Blood Transfusion Practices in Sepsis

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Abstract

For years, blood transfusion followed the 10/30 approach without major deliberations on the adverse effects, if any. From the early 1980s, studies started emerging in various clinical settings, describing the impact of transfusion of blood and blood products on patient outcomes. RCTs (TRICC, EGDT, TRISS, and TRICOP) and observational/epidemiological studies (CRIT, ABC) were almost unanimous about the need to reduce RBC transfusion in patients. The deleterious effects of blood transfusion on patient outcomes came as a surprise for what was till that time thought to be a harmless/beneficial intervention with positive physiological effects on oxygen delivery. Thresholds for triggering RBC transfusion were studied and defined in different clinical patient populations. A restrictive RBC transfusion policy (Hb trigger < 7 gm/dl) was adopted almost universally in critically ill patients with very few exceptions (associated with ischemic heart disease and maybe seriously ill cancer patients). Septic patients were studied with respect to their outcomes in patients receiving RBC transfusions from varying angles. RBC transfusions received within first 24 h of hospitalization or receiving transfusion during entire hospital stay or 28 days before or after developing sepsis have been taken into account. Different outcome measures have been considered. The restrictive transfusion strategy has passed the test on all accounts. Patient blood management programs based on reducing the use of blood and blood products have been advocated to improve patient care. Also incorporating prudent clinical judgement and individualizing according to patient characteristics, the decision to transfuse blood will help in improving the quality of patient care.

Keywords

Anemia in ICU · Red blood cell transfusion · Transfusion threshold · Transfusion trigger · Sepsis · Septic shock

Introduction

A major cause of morbidity and mortality in patients of all age groups (from neonates to geriatric population), Sepsis causes almost 50 million cases and 11 million deaths worldwide [1]. Sepsis is complicated by organ dysfunction

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and organ system failure. Hematological abnormalities are common in patients with sepsis. These include anemia, leukocytosis, thrombocytopenia, and activation of the coagulation cascade.

Anemia in critically ill patients is multifactorial and widely prevalent in intensive care unit (ICU) patients. An editorial reported almost 95% of patients admitted to ICU had hemoglobin (Hb) levels below the normal range within 72 h of hospitalization [2]. When we consider all patients admitted to ICU for more than one week, more than 2/3rd of patients had at least one blood transfusion [3, 4]. The various causes of anemia in critically ill patients admitted to ICU are sepsis, chronic kidney disease, bleeding (posttraumatic, postoperative, Gastrointestinal bleed, blood loss due to frequent investigations), and abnormal erythropoietin production, iron metabolism, and nutritional deficiency. These often lead to what is called acute anemia of chronic disease [5–7]. One important but entirely preventable cause of anemia developing in critically ill patients after ICU admission is due to repeated phlebotomies and repeated aspiration of blood for various investigations and due to invasive hemodynamic catheters. This is somewhat euphemistically known as "anemia of chronic investigation" [8]. Frequent, ill-advised, non-coordinated investigations at varying times of the day can lead to blood loss of almost 50 ml/day [9]. In some ICUs, this is the cause of anemia in 1/3rd of the patients [8].

Anemia in critically ill patients is usually treated with transfusion of blood and blood products. Around 15% of medical ICU patients and almost 1/3rd of surgical patients receive some form of blood transfusion in a 24-h cycle [10]. Though there is a widespread use of blood and blood products in the ICU, there is still some confusion regarding the optimal management of anemia in critically ill patients. Let us take a look at the various aspects of this issue. Some evidence is reviewed in general critically ill patients while other evidence when available is presented in specifically septic patients.

Whether Anemia in Critically Ill Patients Is Associated with Increased Morbidity and Mortality?

The presence of anemia leads to reduced Oxygen delivery (DO2) and a mismatch between DO2 and oxygen consumption (VO2). This mismatch may lead to increased complications, morbidity, and mortality. A large (almost 6000 patients) retrospective study in patients admitted to surgical ICU found reduced hemoglobin levels to be associated with increased severity of illness, higher ICU mortality, and length of stay (LOS) and higher in-hospital mortality and LOS [11]. Another study in patients with chronic obstructive pulmonary disease demonstrated positive effects of correction of anemia on successful liberation from ventilation due to reduction in the work of breathing [12]. The CRIT study showed that a decreasing Hb (<9 gm%) during ICU stay in critically ill patients was associated with greater mortality and LOS [4].

There are several studies with similar findings in postsurgical patients with severe anemia due to various reasons (including non-transfusion of blood or blood products for religious reasons). There was an increased likelihood of death as the Hb levels fell below 7 gm%, or occurrence of increased complications or adverse events in patients with anemia [13–16].

Whether RBC Transfusion to Correct Anemia Is Beneficial in ICU Patients?

This is a debatable topic with evidence overwhelmingly in favor of eliminating/reducing RBC transfusion or giving it until absolutely necessary. Though all the evidence is from observational studies, they direct us toward an unfailing trend that RBC transfusion in critically ill patients (with or without sepsis) is associated consistently with worse outcome measures. One needs to keep in mind the inherent bias that may creep into these observational studies and their results.

Patients who receive RBC transfusion have worse APACHE and SOFA scores (therefore are more seriously ill) and these patient cohorts usually have worse outcomes [17].

RBC Transfusion in General Critically Ill Patients

The CRIT study is a large (4892 patients) prospective multicentric observational study of clinical practices regarding anemia and blood transfusions in ICU patients in the United States. The study observed RBC transfusions to be associated with longer ICU and hospital LOS, more complications and greater mortality [4]. The ABC study was another large (almost 3500 patients), multicentric, prospective, observational European study which looked at the association between blood transfusion and outcomes. It showed an association of transfusion with increased ICU LOS and increased ICU, hospital, and 28 days mortality, even after matching for the severity of organ dysfunction [9]. Patients who received blood transfusion had increased risk of dying [odds ratio 95% confidence interval (OR 95% CI)-1.37 (1.02–1.84)]. A meta-analysis of 45 studies with a total of 272,596 patients was performed to assess the effect of RBC transfusion on outcome measures in critically ill patients [18]. All the studies except 3 showed that RBC transfusion was more riskier than beneficial and it increased the possibility of mortality [OR 95% CI, 1.7 (1.4–1.9)], nosocomial infections [OR 95% CI-1.8 (1.5–2.2)], development of multiorgan dysfunction or acute respiratory distress syndrome [OR 95% CI-2.5 (1.6–3.3)]. Two studies included in the meta-analysis were neutral in their assessment of the effect of blood transfusion on outcome measures, while one study demonstrated a positive effect of RBC transfusion on outcome measures in elderly patients with cardiovascular disease (acute myocardial infarction) and low hematocrit less than 30%. Though the studies included in the meta-analysis were observational studies and not randomized controlled trials, the authors acknowledged the limitations of the data available and recommended the evaluation of the risk–benefit ratio in individual patients prior to RBC transfusion.

RBC Transfusions Specifically in Septic Patients

A retrospective analysis of patients with hematologic malignancies admitted to ICU with sepsis and/or septic shock studied the effect of RBC transfusion received in the first 48 h of ICU admission on mortality of patients. It found that transfusion within 2 days of ICU admission was associated with increased hospital mortality [19]. Another study specifically focused on general surgical ICU patients (excluding cardiac surgery patients) with sepsis to study the possible associations between anemia, RBC transfusion, and long-term (90 days) outcomes of these patients. Patients who were anemic and therefore required RBC transfusion had higher 90 days mortality as compared to patients who did not receive RBC transfusion [20]. Another prospective descriptive study from Turkey, comprising of adult patients admitted to the ICU with sepsis and/or septic shock studied the relation between RBC and platelet transfusion, and ICU and hospital outcomes. They found higher mortality in patients' transfused blood or blood products [21].

A propensity matched analysis of a multicentric prospective observational database of around 1000 patients with community-acquired sepsis and/or septic shock. Patients who received a transfusion had higher 28 day and in-hospital mortality and also stayed in hospital significantly longer. They were also sicker (higher SOFA and APACHE II scores). However, on propensity matched analysis of 152 pairs of patients, transfused patients were less likely to die after 7 or 28 days or in hospital [22]. A single center, retrospective cohort analysis of patients admitted with sepsis who received RBC transfusion within the first 24 h of hospitalization was performed in Taiwan. On propensity score matching, RBC transfusion within the first 24 h of hospitalization was not associated with increased mortality [23]. The SOAP study

was a multicentric, European epidemiologic study of sepsis in acutely ill patients and grouped the patients on whether they received RBC transfusion or not. In multivariate analysis, blood transfusion was not significantly associated with a worse mortality rate. In fact, in the propensity matched pairs of patients, there was a higher 30-day survival rate in the transfusion group than in the other patients ($P = 0.004$) [24].

At What Level of Anemia Should We Transfuse RBCs?

Triggers for transfusion have traditionally been Hb values though there have been some suggestions for physiological triggers. Generally, the 10/30 rule has been followed as a transfusion trigger (Hb < 10 gm/dl and hematocrit <30%) [25]. A consensus conference in 1988 suggested the presence of physiological factors [such as tachycardia, postural hypotension, neurologic symptoms, mixed central venous saturation (ScvO2) less than 60, elevated serum lactate] in addition to anemia as triggers for RBC transfusion [26]. Though the suggestions appear good in theory there is no evidence regarding the use of these physiological factors as transfusion triggers. Hence, Hb value continues to be most commonly used factor to decide regarding initiation of blood transfusion.

RBC Transfusion in General Critically Ill Patients

The TRICC study was a large (838 patients) prospectively randomized controlled trial (RCT) evaluating the effect of a so-called restrictive and liberal (transfusion trigger 10 gm/dl) transfusion strategy in ICU patients [27]. Thirty-day mortality rates in both group were similar, but there was better survival in certain groups of patients, notably patients with lower disease severity and younger patients, in the restrictive strategy group. However, patients with acute cardiovascular diseases [acute myocardial infarction (AMI), unstable angina) did not have better survival with the restrictive strategy.

RBC Transfusions Specifically in Septic Patients

The early goal-directed study (EGDT) by Rivers et al., presented an algorithmic approach to resuscitate patients with sepsis and septic shock [28]. It used the 10/30 transfusion trigger for RBC transfusion to increase DO2. Application of a sepsis bundle comprising several interventions, including RBC transfusion and EGDT could decrease mortality significantly in patients with septic shock.

However, the individual contribution of the intervention related to RBC transfusion could not be evaluated as the effect of the whole sepsis bundle was seen. In fact a single center, retrospective study in patients with septic shock and who received EGDT showed, RBC transfusion was associated with worse clinical outcomes (longer ICU and hospital LOS and more days on mechanical ventilation) [29].

The TRISS trial was a large (998 patients) multicentric, Scandinavian, RCT evaluating the effect of higher (<9 gm/dl) and lower (<7 gm/dl) threshold for blood transfusion in patients admitted with septic shock [30]. There was no difference in mortality or in occurrence of ischemic events.

The TRICOP trial was a single-center RCT in adult patients with cancer presenting with septic shock. It evaluated the effect of a liberal and restrictive transfusion strategy in these very sick patients (overall mortality 50%, mean APACHE II score 57, mean SOFA score 7). There was a better 90 days survival in the liberal strategy group as compared to the restrictive strategy group [31].

Meta-analysis of Trials Using Hb as a Transfusion Trigger

A systematic review and meta-analysis of 37 RCTs with around 19,000 patients (adults as well as children/medical plus surgical ICU) compared liberal versus restrictive strategies for RBC transfusion. The meta-analysis did not find any difference in 30-day mortality, hospital or ICU LOS,

complication rate (including the risk of infection and AMI), and functional recovery [32].

A different meta-analysis used a context-specific approach (based on patient and clinical type) to evaluate 31 trials to compare the liberal versus restrictive RBC transfusion strategy in surgical and critically ill patients. They concluded that restrictive strategy may be harmful in patients undergoing cardiac or vascular surgeries and elderly patients undergoing orthopedic surgeries. These patients had more complications related to inadequate O2 supply (organ-specific ischemic events, cardiac arrhythmias, or unstable angina). These complications were not found to be increased in critically ill patients [33].

What Should Be Our Approach to RBC Transfusion in Patients with Sepsis Considering All the Above Evidence?

Patient blood management (PBM) program should incorporate appropriate evidence-based multidisciplinary interventions but also allow adequate space to incorporate prudent clinical judgement-based decision-making to optimize patient care [34]. Decisions to transfuse a patient should not only be based on Hb values alone but should be individualized to incorporate patient clinical characteristics including symptoms and physiological factors [35]. This leeway for clinical judgement to decide whether this individual patient with this Hb trigger should be transfused or not at this particular moment is an extremely important part of PBM. The restrictive Hb threshold (Hb less than 7 gm/dl) is an appropriate trigger in most patients with sepsis/septic shock. Caution should be exercised in patients who have associated underlying ischemic heart disease and may be in seriously ill cancer patients.

Conclusion

Anemia in critically ill patients is associated with increased morbidity and mortality due to its deleterious effects on oxygen delivery. But the correction of anemia by RBC transfusion is not always beneficial. A restrictive approach to RBC transfusion has been shown repeatedly and in different clinical settings (including sepsis and septic shock) to be more appropriate. Clinical Guidelines of various societies have endorsed the same approach.

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