensitivity, reduced arterial wall shear stress secondary to decreased viscosity and reduced oxygen affinity [31,49–53].

Diaspirin cross-linked hemoglobin (DCLHb) was the first modified tetrameric human hemoglobin solution to complete a Phase III randomized controlled trial in severely critically ill traumatic hemorrhagic shock patients [51]. This trial was stopped after an interim analysis demonstrated a higher mortality in the DCLHb group compared with saline controls (38 vs 15% at 48 h [p = 0.01], 46 vs 17% at 28 days [p = 0.003]). Several explanations for higher mortality in the DCLHb group were put forth, and include methodological issues as well as an observed increase in vascular resistance. DCLHb has since been removed from the market. Polyheme® is another HBOC that was recently evaluated in a multicenter, randomized, controlled trial that included 714 patients with blunt trauma who were hypotensive in the pre-hospital setting. In comparison with the control group that received crystalloid infusions, there was a trend toward an increased 30-day mortality in the Polyheme group (13.4 vs 9.6% for the Polyheme and control groups, respectively, p = 0.127) [54]. Myocardial infarctions reported by the site investigators were also higher in the Polyheme as compared with the control group (3 vs 1% respectively, $p < 0.05$). However, a *post hoc* and blinded committee of experts adjudicated these events and found no differences in myocardial events between the two study groups.

A recent systematic review by Natanson and colleagues examined all published and unpublished randomized, controlled clinical trials of HBOCs and found a 30% increase in the risk of death and a threefold increase in the risk of myocardial infarction associated with HBOCs [55]. However, this systematic review has been criticized for pooling data on heterogeneous patient populations, different types and doses of HBOCs and varying control populations [56–58]. A newer generation HBOC, Hemospan®, is purported to not have adverse effects on vascular resistance, and is currently undergoing evaluation in clinical trials [59]. There is no doubt that there is a real need to identify alternatives to RBC transfusions in the acutely bleeding critically ill patient with high risk of death and no immediately available blood [49]. However, future research with newer generation HBOCs need to ascertain that the risk of death from exposure to these products is less than the risk of death that is associated with usual care treatments for a given injury or disease [60].

Perfluorocarbons are another class of hemoglobin substitutes that have undergone evaluation in Phase II and III trials for acute normovolemic hemodilution in the cardiac and noncardiac surgical setting [31,49]. These compounds are attractive, since they transport both oxygen and carbon dioxide, and can release oxygen to the tissues at approximately twice the rate at which oxygen dissociates from hemoglobin. The perfluorocarbon particles are very small (0.16 µm), and thus may be of added value not only in the anemia setting, but also in the setting of extreme vascular stenosis [61]. Perfluorocarbons have a long shelf-life, and no risk of transmission of blood-borne infections. However, the linear relationship between O_2 partial pressure in blood and O_2 content on perflurocarbons requires administration of 100% inspired oxygen to provide effective perflurocarbon-oxygenation delivery [31]. Such high inspired oxygen concentrations may induce acute lung injury [62]. Oxygent™ (perflubron [Alliance Pharmaceutical Corp., CA, USA]) is a second-generation perflurocarbon that has been evaluated in Phase II and III studies in cardiac and noncardiac surgical settings [63]. Results suggest that these compounds may reduce the incidence of reaching the intraoperative RBC transfusion trigger, and in some studies a reduction in the number of allogeneic RBCs transfused. Reported adverse effects appear to be mild, and include a dose-dependent flu-like syndrome and a transient drop in platelet counts that has not effected the coagulation system or bleeding [63]. A Phase III study in cardiac surgery in 2001 was suspended owing to reported adverse neurological effects, although an expert panel felt the adverse effects

were more likely due to rapid blood harvesting in the early cardiopulmonary bypass procedure rather than the perfluorocarbon itself [61]. The full efficacy and safety profile of perfluorocarbon-based substitutes, and their potential role in critically ill patients remains to be clarified through future studies [63].

Erythropoietin

Recombinant erythropoietin has also been used for the treatment of critically ill patients to increase hemoglobin levels and avoid blood transfusions [64]. Erythropoietin stimulates the production of RBCs over a period of days, and hence is not useful in preventing acute blood loss [45]. In the most recently published trial, Corwin *et al.* randomized 1460 critically ill patients to receive 40,000 units of recombinant erythropoietin or placebo weekly for up to 3 weeks. Patients receiving erythropoietin had greater increases in hemoglobin levels (15.8 ± 19.7 g/l vs 12.0 ± 18.3 g/l, $p < 0.001$) [65]. However, in contrast to previous trials, there were no differences in the number of patients receiving RBC transfusions or the number of units transfused. This failure to affect RBC transfusion requirements was attributed to the use of a more restrictive transfusion strategy. There were no differences in mortality (adjusted hazard ratio 0.79; 95% CI: 0.56–1.10) but there was a significant increase in clinically relevant thrombovascular events in patients who received erythropoietin (hazard ratio: 1.41; 95% CI: 1.06–1.86). Although a subgroup analysis of 402 patients with trauma from this trial found a significantly lower mortality in the erythropoietin group as compared with the control group (adjusted hazard ratio: 0.37; 95% CI: 0.19–0.72), randomized controlled trials in the critically ill trauma patient population are required to determine whether erythropoietin is helpful or harmful in these patients [66]. Based on the clinical evidence to date, erythropoietin can not be recommended for use in the critically ill.

A recent meta-analysis of nine trials in the critically ill also found that erythropoietin in comparison with placebo does not influence mortality (odds ratio: 0.86; 95% CI: 0.71–1.05) [64,66]. The meta-analysis did not reveal an increase in thrombotic events among patients treated with erythropoietin.

Cell salvage

Intra-operative RBC salvage is a well-recognized blood conservation strategy [67], but has limited applicability to critically ill patients. Postoperative blood recovery and transfusion from sterile surgical drains in cardiac surgery has shown only a marginal reduction in RBC transfusion reduction (relative risk: 0.85; 95% CI: 0.79–0.92) [68]. The feasibility and effectiveness of these techniques for other critically ill patients with acute blood loss would be limited.

Antifibrinolytics

Antifibrinolytic and hemostatic agents may have a place in reducing blood loss in the acutely bleeding critically ill patient. The three antifibrinolytic agents are aprotinin, tranexamic acid and aminocaproic acid. A recent multicenter, blinded, randomized, controlled trial in 2331 high-risk cardiac surgical patients examined aprotinin, tranexamic acid and aminocaproic acid, with a primary outcome of massive bleeding (Blood Conservation Using Antifibrinolytics in a Randomized Trial [BART]). There was a trend toward a reduction in massive bleeding in the aprotinin as compared with tranexamic or aminocaproic acid groups (relative risk of aprotinin compared with both groups: 0.79; 95% CI: 0.59–1.05). However, the trial was stopped early by an independent Data Safety and Monitoring Board, because 30-day mortality was higher in the aprotinin group (relative risk of aprotinin compared with both groups: 1.53; 95% CI: 1.06–2.22) [69]. A *post hoc* analysis suggested that the excess death in the aprotinin group may be due to cardiac causes (relative risk: 2.19, 95% CI: 1.25–3.84 for aprotinin compared with the aminocaproic acid and transexemic acid groups combined). Aprotinin has since been temporarily removed from the market, and is only available by special access [102]. A large multicenter, randomized controlled trial evaluating the role of tranexamic acid versus placebo on death and transfusion requirements in 20,000 critically ill trauma patients at risk of hemorrhage is currently ongoing, and will provide some definitive evidence as to the efficacy of tranexamic acid utility in trauma (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage [CRASH II] study) [103].

Recombinant Factor VIIa

Recombinant activated Factor VII (VIIa) is a coagulation factor concentrate that is approved for use in patients with factor deficiencies (hemophilia) or those with factor inhibitors in Europe for congenital platelet disorders [70]. Numerous case reports and series involving peri-operative and trauma patients, those with massive transfusion, liver disease and gastrointestinal bleeding, have reported reduced blood loss after use of recombinant Factor VIIa [70]. However,

randomized, controlled trials have evaluated recombinant Factor VIIa in critically ill trauma patients [36,71], gastrointestinal bleeding [72], cardiac surgery [73], liver transplantation and resection [74,75], and intracranial hemorrhage [76]. A recent systematic review examined the evidence for prophylactic and therapeutic use of recombinant Factor VIIa in nonhemophilia patients, and concluded that its effectiveness as a hemostatic agent remains uncertain [77]. In this review, the pooled estimates for adverse outcomes showed trends for increased thromboembolic complications (relative risk: 1.28; 95% CI: 0.84–1.95), cardiovascular events (relative risk: 2.18, 95% CI: 0.82–5.79) and stroke (relative risk: 2.02; 95% CI: 0.57–7.17).

Boffard and colleagues recently published two parallel multicenter randomized controlled trials that examined recombinant Factor VIIa versus placebo in blunt (n = 143) and penetrating (n = 134) trauma victims [36]. Patients receiving eight units of at least six RBC transfusions within 4 h of hospital admission were randomized to receive recombinant Factor VIIa (200 µg/kg) or placebo following the eighth unit of RBCs, with addditional doses (100 µg/kg) 1 and 3 h later or placebo. Overall, there were no significant differences in RBC transfusions. In patients surviving for more than 48 h, the primary outcome of RBC transfusions, the transfusion was reduced by 2.6 units (90% confidence interval: 0.7–4.6, p = 0.02) in the blunt trauma group and 1.0 unit (90% confidence interval: 0.0–4.6, p = 0.10) in the penetrating trauma group. No differences in mortality or thromboembolic events between groups were noted, but the trial was not powered to evaluate these end points. Narayan and colleagues conducted a double-blind, randomized controlled trial of 97 patients with traumatic intracerebral hemorrhage, and compared escalating doses of Factor VIIa versus placebo. No differences in death were found between the study groups, but there was a trend toward an increase in thromboembolic events for the combined doses of Factor VIIa as compared with placebo (odds ratio: 3.3; 95% CI: 0.69–16.2) [71].

Bosch *et al.* evaluated the use recombinant Factor VIIa in a randomized controlled trial of 245 patients with upper gastrointestinal bleeding and cirrhosis [72]. In addition to endoscopy and standard care, patients were randomized to receive eight doses of 100 µg/kg of recombinant Factor VIIa or placebo over 30 h. No differences in acute bleeding within 24 h, rebleeding, RBC transfusions or death were observed.

For patients with cerebrovascular accidents due to intracranial hemorrhage, a Phase II multicenter randomized, double-blind, dose-finding study of recombinant Factor VIIa (n = 399) showed a reduction in mortality (overall odds ratio: 1.8, 95% CI: 1.1–3.0) and disability using the modified Rankin score (odds ratio: 2.2, 95% CI: 1.3–3.8) [76]. There was a nonsignificant increase in thrombotic events in patients receiving recombinant Factor VIIa. A subsequent multicenter randomized controlled trial comparing two doses of recombinant Factor VIIa (20 µg/kg and 80 µg/kg) versus placebo in 841 patients with intracranial hemorrhage did not show similar benefits in reducing morbidity and mortality, but did demonstrate a significant increase in arterial events in the Factor VIIa 80 µg/kg group as compared with placebo (25 [8%] vs 11 [4%] respectively, p = 0.04) [78].

Based on the studies to date, the routine use of recombinant Factor VIIa for critically ill patient populations cannot be recommended owing to a lack of clinical benefit from published clinical trials and because of the potential for harm, specifically thrombotic risks. However, use in specific patients with massive uncontrolled bleeding who are nonresponsive to standard treatments and conventional blood components may still be considered, but the lack of evidence for benefit, the cost and the potential risks of thrombotic complications need to be carefully considered [79].

Preventative strategies to minimize blood loss in the critically ill

Blood loss due to phlebotomy

Diagnostic phlebotomy is an important cause of blood loss, and hence anemia in critically ill patients [1,2,29]. There appears to be a correlation between the severity of illness and both the number of blood draws and the total amount of phlebotomized blood [2,29]. A recent large study of 145 European intensive care units showed that phlebotomies were associated with an average blood loss of 41.1 ml/day [2]. In one study of patients admitted to an intensive care unit for more than 3 days, phlebotomy accounted for 17% of the total blood loss [80]. In two American retrospective studies, phlebotomy accounted for 50% of the variation in the amount of RBCs transfused [81,82].

Small-volume blood collection tubes and minimization of discarded blood

The use of small-volume (pediatric) blood collection tubes, the elimination or reduction of

Executive summary

- Anemia is very common in the critically ill patient. It occurs in approximately 90% of patients.
- Although the blood system has become much safer over time, there remain many potential noninfectious risks for the physician to consider.
- There is little clinical evidence that the administration of a red blood cell (RBC) transfusion for the nonacutely bleeding critically ill patient improves clinical outcome.
  - One possible exception is the critically ill patient with active ischemic heart disease. This subgroup of patients requires further study to understand the magnitude of benefit or harm that may be afforded with use of RBCs in this setting.
- There are several alternatives to RBC transfusions. These include the use of RBC substitutes (hemoglobin-based oxygen substitutes [HBOCs]) and perfluorocarbons, erythropoietin, antifibrinolytics, cell salvage and other nonmedicinal strategies to minimize blood loss in the critically ill.
  - There is no evidence from randomized controlled trials that HBOCs or perfluorocarbons improve clinical outcomes in the critically ill acutely bleeding patient; a recent systematic review of the literature suggests that the use of HBOCs may be associated with harm (increased risk of death and myocardial infarction).
  - Evidence from randomized controlled trials suggest that erythropoietin is not effective, and may be associated with an increase in thrombotic risk. A subgroup of patients where erythropoietin may be beneficial is the trauma population; future research is required to ascertain the effects of erythropoietin in this setting.
  - A randomized controlled trial is currently ongoing to examine the use of tranexemic acid versus placebo on clinical outcome in the trauma setting (CRASH II study). A randomized controlled trial evaluating aprotinin versus aminocaproic acid versus tranexemic acid in the cardiac surgical setting was stopped early by an independent Data Safety and Monitoring Board because 30-day mortality was higher in the aprotinin group as compared with the aminocaproic and tranexemic acid study groups. Presently, aprotinin has been temporarily removed from the market and is available only by special release.
  - Several other strategies to minimize blood loss that have not been evaluated in large randomized controlled trials, but may be effective, include audits, educational programs and reminders for physicians and nurses about their use of blood and transfusion thresholds. Other potentially useful strategies include the use of pediatric tubes for blood draws and closed arterial systems to minimize blood wastage.

initial blood discard with indwelling catheters, and altering test order behavior are strategies that may reduce iatrogenic blood loss in the critically ill [83]. In two studies that examined the use of pediatric blood collection tubes, the use of these tubes reduced the extracted volume by 37 [84] and 47% [40] and, in one study, resulted in a significant reduction in the proportion of patients transfused [84]. Point-of-care testing may further reduce the volume of samples for diagnostic testing. In addition to improved turnaround and decreased personnel time, these bedside diagnostic tests often require less than 0.5 ml. As the reliability and affordability of these technologies improve, they may become a valuable addition to blood conservation strategies.

Current technology exists to eliminate the loss of discarded blood associated with indwelling catheters. This blood conservation strategy can reduce the mean amount of blood lost through phlebotomy by 50% [43]. Similar reductions in blood loss associated with phlebotomy have been demonstrated with automated closed arterial systems [85–87]. Eliminating the loss of 'discarded' blood prior to diagnostic phlebotomy was associated with higher hemoglobin levels in most studies [43,86,87], but none of the studies reported a reduction in RBC transfusions. While this may be owing to the small number of patients included in these studies, the amount of blood saved with these techniques alone may not be large enough to avoid RBC transfusion in critically ill patients. Further research to examine a multifaceted strategy to examine effects on blood loss and requirements for blood transfusions in the critically ill are warranted.

Conclusion

We have provided an overview of the currently available strategies to reduce the utilization of RBCs in critically ill patients. Although a number of strategies exist to reduce RBC transfusion, including pharmacologic hemostatic drugs, RBC production stimulants and artificial oxygen carriers, the most effective remains the simplest and likely least costly. Indeed, blood conservation strategies that target and limit appropriate use of diagnostic phlebotomy is a simple and practical intervention that may reduce the burden of anemia among critically ill patients. Adoption of a restrictive transfusion threshold is the only intervention that has been evaluated in large clinical randomized trials, and been found to reduce RBC use without increasing morbidity or mortality. Other simple interventions, such as audit programs, educational programs and/or reminders, can be effective in changing physician transfusion practice, and could be used to increase compliance to adopting a lower RBC transfusion threshold. Additional pharmacological and mechanical therapies to reduce blood loss and the transfusion of blood

products may also prove beneficial, but the effectiveness and safety of these interventions requires further rigorous evaluations from randomized controlled trials.

Future perspective

There are many potential effects of RBCs that go beyond the optimization of oxygen delivery and that may afford benefit or harm in the critically ill. Future research requires an exploration of these potential benefits and harms with specific subpopulations of the critically ill (i.e., ischemic heart disease). Future research with RBCs should also consider whether the RBC storage lesion impacts clinical outcome in the critically ill. Further preclinical and clinical research is warranted on new and modified artificial oxygen carriers (HBOCs and perfluorocarbons) to examine their efficacy and safety in the critically ill.

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