Red Blood Cell Transfusion Trigger in Sepsis

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Abstract

Blood transfusions are a relatively common event in patients with sepsis. Although severe anemia is associated with worse outcomes, hemoglobin levels less than the classically quoted 10 g/dl are well tolerated in many patients, and it is difficult to determine whether or when such patients should be transfused. Importantly, there can be no one transfusion trigger or threshold for all patients, rather the benefit/risk ratio of transfusion should be assessed in each patient taking into account multiple factors including physiological variables, age, disease severity, and coexisting cardiac ischemia. The ultimate goal of transfusion is to improve tissue oxygenation, but our ability to measure these changes and hence determine the need for and response to transfusion is still limited.

3.1 Introduction

Patients with sepsis make up a large proportion of the intensive care unit (ICU) population, and although outcomes have improved over the last decade [1], these patients, particularly those with septic shock, still have mortality rates in the region of 20–30 % [2, 3]. There are no effective specific antisepsis treatments, and management of patients with sepsis thus relies largely on early recognition allowing timely administration of appropriate antibiotics, suitable source control measures, and effective resuscitation strategies. The aims of resuscitation are essentially to restore and maintain tissue oxygen delivery (DO_2) so that organs can function optimally.

There are various means by which DO_2 can be improved, including fluid administration, vasopressor agents to restore perfusion pressure, and inotropic agents to

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support cardiac function and increase cardiac output. Blood transfusions have also been widely used as a means of improving tissue DO_2, although this relationship is not straightforward. Indeed, the increased blood viscosity as a result of the transfusion can lead to a decrease in cardiac output (CO) and hence in DO_2 [4], except in conditions of hemorrhage and hemodilution in which increased viscosity can improve microcirculatory flow and hence DO_2 [5]. As many as 30 % of intensive care unit (ICU) patients receive a transfusion at some point during their ICU stay [6–11], but there is still considerable debate about the benefit/risk ratio of this intervention and when or if any individual patient should be transfused.

In this chapter, we will review the balance between DO_2 and oxygen uptake (VO_2) in sepsis and the effects of red blood cell transfusion on this balance and discuss some of the more recent trials that have investigated hemoglobin levels and the beneficial and adverse effects of transfusion in critically ill patients.

3.2 Oxygen Delivery and Consumption in Sepsis

Tissue oxygenation essentially relies on DO_2, VO_2, and the ability of the tissue to extract oxygen. DO_2 is the rate at which oxygen is transported from the lungs to the tissues and is the product of the CO and the arterial oxygen content (CaO_2): $DO_2 = CO \times CaO_2$, where CaO_2 = hemoglobin concentration (Hb) × arterial oxygen saturation (SaO_2) × 1.34 (the oxygen carrying capacity of Hb). DO_2 can, therefore, be influenced by changes in CO, hemoglobin concentration, and oxygen saturation. VO_2 is the amount of oxygen removed from the blood by the tissues per minute and is the product of the CO and the difference between CaO_2 and mixed venous oxygen content (CvO_2): $VO_2 = CO \times (CaO_2 - CvO_2)$. VO_2 is determined by the metabolic rate of the tissues, which increases during physical activity, hyperthermia, shivering, etc. The ratio of the oxygen consumed to that delivered (VO_2/DO_2) represents the amount of oxygen extracted by the tissues, the oxygen extraction ratio (O_2ER).

As tissues are unable to store oxygen, it is important for them to have a system by which delivery of oxygen can be adjusted efficiently to oxygen demands. Under normal physiological conditions, as DO_2 decreases, oxygen extraction increases to compensate and maintain VO_2, ensuring adequate tissue oxygenation for aerobic metabolism and normal cellular function: VO_2 is independent of DO_2. Indeed, at rest, VO_2 is only about 25 % of DO_2, so that there is a large reserve of oxygen available for extraction if needed as DO_2 falls [12]. However, a point is reached at which oxygen extraction is unable to increase further and a so-called critical DO_2 is attained at which VO_2 becomes dependent on DO_2; any further decrease in DO_2 is associated with a decrease in VO_2 and anaerobic metabolism with a rise in blood lactate levels [13–15].

During septic shock, the ability of tissues to extract oxygen is reduced so that this VO_2/DO_2 relationship can be altered with the critical DO_2 set at higher values such that VO_2 is dependent on DO_2 over a larger range of values [13–15]. The reasons for the reduced oxygen extraction abilities in sepsis have not been fully elucidated but

are likely to be related in part to the microcirculatory changes seen in sepsis, including increased heterogeneity, increased stop-flow capillaries, and increased shunting of DO_2 from arterioles to venules [12]. Impaired ability of mitochondria to use the available oxygen may also play a role in microcirculatory dysoxia [16].

3.3 Anemia in Sepsis

Anemia, widely defined in ICU studies as a hemoglobin level <12 g/dl [7, 17], is common in critically ill patients [6, 7, 18]. In the ABC study [3], 29 % of patients had a hemoglobin concentration <10 g/dl on admission. In a Scottish cohort, 25 % of patients had a hemoglobin concentration <9 g/dl on ICU admission [19]. Hemoglobin concentrations decrease during the ICU stay, particularly in septic patients, in whom Nguyen et al. [20] reported a decrease of 0.68 ± 0.66 g/dl/day; this study also noted that hemoglobin concentrations continued to decrease after the third day in patients with sepsis but not in those without [20].

Multiple factors act together to cause anemia in the critically ill patient, including primary blood losses (trauma, surgery, gastrointestinal bleeding, etc.), phlebotomy losses, which can reach as much as 40 ml/day [20], hemodilution secondary to fluid resuscitation, blunted erythropoietin (EPO) production, abnormalities in iron metabolism, and altered red blood cell production and maturation [21–23]. In healthy subjects, compensatory mechanisms, including the increased oxygen extraction discussed above, but also reflex increases in CO because of decreased blood viscosity, increased adrenergic response, causing tachycardia and increased myocardial contractility, and blood flow redistribution (to heart and brain) enable severe anemia to be tolerated [24]. However, in critically ill patients, compensatory mechanisms are less efficient, and oxygen reserves are reduced so that lesser degrees of anemia may have greater consequences on organ function and outcome. Oddo et al., in a retrospective study of patients with traumatic brain injury who had had brain tissue oxygen tension ($PbtO_2$) measured, noted that anemia associated with reduced $PbtO_2$ was a risk factor for unfavorable outcome, but not anemia alone [25]. Patients with myocardial ischemic disease may be particularly sensitive to the effects of anemia because the associated tachycardia and increased contractility may increase myocardial oxygen demand, which will need to be met by increased coronary blood flow as myocardial oxygen extraction is almost maximal already at rest [23, 26].

3.4 Monitoring VO_2/DO_2 and Tissue Oxygenation During Transfusion

Because DO_2 is the product of CO and CaO_2 is determined in part by the hemoglobin concentration, when the hemoglobin concentration decreases, DO_2 will decrease (if CO remains unchanged). Hence, one may anticipate that increasing the hemoglobin by giving a transfusion would help increase DO_2 as has indeed

been shown in several studies [27–29]; although by increasing blood viscosity, some of the compensatory mechanisms of acute anemia on left ventricular pre- and afterload will be reduced, thus limiting the effects on DO_2 [5]. Moreover, even if DO_2 does increase, there is no guarantee that VO_2 and hence oxygen availability to the tissues will also increase, particularly in patients with an abnormal VO_2/DO_2 relationship and an altered microcirculation, such as those with sepsis [27, 29, 30]. There are several possible reasons for this including the fact that the ability of hemoglobin to download oxygen may be altered in sepsis because of microcirculatory changes, such as altered red blood cell deformability, altered oxygen extraction capabilities, reduced functional capillary density, and increased heterogeneity of flow. The ability of hemoglobin to deliver oxygen may also be influenced by changes that occur during storage of blood [31] and by increased blood viscosity following transfusion leading to reduced microcirculatory flow. Additionally, tissue oxygen demands are increased in patients with sepsis.

Importantly, different tissues have different critical DO_2 values and VO_2/DO_2 relationships and develop hypoxia at different degrees of acute anemia [32]. Hence, global assessment of the VO_2/DO_2 relationship cannot be used to guide therapy. "Coupling of data," which occurs when both variables have been calculated from the same values, is also a problem when using this relationship [15]. Cardiac output represents total body blood flow and can be monitored almost continuously but offers no information on regional organ perfusion. Cardiac output is also highly variable among individuals and varies according to oxygen requirements; for example, in sepsis the typically "normal" or high CO seen may be insufficient because of increased sepsis-related tissue oxygen requirements.

Mixed venous oxygen saturation (SvO_2) has been widely used as a marker of tissue oxygenation, and, indeed, as oxygen extraction increases to meet oxygen demands, SvO_2 will decrease. However, although low SvO_2 indicates poor tissue oxygenation, normal or high SvO_2 values do not necessarily mean that tissue oxygenation is adequate; for example, if a tissue is unable to extract oxygen, the venous return from that area may still have a high oxygen content although the tissues may be hypoxic. Central venous oxygen saturation ($ScvO_2$) is increasingly used as a less invasive surrogate for SvO_2, but again this is a global measure. Rivers et al. [33], in their landmark study, randomized patients admitted to an emergency department with severe sepsis and septic shock to receive standard therapy (targeted at a central venous pressure [CVP] of 8–12 mmHg, mean arterial pressure [MAP] ≥65 mmHg, and urine output ≥0.5 ml/kg/h) or to the so-called early goal-directed therapy (EGDT) in which an $ScvO_2$ of at least 70 % was also targeted by optimizing fluid administration, giving blood transfusions to maintain hematocrit ≥30 %, and/or giving dobutamine to a maximum of 20 μg/kg/min. The EGDT group received more fluids, and more were treated with dobutamine; the number of transfused patients was also greater than in the standard therapy group. Patients in the EGDT group had significantly lower mortality rates than other patients, and this study therefore seemed to support the use of $ScvO_2$ values to guide therapy, including transfusions [33]. However, in the recently published Protocolized Care for Early

Septic Shock (ProCESS) study [34], there were no significant differences in 90-day mortality, 1-year mortality, or the need for organ support in patients managed with protocolized EGDT – using a similar protocol to that used by Rivers et al., protocolized standard therapy or usual care.

The O_2ER is easy to calculate, and plotting cardiac index (CI) against O_2ER and relating them to isopleths of VO_2 can help identify whether a patient has reached the point of VO_2/DO_2 dependency and evaluate the adequacy of CO in complex patients [35]. In patients with anemia and normal cardiac function, a CI/O_2ER ratio <10 suggests an inadequate CI that is likely due to hypovolemia [35].

As tissue oxygenation becomes inadequate, anaerobic metabolism begins to take over from aerobic metabolism and blood lactate levels rise. Although other factors can also result in increased blood lactate levels [36], a blood lactate level greater than 2 mEq/l suggests inadequate tissue perfusion and oxygenation. Hyperlactatemia is associated with a poor prognosis in critically ill patients in general and in those with sepsis [37]. As with many other measures, trends in lactate levels are of greater value than any individual value [38].

There is no ideal measure for determining optimal tissue oxygenation, and adequacy of DO_2 must be assessed using a combination of the above variables along with clinical examination.

3.5 Microcirculatory Effects of Blood Transfusions

With the advent of new techniques to monitor the microcirculation, several studies have now reported the effects of transfusion on the microcirculation in human subjects. In a small early study using orthogonal polarization spectral (OPS) imaging, Genzel-Boroviczény et al. reported an improvement in functional capillary density following transfusion in anemic preterm infants, indicating improved microvascular perfusion [39]. In patients undergoing on-pump cardiac surgery, Yuruk and colleagues [40] reported, using sidestream dark-field (SDF) imaging, that blood transfusion was associated with microcirculatory recruitment resulting in increased capillary density, thus reducing the oxygen diffusion distance to the cells. Using near-infrared spectroscopy (NIRS), the same authors reported that transfusion increased thenar and sublingual tissue oxygen saturation (StO_2) and thenar and sublingual tissue hemoglobin index (THI) in outpatients with chronic anemia [41]. In critically ill patients, Creteur et al., using the same NIRS technique, noted that blood transfusion was not associated with changes in muscle tissue oxygenation, VO_2, or microvascular reactivity in all patients, but that muscle VO_2 and microvascular reactivity did improve in patients in whom these variables were altered prior to the transfusion [42]. Similar findings have been made in patients with severe sepsis [43, 44] and trauma [45]. In a retrospective study of patients with severe sepsis who had a microdialysis catheter inserted for interstitial fluid measurements, blood transfusion was associated with a decrease in the interstitial lactate/pyruvate ratio, and these changes were again correlated with the pre-transfusion lactate/pyruvate ratio [46].

Studies have also assessed the impact of transfusion of fresh versus stored blood cell units on the microcirculation. In healthy volunteers, there were no differences in sublingual OPS-derived microcirculatory variables or NIRS-derived StO_2 after transfusion with 7-day or 42-day stored blood [47]. Walsh et al. reported no difference between stored (>20 days) and fresh (<5 days) cells on gastric tonometry indices in anemic critically ill patients [48], but Weinberg et al. reported a decrease in NIRS StO_2 and sidestream dark-field (SDF) capillary vascular density with transfusion of older units in trauma patients [49]. Some of the negative effects of blood transfusion may be due to the presence of leukocytes, and it has been proposed that use of leukodepleted blood should be preferred in critically ill patients. A recent pilot study in which 20 patients with sepsis were randomized to receive either leukodepleted or non-leukodepleted blood showed no clear superiority of leukodepleted over non-leukodepleted blood although leukodepleted blood was associated with more favorable changes in MFI and blood flow velocity [50].

3.6 Putting the Theory into Practice: Clinical Trials of Transfusion Triggers in Septic Patients

We have seen that blood transfusion can improve DO_2 but may not directly help improve tissue oxygenation. Patients with sepsis frequently develop anemia [20], which is known to be associated with worse outcomes in critically ill patients [11, 51, 52], but are blood transfusions actually of benefit? When should critically ill patients with sepsis be transfused? Several early observational studies suggested worse outcomes in critically ill patients who received a transfusion compared to those who did not [6, 7], casting doubt on the supposed benefits of transfusion, but more recent studies have suggested the opposite [8, 11]. Some of these differences may be related to the timing of transfusion as benefits are likely to be greatest in the early stages of disease than in later phases when patients are stable or already have established organ failure [53]. Indeed, the Surviving Sepsis Campaign guidelines give different recommendations based on the duration of the septic episode: during the first 6 h of resuscitation, they suggest that transfusion should be given to maintain the hematocrit above 30 % if $ScvO_2$ remains below 70 % despite initial fluid and vasopressor therapy; this recommendation was, however, largely based on the Rivers study [33], so may need to be reconsidered in light of the ProCESS results [34]. After this initial period, the SSC guidelines recommend transfusion when the hemoglobin concentration is less than 7.0 g/dl to maintain a concentration of 7.0–9.0 g/dl (grade 1B). In certain circumstances, such as severe hypoxemia, ischemic coronary artery disease, or acute hemorrhage, higher thresholds may be warranted [54]. Guidelines from the British Committee for Standards in Hematology make similar recommendations [55].

The Transfusion Requirements in Critical Care (TRICC) study published in 1999 [56] changed many intensivists' conceptions of blood transfusion, and physicians worldwide began to reconsider their transfusion thresholds [57], although one recent study suggested that transfusion rates only decreased in high-volume ICUs

(>200 admissions per year) but continued to increase in low-volume hospitals [58]. Importantly, much has changed in intensive care since 1994–1997 when the TRICC study was conducted. Blood transfusion medicine has evolved so that blood transfusions are now safer. The general process of care has improved, and patients are being diagnosed and treated more rapidly with appropriate and effective resuscitation. So what new evidence is available on transfusion thresholds? There have been no large-scale studies comparing one transfusion trigger with another in a general population of critically ill patients since the TRICC study, and there are few specific data in septic patients. But there have been several studies comparing different thresholds in other groups of patients. A randomized controlled study in more than 500 patients undergoing cardiac surgery with cardiopulmonary bypass reported that a perioperative restrictive transfusion strategy (to maintain a hematocrit at least 24 %) was associated with similar morbidity/mortality outcomes compared to a more liberal strategy (to maintain a hematocrit of at least 30 %) [59]. In addition, regardless of the transfusion strategy, the number of transfused red blood cell units was an independent risk factor for clinical complications or death at 30 days (hazard ratio 1.21 for each additional unit transfused; 95 % confidence interval 1.1–1.4, $P = .002$). In a recent pilot study that included 100 elderly (>55 years), mechanically ventilated ICU patients, there was a trend to reduced mortality in patients managed using a restrictive (hemoglobin threshold 7.0 g/dl) compared to a more liberal (9.0 g/dl) strategy [60]. In a small randomized study in 44 patients with subarachnoid hemorrhage and high risk of vasospasm, Naidech et al. [61] reported that targeting a higher hemoglobin concentration (11.5 g/dl) was as safe as targeting a lower hemoglobin level (10 g/dl) and may have reduced the incidence of cortical cerebral infarction. In a randomized study of 2,016 patients ≥50 years of age with a history of or risk factors for cardiovascular disease after hip fracture surgery, a liberal transfusion strategy (hemoglobin threshold 10 g/dl) was not associated with reduced mortality or function at 60 days compared with a restrictive strategy (symptoms of anemia or physician discretion for a hemoglobin level of <8 g/dl) [62].

3.7 Conclusion

Anemia is common in the critically ill patient and is associated with worse outcomes. Nevertheless, most patients can tolerate a degree of anemia, and it is difficult to determine whether or when such patients should be transfused. Strategies to reduce the development of anemia should be employed, including minimizing iatrogenic blood loss and oxygen consumption. Exogenous erythropoietin, iron, and Hb-based oxygen carriers may have a place in some patients, but further study is needed to determine their role.

Microcirculatory "shunting" can create local hypoxia even if global oxygenation parameters are normal, and strategies that act directly on regional perfusion or cellular metabolism are likely to be more effective than strategies aimed at increasing global DO_2. Transfusions seem to improve microcirculatory parameters in patients in whom these variables are altered prior to transfusion, and further study is needed

to determine whether such variables could be used to guide transfusion. Current guidelines suggest targeting a hematocrit of >30 % in the early phase of sepsis [54], but this threshold should be assessed on an individual basis taking into account multiple factors including physiological variables, age, and coexisting cardiac ischemia [63, 64].

A study comparing a restrictive (at hemoglobin ≤7 g/dl) versus liberal (at hemoglobin ≤9 g/dl) transfusion protocol in patients with septic shock is currently ongoing (Transfusion Requirements in Septic Shock [TRISS] trial) [65] and may help provide additional guidance when considering transfusing patients with sepsis.

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