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REVIEW ARTICLE

Red cell transfusion in critical care: Could less be more?

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ABSTRACT

Blood transfusion has a very important place in ancient medicine where it is associated with vitality. In the era of modern medicine, it still holds an important place. Critical events in the history led to the development of the physiological knowledge of blood flow and pathological processes associated with anemia. These still have a strong foothold in the practice of transfusion medicine which until very recently led physicians to liberally transfuse red blood cells to patients. However, the past few decades have revealed the darker side associated with transfusion of red blood cells. Recent evidences strongly suggest that the arbitrary transfusion triggers that had been historically set might have been too high, possibly causing unnecessary harm. Here, in this narrative review, the authors have tried to explore the evidences favoring lower transfusion threshold and without added adverse events thus supporting the notion – less is more.

Keywords: *critical care, red blood cells, transfusion.*

INTRODUCTION

Blood has been referred to as the "river of life". Almost all cultures and religions have a special place when it comes to blood. Be it regarding the purity of blood which leads to blood being rejected by Jehovah's witnesses once it gets out of the body, it's vitality which led the Roman emperors to bathe in it to increase the vitality or the blood-letting done in various cultures to release the impurities.[1]

The first documented transfusion of blood to a human was done by Blundell in 1818 when a female with post-partum hemorrhage was salvaged by transfusing blood from her husband. But when a particular patient succumbed, although later found to be murdered by his wife by poisoning him with arsenic, led him to stop doing experiments with blood transfusions altogether.[2] However, this was the first time when both the importance and the adverse effects of blood transfusion was noted.

Further works by various authors have allowed for safer transfusion practices including the works of Landsteiner who discovered the major RBC antigens and Lewisohn which led to the possibility of storage of blood for days. World War I saw the development of "blood depot" while World War II was a major milestone in the history of development of blood transfusion when the program "Plasma for Britain" was started by the US government for its troops in the British Isles which no doubt had led onto saving thousands of lives. The value of blood transfusion was ever so increasing.[2] But, a major spectrum of adverse effects of blood was seen with the discovery of transfusion related infections especially with the HIV epidemic. Many other infectious complications were being reported and various guidelines were being formulated to screen for increasing number of diseases including Creutzfeldt-Jakob Disease, hepatitis B and C, HTLV infection, syphilis and so on.[3] Various non-infectious complications were also being reported and newer terms were also being coined which included Transfusion Associated Circulatory Overload (TACO), Transfusion Related Acute Lung Injury (TRALI) and Transfusion Related Immunomodulation (TRIM).[4,5] The notion of "less is more" was being revived.

The optimal transfusion trigger for red blood cell

Oxygen delivery to the tissue by blood is calculated as

$$DO_2 = CO \times CaO_2$$

$$(\text{where } CaO_2 = Hb \times SaO_2 \times 1.34 \text{ ml}).$$

Where DO_2 is the total oxygen delivery by the heart to the tissues; CO is the cardiac output; CaO_2 is the arterial oxygen content; SaO_2 is the arterial oxygen saturation and 1.34 is the amount(ml) of oxygen carried by a gram of hemoglobin molecules.[6,7]

It is clear here that hemoglobin is an important factor determining the oxygen delivery to the tissues. Increasing the hemoglobin content thus increases the oxygen delivery to the tissue. Different organs have different extraction ratios (EO_2) for oxygen which ultimately in conjunction with the degree of anemia culminate to the final effect in the tissue/organ system.

$$EO_2 = (SaO_2 - SvO_2)/\ SaO_2,$$

where SvO^2 is the venous oxygen saturation.

In cases of decreased oxygen delivery, oxygen extraction increases and thus the SvO_2 decreases albeit differently across different tissue/organ systems.[8] A final marker of this is also seen as a decrease in the central venous oxygen saturation ($ScvO_2$). If the maximum extraction of oxygen along with the increase in CO associated with anemia is not able to meet the oxygen demand, tissue hypoxia ensues.[9] Red blood cell transfusion is aimed thus at increasing the oxygen content, delivery and thus improve the tissue oxygenation.

Table 1: Possible triggers for transfusion of red cells

SN	Triggers	Comments
1.	Generalised oxygenation impairment triggers	
	a. Hemoglobin/ hematocrit	a. Most commonly used transfusion trigger.
	b. SvO_2 and $ScvO_2$	b. Denotes venous and central venous oxygen saturation which reflects increased oxygen extraction and decreased delivery
	c. Serum lactate	c. Denotes the product of anaerobic metabolism suggesting decreased oxygen delivery
2.	Myocardial oxygenation impairment triggers	
	a. SBP X HR (Target <1200)	a. Higher product reflects increasing myocardial oxygen extraction
	b. ECG changes	b. Denotes myocardial oxygen extraction and delivery
3.	Cerebral oxygenation impairment triggers	
	a. Digit symbol subtraction test	a. Delayed memory
	b. P300	b. Reaction time
	c. NIRS	c. Measures transcranial oxygen saturation

However, though adequate delivery of oxygen is no doubt very important for maintaining the physiological oxygen demands of tissues, the arterial content and delivery are not linearly related with the uptake at all tissue levels. Various physiological and microcirculatory changes occur which lead to redistribution of blood from less to more vital organs including the heart, brain and kidneys.[6,8] Anemia is also associated with stress responses and hemodilution which cause increased cardiac output further offsetting the linear relationship between hemoglobin concentration and tissue oxygenation making hemoglobin based transfusion trigger too empiric rendering the classical rule of 10/30 (hemoglobin of 10 and hematocrit of 30%) inaccurate.[10] Based on the above pathophysiological concepts, various other physiological transfusion triggers have been put forward (Table 1). Many of these transfusion triggers are however yet to find their place in clinical practice. Furthermore, optimal triggers may be different for individual patient groups.

Critically ill patients

As much as 50% of critically ill patients have hemoglobin level in the anemic range if defined as per the World Health Organization.[11,12] Anemia in the ICU can be present pre-ICU admission.[13] A drastic drop even in non-bleeding patients is seen in the first week more so within the first three days.[14] This can be attributed to a majority of cases which can be grouped as being either related to decrease production or increased losses (Table 2). Decreased production has been linked to the infectious and inflammatory processes which produce a state of relative iron deficiency and cause a blunted marrow response to erythropoietin.[13] In addition, the iatrogenic blood loss has a significant role positively correlating with the sickness, with more iatrogenic losses in sicker patients.[15] This is probably related to the fact that sicker patients have a far higher number of blood samplings and vascular related procedures like central venous cannulations and renal replacement therapies.[14] These were reflected in the findings by a large observational study across the United States which showed that almost half of the patients admitted to the ICU were transfused with at least one unit of red cell product during their stay. Another important finding noted in this study was that the number of red cell units transfused was an independent risk factor for a poorer clinical outcome.[16] The landmark study by Rivers et al., targeted a higher CVP and hematocrit among others.[17] Both have a physiological background on improving the tissue delivery of oxygenated blood to counteract the effects of tissue hypoperfusion brought about by septic shock. In contrast to the proposed beneficial effects, other studies were finding higher risks of transfusion which led to various other studies being designed and conducted to find a lower transfusion trigger to minimize the adverse events. Two major trials, TRISS and TRICC both found that a restrictive strategy was non-inferior to a liberal strategy of transfusion in terms of mortality or the length of hospital stay but resulted in far lesser transfusions.[18,19] In addition, TRICC had found a significant difference (13% vs 21%) in the incidence of major cardiac events and even found a mortality benefit by transfusing less in a subgroup of lesser sick patients.[18] The TRIPICU trial on pediatric critically ill patients also came to a similar conclusion of a hemoglobin trigger of 7 g/dL, reducing transfusion requirements without any increase in adverse events.[20] Even lower hemoglobin levels could well be tolerated by these patient population so much so that red cell transfusion guidelines for pediatric critically ill patients recommend a transfusion trigger of <5g/dL.[21] A recent Cochrane review has found the restrictive strategy of transfusion comparable with liberal transfusion strategy.[22]

Table 2: Causes of anemia in critically ill patients

1. Decrease production
a. Blunted erythropoietin response
b. Lack of substrates (Iron, Vitamin B12, Folate)
c. Presence of renal failure
2. Increased losses
a. Disease related
i. Traumatic blood loss
ii. Coagulopathy
iii. Haemolysis
iv. Gastrointestinal losses
b. Secondary- iatrogenic
i. Sampling¶
ii. Others- vascular cunnulations, RRT, surgeries
¶May account for upto 40ml/day and one unit/week of blood loss.

Patients undergoing surgeries

A very famous publication in JAMA was a case series of 542 consecutive patients in 20 years who underwent cardiovascular surgery without any transfusion. This case series included Jehovah's witnesses with age of the patients being between one day to 89 years. The reported mortality in this series was 9.4%. A thing to be noted here is that this was published in the year 1977 before many medical advances were yet to be made. Nevertheless, anemia was attributed as a cause of death in only 12 patients, remaining being secondary to surgical complications.[23]

With an increase in the life expectancy and improved health care systems all over, increasing number of surgical procedures are being performed globally, which can be expected to increase further. In addition, the age and cardiovascular comorbidities of the patients undergoing surgery are also expected to increase both of which can lead to bleeding and transfusion peri-operatively especially in major orthopedics and cardiovascular surgeries. The changing physiology of an aged morbid patient supports the notion that anemia should be aggressively treated especially during an acute loss as in the perioperative period. The FOCUS study which enrolled

2016 patients with documented coronary artery disease undergoing hip surgeries of an average age of >81 years compared a restrictive vs liberal transfusion strategy. They found no difference whatsoever between the two cohorts receiving transfusion at 8 or 10g/dL in terms of mortality, length of stay or functional outcome.[18]

Surgery is one of the most important situations which accounts for upto 70% of all transfusions.[24,25] Yet contradicting reports about the actual clinical role and possible harm has led transfusion to undergo scrutiny over the past few decades. The concept of "Patient Blood Management" has been coined and interventions to decrease peri-operative transfusion have been devised.[26] Preoperative use of erythropoietin, autologous transfusion, use of tranexamic acid and allowable hemodilution, all have found a role in the perioperative blood management.[27–30] The aim here is to manage the patient and not the blood product since even a single unit of red blood cell transfusion has been shown to be associated with harms.[31,32]

Patients with myocardial ischemia

Myocardial ischemia is related to supply and demand of oxygen in the cardiac tissue. Electrocardiographic changes with induced anemia have been demonstrated in numerous animal and healthy volunteer studies.[33] So the generally accepted idea is to transfuse at a higher hemoglobin level as compared to other patients not having an ischemic event and so is the clinical practice. A large study including almost 79,000 patients had found that anemia was associated with an increase in 30 day mortality which however was severely biased. This study was a retrospective record based observational study and could only correlate anemia with increased mortality. This study was not designed to study the effects of transfusion.[34] The recent REALITY trial shows improved outcomes with transfusion at 8 gm/dL when compared with 10g/dL in patients with ongoing myocardial ischemia.[35] Though, the restrictive threshold in this study is still higher than that in non-cardiac patients, this again should make us ponder if a lower than the generally accepted threshold for transfusion should be sought for.

Acutely bleeding patients

Hemorrhagic shock is the most important cause of shock in trauma patients. Six people out of 10 die within three hours because of hemorrhage.[36] Nowhere else is the role of blood more important than an acutely bleeding patient. But the harms have equally been documented leading to the recommended target of 7-9 g/dL in even an acutely bleeding trauma patient. Similar is the finding in patients with an upper gastrointestinal bleed where too bleeding is a common cause of death in patients with chronic liver disease. More harm of transfusion has been seen in less sicker patients with Child Pugh class A and B.[37]

Neurological patients

Cerebral blood flow is autoregulated by various mechanisms. Anemia increases carotid output by activation of carotid and aortic chemoreceptors by increasing both the heart rate and stroke volume. In the cerebral microcirculation, release of nitric oxide ensues which causes vasodilatation to improve the cerebral blood flow. As discussed earlier, oxygen extraction also increases which prevents the brain cells from undergoing hypoxic injury. Brain pathology disrupt these compensatory mechanisms which make the brain suffer secondary insult if oxygen delivery is compromised.[38] Nevertheless, despite the existence of physiological basis for benefit, definite advantage has been seen only in a few reports while many other studies report harm including an increased risk of mortality.[39,40]

CONCLUSION

With the evolution of the evidence based medicine, harms associated with red blood transfusion are being discovered. Majority of recent evidences point towards limiting the use of blood to the bare minimum. An exact transfusion trigger in different clinical scenarios is yet to be determined. The most rudiment but time tested trigger, hemoglobin, is on the test at the moment. Individual patient groups and furthermore individual patients may have different factors at play which may be the cause for inability to set a specific transfusion trigger. Precision medicine may be the answer for the individualized transfusion trigger. Developments of an ideal oxygen carrier can be an alternative to transfusion and thus to prevent adverse effects of red cell transfusion. Till then, as has been proven in many fields of medical sciences, in transfusion medicine too, less could be more.

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