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**EDITORIAL OFFICE**
**Dr. Sandhya Talekar**
Chief Editor, IJCCM
Shree Medical Foundation, Prayag Hospital, 1247, Deccan Gymkhana, Pune 411004, India.
Tel: 91 20 553 2812 /553 2490
Fax: 91 20 553 4448
E-mail: editor@ijccm.org

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CONTENTS

Editorial

# The ideal transfusion trigger in critically ill patients

**M. B. Agarwal**

Anemia is a common problem in critically ill patients.[1] Adverse effects of anemia include increased risk of cardiac morbidity and mortality. In addition, the consequences of anemia may be compounded as critical illness increases metabolic demand.

Among the many causes of anemia in the critically ill, some of the most important are occult blood loss, including frequent blood sampling, shortening of red cell lifespan, inflammation / infection related hepcidin induced functional iron deficiency and decreased production of endogenous erythropoietin (EPO). One may be surprised to note that on an average, 40 ml of blood is drawn each day from a typical ICU patient. This is an important source of blood loss.[2]

Impact of anemia on an ICU patient's morbidity and mortality, however, remains ill-defined. Similarly, the optimal hemoglobin (Hb) level also remains ill defined.[3]

Anemia is typically treated with red cell transfusions. This is to maintain adequate oxygen delivery. Groeger *et al*,[4] found that 16% of patients in medical ICUs and 27% of those in surgical ICUs are transfused on any given day. In an analysis in the US, 85% of patients with an ICU stay of greater than one week, received at least one red cell transfusion. The mean number of units of red cell transfused per patients were 9.5.[3]

**From:**
Department of Haematology, Bombay Hospital Institute of Medical Sciences, Marine Lines, Mumbai - 400 020 Email: mbagarwal@hotmail.com

**Correspondence:**
M. B. Agarwal,
Email: mbagarwal@hotmail.com

The trigger for red cell transfusion in ICU remain ill-defined and has been the subject of considerable debate in recent years.[5] Concerns and doubts have emerged regarding the benefits and safety of red cell transfusion, in part due to the lack of evidence of better outcome and in part related to increased risk of infection and other adverse effects. As a result of these concerns and also in view of several studies (vide infra) suggesting better or similar outcomes with a lower transfusion trigger, there has been a general tendency to decrease the transfusion threshold from the classic 10 g/dl to lower values.

In the CRIT study in the year 2004,[6] data on red cell transfusion and outcome were prospectively collected on 4892 patients from 284 ICUs in 213 US hospitals. Earlier, a similar study was performed in Europe (The ABC study; anemia and blood transfusion in critically ill) in 1999. Both these studies yielded very similar results. Transfused patients had longer ICU stay and more severe organ failure. Transfused patients had higher mortality rates at every admitting Hb level. Compared with non-transfused patients, there was also a dose-response relationship with increasing mortality rates as the number of red cell units transfused increased. The association between red cell transfusion and mortality was particularly pronounced with more than 2 red cell units transfused.

Although, these studies were large and data acquisition was prospective, these were purely observational studies and therefore did not strongly assist clinicians in deciding when to transfuse. Despite the finest statistical models used to show that allogeneic red cell transfusions were independently associated with higher mortality,[2,6] it remained unclear whether adverse outcome was due to red cell transfusion itself or it merely reflected the fact that patients in ICU needing red cell support were sicker

to start with.

A large, randomized controlled trial by the Canadian Critical Care Trials Group[7] comparing restrictive transfusion regimen (Hb < 7 g/dl) with a liberal transfusion regimen (Hb < 9.0 g/dl) in ICU patients, indicated that liberal use of transfusions resulted in higher mortality rates. The 30-day mortality in the restrictive transfusion regimen in patients younger than 55 years of age and in patients with an APACHE II score < 20 was lower ($P$<0.06).

Combining all available prospective randomized trials comparing restrictive and liberal transfusion regimens with mortality data (N = 1568), a higher mortality was confirmed in the liberal transfusion group.[8] Therefore, the conclusion is that red cell transfusions are efficacious only in very specific situations, such as when pre-transfusion oxygen delivery is low.

In addition, red cell transfusions carry the risk of allergic reactions, infection transmission and immunosuppression. Since, the immunosuppressive effect may be mediated via leukocytes, universal leuko-depletion has been introduced in many countries. Its effect on transfusion related adverse effects, however, is only modest. Post-transfusion non-hemolytic febrile reactions decreased but serious nosocomial infections remained unchanged and the effect on mortality was negligible. No in-depth information regarding the type of red cells transfused and their effect on outcome are available from the CRIT and ABC studies. Blood transfusions are also associated with significant administrative, logistic and economic implications.

Another fact is that the old stored red cells, may not consistently improve tissue oxygenation. Interestingly, in both CRIT and ABC study, the age of the transfused red cells was recorded. It was shown that older blood was not associated with a higher mortality or morbidity. Another recent study in 897 cardiac surgery patients confirmed lack of association between the age of transfused red cells and the outcome except for higher risk of pneumonia with red cells older than 28 days.[9]

These observations raise important questions: Are allogeneic red cell transfusions beneficial or harmful? Can red cell management be improved in ICUs? Can the transfusion trigger be lowered?

Very often, the only reason for giving blood transfusion to patients in ICUs is low hemoglobin level. It is assumed that a low Hb value reflects inadequate oxygen delivery to the tissues. It is also assumed that raising the Hb will result in improved oxygen delivery. However, it is not possible to determine oxygen delivery and even more importantly, the tissue extraction. A Hb-based transfusion trigger does not take into account the individual patient's ability to tolerate and compensate for anemia.

In view of the various adverse effects, limited efficacy and high cost, a restricted red cell transfusion policy in intensive care medicine is mandatory. The options include establishing restrictive multi-disciplinary transfusion guidelines and implementing them in daily practice, minimizing blood loss for diagnostic purposes (including using pediatric sampling tubes), achieving better hemostasis and using universal hemostatic agents, using alternative treatments of treating anemia such as recombinant human erythropoietin (rhEPO) and developing artificial oxygen carriers.

Appropriate transfusion guidelines should be based primarily on physiological transfusions triggers, where as Hb-based transfusion triggers should serve as an aid only in cases of insufficient or unreliable information on patient's global or regional tissue oxygenation. We must move away from general guidelines based on Hb level to more individualized blood transfusion practices. Global signs of inadequate oxygenation should be respected. These include signs of hemodynamic instability, oxygen extraction (O2ER) > 50%, a mixed venous oxygen saturation (SVO2) < 50%, a low mixed venous oxygen partial pressure (PVO2) decrease in VO2 and evidence of myocardial ischemia.

The adoption of available blood conservation techniques will result in reducing transfusions. Methods of conservation include meticulous hemostasis in surgical patients use of desmopressin and Recombinant Factor VIIA (rFVIIa), use of hemodilution, reduction of phlebotomy losses, rhEPO administration and of course, reduction of trigger for giving red cells.

Use of pediatric sampling tubes has been shown to reduce diagnostic blood loss to half. The administration

of rhEPO has been shown to raise reticulocyte count and hematocrit. There was also reduction in total number of units of transfused blood.[10] Its use in daily clinical practice, however, may be limited by its high prize, but, slowly, rhEPO is finding its place.

Artificial oxygen carriers are fascinating new drugs in clinical development. Although, by using them, peri-operative transfusion requirements were reduced in several phase three studies,[11] none of these substances is yet licensed for human use.

From the pooled data regarding the efficacy of red cell transfusions in the critically ill, restrictive red cell transfusion strategies are gaining popularity. The TRICC trial has established the safety of such strategy, suggesting that physicians should minimize exposing their patients to allogeneic RBCs by lowering the transfusion trigger. Additional studies are needed to identify patients who will surely improve from red cell support and also, to determine the effects of red cell storage time as well as leuko-depletion.

So, let us continue to work on these areas but, for the moment, let us implement the changes that can make a difference today.

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