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Review Article

Blood Transfusion in the Critically Ill Patient

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Abstract

Anaemia is commonly seen in the intensive care unit and is a cause of increased morbidity in the critically ill patients. Blood transfusion seems to be the physiological solution for anaemia, however it is not without complications and associated risks, questioning the benefit of packed red blood cell transfusion in this population. Physiological thresholds for transfusion seem to be an interesting concept, but currently lack evidence. The transfusion trigger across most populations favours a restrictive strategy for packed red blood cell transfusion, with the exception of some subgroups. Despite the presence of storage lesions in old blood, evidence suggest that the freshest available blood, does not fare better than the oldest available blood from the blood bank. This article is a review of the current evidence with blood transfusion practices in the critically ill patients.

Keywords : *Anaemia in ICU; Transfusion threshold; Transfusion trigger; Packed red blood cell transfusion; Bleeding in ICU*

Introduction:

Anaemia is a widespread problem occurring frequently in critically ill patients. The aetiology of anaemia is multi factorial and includes frequent phlebotomies, acute bleeding in trauma/ post-surgical patients, apparent and/or occult blood loss from the gastrointestinal tract due to erosive gastrointestinal mucosal disease or trauma, inappropriate erythropoietin synthesis, and anaemia of inflammation.[1] In critically ill patients, repeated phlebotomies for investigations might account to as much as 40 to 70 mL of blood per day in the intensive care unit (ICU), which exceeds the normal rate of replacement.[2] Barie et al termed this as "anaemia of chronic investigation", which may account for as much as 30% of required blood transfusions.[3] Anaemia secondary to chronic renal disease, iron deficiency or other nutritional deficiency and infections like malaria are also common in the critically ill patients. As many as 95% of patients in ICU become anaemic by day two or three and require transfusions of red blood cells (RBC) to maintain a normal haemoglobin.[4]

The real question is whether RBC transfusion is beneficial or not in these patients? Two large observational studies from North America[5] and Europe [6] suggested that RBC transfusion although highly prevalent in critically ill patients, might be harmful. Anaemia and RBC transfusion correlated with prolonged ICU stay, increased ICU mortality and a higher incurring cost. However, these findings were refuted by the multicentre Sepsis in European intensive care units (SOAP) study.[7] After propensity matching, they concluded that the 30-day survival rate was significantly higher in patients receiving RBC transfusions. It is assumed that a change in practice to transfuse only leuco depleted blood was responsible for the discrepant data from these trials. There has been considerable confusion regarding the transfusion practices among various groups of critically ill patients and regarding the safety and efficacy of blood on storage. This article will attempt to review the current evidence with blood transfusion practices in ICU.

IS ANAEMIA ASSOCIATED WITH AN INCREASED MORTALITY AND MORBIDITY?

Anaemia results in an imbalance between oxygen delivery (DO2) and oxygen consumption (VO2) which is associated with increased complications in critically ill patients. Both anaemia and RBC transfusions were found to correlate with increased morbidity in critically ill patients.[5,6] Data from the critically ill surgical patients also suggests an association between anaemia with prolonged ventilation days, increased risk of myocardial infarction and mortality. Sakr et al in a retrospective analysis of 6000 general surgical patients suggested that anaemia was associated with a higher disease severity, higher ICU and hospital mortality rates and length of stay.[8] In the post-operative population, as haemoglobin falls below 7g/dL to 3 gm/dL, the mortality also increases in parallel from 0.9 % to 62.1%.[9] In a retrospective study of five patients with Chronic Obstructive Pulmonary Disease(COPD), Schönhofer et al suggested that improving haemoglobin levels from 8.7 +/- 0.8 g/dl to 12 g/dl or higher with transfusion was associated with successful weaning.[10] Transfusion in COPD patients with low haemoglobin resulted in a reduction of minute ventilation and work of breathing.[11] Karon et al, showed that a reduced haematocrit among

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critically ill patients was found to interfere with point of care glucose monitoring and increasing the risk of hypoglycaemia if acted upon.[12]

THEORETICAL BENEFITS OF BLOOD TRANSFUSION

Critical illness and sepsis is associated with an increased oxygen demand and reduced oxygen delivery. The DO2 is directly proportional to the cardiac output and haemoglobin as understood from the formula - DO2 = cardiac output x (Hgb x 13.4 x % O_2Sat) + (PaO_2 x 0.031). Even in anaemia, it might be argued that the DO2 could still be maintained by an augmentation in cardiac output, an increased oxygen extraction in tissues, and a rightward shift of oxygen-dissociation curve.[13] However sick patients might not be able to effectively increase their CO to meet the increased demand. The physiological effects of anaemia that help in improving oxygenation, like tachycardia and reduced viscosity, fail when a lower limit is reached. In patients who refuse blood transfusion due to religious practises, it has been seen that the VO2 starts to decrease at a haemoglobin concentration of roughly 4.0 g/dL, because of insufficient oxygen delivery DO2.[9] Hence, it seems logical to increase oxygen delivery by RBC transfusion in anaemic patients with features of oxygen debt.

IS BLOOD TRANSFUSION HARMFUL?

Blood transfusion is not without complications. It was noticed in early 1950, that infections could be transmitted through blood transfusion, which initiated a vigorous process of screening before transfusion.[14] A list of complications associated with blood transfusion, including prion diseases, immunomodulation, immunosuppression, etc. are enumerated in **Table 1**. A detailed description of the complications associated with transfusion is out of the scope of this article. The Serious Hazards of Transfusion (SHOT) annual report gives a comprehensive review of possibly preventable and serious adverse effects of blood transfusion.[15]

Table 1. Complications associated with blood transfusion

- Haemolytic reactions – immediate and delayed
- Non-haemolytic febrile reactions
- Transfusion-related acute lung injury
- Transfusion - related circulatory overload
- Hyperkalaemia
- Hypothermia
- Dilutional coagulopathies
- Transmission of infection
- Viral (Hepatitis B, Hepatitis C, Human immunodeficiency virus, Cytomegalovirus)
- Bacterial (Treponema Pallidum, Salmonella)
- Parasites (Malaria, Toxoplasma)

DOES RBC TRANSFUSION IMPROVE MISMATCH OF OXYGEN DELIVERY (DO2) AND CONSUMPTION (VO2)?

As mentioned the aim of RBC transfusion is to meet the increased oxygen demand of the body and alleviate signs of tissue hypoxia. Studies looking in to the effects of RBC transfusion on DO2 - VO2 mismatch found that although the DO2 increased consistently with transfusion, the VO2 did not increase uniformly across the studies[16]. This could be because of the absence of an oxygen debt prior to transfusion or the RBC dysfunction that may occur during storage (storage lesions). In a retrospective cohort of cardiovascular patients, Cassutt et al [17] found that the effect of an allogeneic blood transfusion correlated well to the DO2-VO2 variables before a blood transfusion and not to pre-transfusion haemoglobin levels. Similarly Sehgal et al [18] suggested that the use of oxygen extraction ratio as a transfusion trigger might reduce allogenic RBC transfusion(18). So probably an algorithm for identifying patients who might improve VO2 after transfusion should also be taken into consideration before transfusion[19].

PHYSIOLOGICAL TRANSFUSION TRIGGERS IN CRITICALLY ILL PATIENTS

The Health Consensus Conference on Perioperative Red Blood Cell Transfusions in 1988, suggested that multiple factors related to the patient's clinical status and oxygen delivery need should be considered for RBC transfusion.[20,21] This is supported by the numerous guidelines to balance the benefit of treating anaemia and avoiding unnecessary cost and risk of transfusion. It thus seems logical to include physiological triggers suggestive of anaemia, such as chest pain, congestive heart failure and persistent postural hypotension unresponsive to fluids to decide on RBC transfusion. **Table 2** shows a list of physiologic triggers for blood transfusion. Although physiological transfusion triggers seem better markers of tissue hypoxia, its use alone to guide blood transfusion lacks evidence currently. Hence threshold values of haemoglobin are still the most commonly used and well identified transfusion trigger across most trials.

Table 2. Physiological transfusion triggers (assuming normal oxygen saturation and normovolumia)

- Tachycardia / palpitation, cardiac arrhythmia or ECG changes (ST-segment elevation>0.2 mV or depression> 0.1mV)
- New onset regional wall motion abnormalities on echocardiography (Trans- oesophageal)
- Postural hypotension or persistent tachycardia despite euvolumia
- Neurologic symptoms/ cerebrovascular symptoms for which no other cause can be elucidated – fatigue, poor memory
- Increased oxygen extraction ratio or decreased mixed venous oxygen saturation (ScvO2) less than 60
- Hyperlactatemia for which no other cause is evident

HAEMOGLOBIN CONCENTRATION AS A TRANSFUSION TRIGGER

As early as 1941, patients were transfused when the haemoglobin fell below 10gm% and haematocrit fell below 30% (10/30 rule). This practice was judiciously followed till probably until the Transfusion Requirements In Critically Ill Patients (TRICC) trial was published in 1999. In this study, critically ill patients after initial fluid resuscitation were randomised to a liberal (10g/dL) versus restrictive group (7gm/dL) of blood transfusion.[22] This trial results suggested that a restrictive transfusion strategy had significant reduction in-hospital mortality and a similar trend to 30-day mortality.This benefit was more pronounced among young patients and those with lesser disease severity. The restrictive group received lesser blood transfusions and had lesser complications such as ARDS as compared to the liberal group. This was the first randomised control trial in transfusion medicine that initiated the thought of "less being more". Although they had a low screening to enrolment ratio, the results of this trial lead to a change in transfusion practices. A Cochrane review including the TRICC trial and 30 other trials, with a total number of 3746 patients also favoured a restrictive strategy as it was found to be associated with reduced transfusion rates, without adverse patient outcomes.[23] Though data is sparse across special groups such as obstetrics patients and patients with acute brain injury, several studies have been conducted in other patient groups.

In patients with sepsis and septic shock :

The landmark paper by Rivers on early goal directed therapy (EGDT) in sepsis, had started its enrolment prior to publication of the TRICC trial and used a transfusion threshold of 10/30 in septic patients.[24] With a series of interventions that included a 10/30 threshold for RBC transfusion, Rivers could find a significant mortality benefit among septic shock patients. The surviving sepsis campaign guidelines published in 2013, considered both the EGDT trial of Rivers et al and the TRICC trial. These guidelines gave a strong recommendation towards a restrictive strategy in septic shock, once the tissue hypoperfusion had resolved, provided there were no adverse factors such as myocardial ischemia or ischemic heart disease, severe hypoxemia or ongoing bleeding.[25] However, data from this period suggested that many clinicians were not following these recommendations in managing sepsis patients.[26] Thus a prospective trial looking at transfusion triggers in septic shock patients was required.

The"Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock" (TRISS trial), a multicenter trial conducted in Scandinavia among patients with septic shock attempted to answer this question. Patients were randomised to receive transfusion at hemoglobin level of 7 g/dl or 9 g/dl, and were stratified by the presence of hematological malignancy and centre.[27] The authors concluded that in patients with septic shock, a transfusion threshold of 7g/dl compared with 9g/dl resulted in no increased mortality or ischemic events. However, almost all patients in the liberal transfusion group and two thirds of patients in the restrictive strategy group, received a blood transfusion, a much higher rate than in usual practice, making this more a study of over-transfusions. Patients with myocardial infarction were excluded from the study.

More recently Bargemen et al [28] in an RCT: The Transfusion Requirements In Critically ill Oncologic Patients (TRICOP) trial, including 300 adult patients with solid tumours in septic shock, compared a transfusion threshold of 7 gm/dL versus 9 gm /dL and found a significant survival trend among the liberal transfusion group at 90 days. The patients included were very sick with an overall mortality rate close to 50%. (mean Simplified Acute Physiology Score (SAPS) II of about 57 and a sequential organ failure assessment (SOFA) score of around 7). This study shows that the sicker the patient, the greater is the likely benefit of transfusion. [29]

In the bleeding patients :

As the above-mentioned trials did not specifically investigate the effect of transfusion triggers in patients with active bleeding, the results of the same may not be applicable in such patients. Villanueva et al[30] conducted a trial in which patients with acute upper gastrointestinal bleeding were assigned to a restrictive strategy of 7gm/dL compared to a liberal strategy of 9 gm/dL. A restrictive approach of 7gm/dL even in the bleeding patients did not affect the survival and was associated with significantly lesser transfusions and lesser complications such as re-bleeding, hospital days, acute kidney injury, infections, and transfusion reactions. On the contrary, in patients who received liberal transfusions, the portal pressures also rose significantly and might have been responsible for increased re-bleeding. Though this trial supports a restrictive strategy in patients with upper GI bleed, caution is required regarding early identification and appropriate resuscitation of an exsanguinating patient. The data from the restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER trial), an open label feasibility trial, suggests no mortality benefit from a restrictive strategy. However the haemoglobin difference between the two groups were not statistically or clinically different (10.3 gm/dL versus 9.8 gm/dL) and the trial was not powered to assess a mortality benefit.[31]

In pediatric patients :

The similar findings of the TRICC trial was replicated in patients in the Paediatric Intensive Care Unit by the Transfusion Strategies for Patients in Paediatric Intensive Care Units (TRIPICU) trial.[32] Of the 637 critically ill, but hemodynamically stable children randomised to a restrictive or a liberal transfusion group, with a transfusion threshold of 7 g/dL versus 9.5 g/dL respectively, patients in the restrictive group received 44% less blood transfusion without any difference in the occurrence of MODS or any secondary outcome. No statistically significant differences for development of MODS were observed in the sub groups of sepsis, surgical and cardiothoracic patients.

In patients with acute coronary syndrome :

Patients with acute coronary syndrome have usually been excluded from RCTs in this field as the initial response to normovolemic anaemia is an adrenergic response which

results in an increase myocardial oxygen demand. Rao et al, in a large meta-analysis of 24,112 patients found that blood transfusion was independently associated with an increased risk for death even after correcting for baseline characteristics (hazard ratio for death of 3.94). There was a significant association between transfusion and increased 30-day mortality in patients with a hematocrit above 25% in this study. This study included patients of all ages, risk of bleeding and interventions.[33] A prospective database of 2,358 patients with acute coronary syndrome, also found similar results of a statistically significant higher mortality in patients receiving transfusion above a haemoglobin >8 g/dL.[34] However, these conclusions have been made from analysing databases and not prospective studies.

An RCT was surprisingly conducted in patients with symptomatic coronary artery disease, however this had to be discontinued due to substantially higher mortality rate in the restrictive than in the liberal transfusion group (13% *vs*. 2%, respectively, P=0.03).[35] This prospective study shows that a liberal transfusion may be beneficial in patients with acute coronary syndrome. A recent metaanalysis[36] among patients with ongoing coronary syndrome or chronic cardiac disease suggests that a restrictive approach of less than 8 gm/dL may increase the risk of acute coronary syndrome. However the effect of mortality or other end points needs to be validated.

In cardiac surgical patients :

Transfusion strategies among cardiac surgical patients seems to trend parallel to the generalised trend of a restrictive transfusion although data is conflicting. Earlier observational studies suggested that in uncomplicated surgeries, a restrictive strategy is associated with less mortality than a liberal strategy.[37] The TITRe 2 trial (Liberal or Restrictive Transfusion after Cardiac Surgery [30,] a multicentre randomised controlled trial across 17 centres of UK among patients undergoing non-emergency cardiac surgery randomised patients to a restrictive (haemoglobin level <7.5 g/dL) or a liberal transfusion threshold (haemoglobin level <9 g/dL). [38] There was a trend of non-significant but increased mortality among patients in the restrictive blood transfusion strategy group. However, there was only a modest 1g/dL difference between the two groups which could explain the difference in mortality. This results were in conflict with the TRACS (Transfusion requirements after cardiac surgery) trial done in a similar cohort [39] The TRACS trial had suggested that a restrictive strategy of 9 gm/dL was as good as 10.4 gm/dL, with less transfusions and no increased complications. A multi-centre multi country study Transfusion Requirements in Cardiac Surgery III (TRICS 3) which randomised 4,860 high risk patients to a similar transfusion strategy (7.5g/dL versus 9.5 g/dL) concluded with similar findings of the TRACS study. They suggested that a restrictive transfusion strategy as compared to the liberal transfusion strategy had no added complications such as mortality or infections.[40]

In the burns patients :

Among all patient groups, it will be required to specifically address burn patients differently. Due to the extensive loss of skin, burn patients are at increased risk of infections. The effect of a restrictive blood transfusion in burn patients is not clear due to sparse and poor-quality data. Majority of the data comes from either single centre studies or retrospective studies. Palmieri et al[41] in a multi-centre RCT that included eighteen burn centres with 345 patients having 20% or more total body surface area burn, found that a restrictive strategy (7- 8 gm/dL) was non-inferior to a liberal strategy (10 – 11 gm/dL). The patients randomised to a restrictive strategy received almost half of the blood transfused in the liberal group. However, there was no difference in organ dysfunction or blood stream infection across both groups.

In the cancer patient :

Oncology patients remain excluded from majority of transfusion trials and hence there is no definitive evidence to support the superiority of any transfusion strategy in these subsets of patients. The Transfusion requirements in surgical oncology patients (TRISOP) trial[42] suggested a liberal transfusion strategy (transfusion trigger of 9 g/dL) to be associated with a better composite outcome of mortality and major complications in cancer patients undergoing abdominal surgeries. This study was criticised for a lack of difference between the transfused RBC units among both groups. Similarly, the TRICOP study from Brazil (34) in adult patients with solid tumours and septic shock found a significant survival trend among the liberal transfusion group at 90 days. There was however no difference in the other primary or secondary outcomes. These two trials among oncology patients seem to stand out among the growing evidence favouring a liberal transfusion strategy in these patients. Haematological malignancy has been routinely excluded in trials of blood transfusion. A pilot study by De Zern et al [43] suggests that it is feasible to conduct a study in the target population without much safety concerns. A large randomised trial addressing more pragmatic end points including mortality and long term patient outcome in this subset of patients might be helpful to have a uniformity of practice among these groups of patients.

In the elderly :

There is sparse data that specifically investigates the group of elderly patients and evidence for transfusion. In the Transfusion Requirements In Frail Elderly (TRIFE) trial [44] elderly postoperative patients were evaluated for a liberal versus restrictive strategy (9.7 versus 11.3 gm/dL). The investigators found no significant differences in any of the primary outcomes including daily living activities or mortality at 90 days. A meta-analysis of trials looking specifically in elderly patients [45] suggested that liberal rather than a restrictive transfusion strategy might be beneficial in this sub group as it improved 30-day and 90-day mortality without an added risk of infection. However, although the mean age was 64, the trials included for meta-analysis had patients aged from 18 years onwards. A few trials with the population of interest were also omitted in the meta-analysis, further reducing its generalisability. Hence it is difficult to account for the differences found in the meta-analysis and to adapt it into clinical practice based on this metaanalysis alone.

DOES THE AGE OF TRANSFUSED BLOOD MATTER?

The lack of benefit of blood transfusion across most groups have been attributed to the presence of "storage lesions" in stored blood. On storage there is a progressive depletion of 2, 3-diphosphoglycerate (2, 3- DPG) which shifts the oxygen haemoglobin curve to the left and increases the affinity of haemoglobin for oxygen. Thus, although the oxygen carrying capacity of blood increases with transfusion, it may not happen till 2 – 3 DPG is replenished. Storage of RBC is also

associated with membrane changes and a change in RBC that disturbs the flow of RBCs across micro-capillaries. Depletion of adenosine tri phosphate (ATP), lipid peroxidation, increase in lactate with a resulting drop in pH, increased potassium etc. also tends to occur more as the age of transfused blood increases. As RBC ages, literature suggests[46] that the pH might drop from 6.8 ± 0.03 to as much as 6.37± 0.04, the potassium can rise from 3.9 ± 0.6 mmol/L to 46.6 ± 4.1 mmol/L and the iron content also rises from 3.8 ± 0.9 mmol/L to 14.2 ± 2.9 mmol/L. So there remained a theoretical possibility that the benefits of blood transfusion might be undone by these storage lesions and fresh blood might be beneficial than older blood.

In a retrospective study by Koch et al[47] in 6002 post-operative cardiac surgery patients, patients receiving RBC stored for more than two weeks, had significantly increased post-operative complications and an increased short term and long-term mortality. This triggered a series of trials that specifically investigated the effect of storage on mortality and morbidity. As cardiac surgeries require the use of a bypass pump, with additional and significant hemolysis caused by pump, Koch et al suggested that fresh blood transfusion could have a potential benefit on mortality among these subsets of patients. This was investigated in Red-Cell Storage Duration Study (RECESS) trial.[48] The Age of Blood Evaluation (ABLE)[49], Informing Fresh versus Old Red Cell Management (INFORM) [50] and Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) [51] trials investigated the effect of storage of blood on morbidity and mortality and showed no difference. A summary of these trials that have investigated old versus freshest available RBC in adult patients is given in **Table 3**. Although several eligible patients did not undergo randomization, the TRANSFUSE trial [51] specifically puts to rest the fear of transfusing older blood in adult critically ill patients.

Table 3. Summary of trials that have investigated old versus freshest available RBC in adult patients

Trial Name	Number of Patients	Patient population	Comparison	Result	Limitations
RECESSTRIAL Steiner et al **(2015)**	1098	Post operative cardiac surgical patients including bypass	Blood ≤ 10 days versus ≥21 days	No difference in MODS	Not blinded Primary end point MODS Not studied the effects of aged blood (35- 42 days)
ABLE Lacroixet al **(2015)**	2430	Criticallyill patients	Blood < 8 days versus older blood.	No decrease in the 90-day mortality	Excluded > 700 potentially eligible patients Small sample size Approx 10 hours delay between randomization and first transfusion
INFORM Heddle et al **(2016)**	24,736 in – hospital(10578 were critically ill)	Included hospitalised patients, critically ill patients and also patients with malignancy	Received the freshest available blood or for the oldest available (mean age for old was 23.6 days)	No significant difference in the in hospital mortality	Low mortality (9%) May not be able to extrapolate results to the sicker patients Non blinded study
TRANSFUSE Cooper et al **(2017)**	4994	Criticallyill patients	Freshest available RBCversus standard issue (mean duration 11.8±5.3 days verses22.4 ±7.5)	No difference in 90 day mortality	1353 eligible patients not randomised

The Age of Red blood cells In Premature Infants (ARIPI) trial [52], a multicentre RCT from Canada among 377 premature infants with birth weights less than 1,250 grams concluded that RBCs stored for seven days or less, as compared with the standard of care, had no difference with respect to major nosocomial infection or organ dysfunction. However, the median age of blood in the standard care arm was approximately 14.6 days and this was compared to blood less than 7 days old.

Theoretically fresher blood with more intra cellular 2, 3 DPG should be able to improve oxygenation and there by clear lactic acidosis better than older blood. However, among 290 children, with severe anaemia, malaria and sickle cell disease, the Tissue Oxygenation by Transfusion in severe Anemia with Lactic acidosis (TOTAL) trial [53], could not demonstrate a superiority of fresh blood (1- 10 days) over older blood units (25- 35 days) in resolving tissue hypoxia, thus showing that transfusion of fresh blood does not improve tissue oxygenation and lactic acidosis.

CONCLUSION

Although the degree of anaemia is proportional to mortality, making blood transfusion seem intuitive, the evidence favors a restrictive strategy, rather than a liberal one across most patient groups. The exception may be patients with acute coronary syndrome and patients with a high severity of the illness, both benefiting from a liberal strategy. Oncology patients seem to benefit from a liberal strategy of blood transfusion, but this needs further evaluation.

Transfusion decision should not be based haemoglobin concentration alone. However, though physiological triggers seem to be a better target for transfusion, there is lack of evidence to use it in isolation. And finally, despite the theoretical concerns about storage lesions, there is no proven advantage of transfusing fresh blood over old blood.

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