

# Indications for blood transfusions in critical illness

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## ABSTRACT

Transfusion of blood products should improve tissue oxygenation and reduce negative consequences of anaemia. At the same time, adverse effects of transfusion, such as infections, immunologic reactions and mistransfusion, could be deleterious. Most transfusion guidelines suggest looking at the combination of haemoglobin or haematocrit levels in addition to clinical signs in the decision making process for a blood transfusion. The problem with such indications is that the clinical evaluation may be misleading in severely ill patients and haemoglobin levels that impair oxygen delivery cannot be determined easily. Many studies attempted to establish more convenient parameters, such as oxygen saturation from mixed and central venous blood, tissue oxygen extraction and other methods. Although the results from these studies are conflicting, it appears that global oxygenation parameters are a good indicator for a blood transfusion in some categories of critically ill patients.

*Key words: haemoglobin concentration, global oxygenation parameters, transfusion, critical illness*

## INTRODUCTION

According to the World Health Organisation, anaemia represents a condition of decreased haemoglobin (Hgb) concentration (<12 g/dL in women and <13 g/dL in men). In a critically ill population, two-thirds of patients match this criteria. The aetiology of anaemia in critical illness relates to haemodilution, bleeding, blood sampling, increased haemolysis, nutritional deficiencies, blunted erythropoietin production, abnormalities in iron metabolism, etc. (1,

2) The ability to develop compensatory mechanisms that would assure metabolic needs, will determine the tolerance of anaemia in each patient. These mechanisms include: blood flow redistribution, increased cardiac output (CO) and increased oxygen extraction ratio (ERO<sub>2</sub>), among others. (3, 4) Negative effects of anaemia are a result of impaired tissue oxygen delivery (DO<sub>2</sub>) that may increase the risk of morbidity and mortality in critically ill patients, especially at Hgb levels below 5-6 g/dL. (5) The transfusion of blood products should improve tissue oxygenation and reduce negative consequences of anaemia. At the same time, the adverse effects of transfusion, such as infections, immunologic reactions and mistransfusion, could be deleterious. (4) According to the American Society of Anesthesiologists (ASA), the Society of Thoracic Surgeons (STS) and the Society of Cardiovascular Anesthesiologists (SCA), red blood cells (RBCs) should be administered when DO<sub>2</sub> decreases below a critical level or when euvolemic patients develop complications from disturbed tissue oxygenation. (1, 6)

## HAEMOGLOBIN/HAEMATOCRIT THRESHOLDS FOR BLOOD TRANSFUSIONS IN CRITICAL ILLNESS

Although the main goal of RBCs transfusions is to improve oxygen delivery and tissue utilisation, a number of intensivists still use Hgb and haematocrit (Htc) levels as an exclusive transfusion trigger. Since a critical Hgb level that impairs DO<sub>2</sub> cannot be easily determined, such clinical practice is questionable. (7 - 9) The patient's age, primary diagnosis and clinical symptoms, volume status, aetiology and duration of anaemia, surgery duration, ongoing bleeding, compensatory mechanisms, pulmo-

nary, cardiovascular and cerebrovascular comorbidities, and signs of poor end organ perfusion or ischaemia, should significantly affect decisions for transfusion therapy. (1, 3, 6, 7, 9) Throughout the years, Hgb/Htc thresholds for RBCs transfusions have decreased considerably, without adverse effects and worsening clinical outcomes. (10, 11) The results of the TRICC study demonstrated that 30 day mortality, frequency of myocardial infarction, acute respiratory distress syndrome (ARDS) and pulmonary oedema were reduced when RBCs were administered at lower Hgb levels or when they were not administered at all. (11) Some other studies of critically ill patients (ABC, CRIT), linked transfusion therapy and the number of transfused units to a higher risk of mortality and prolonged intensive care unit (ICU) and hospital stays. In contrast, similar mortality rates between transfused and nontransfused patients were found in 1,040 septic patients who received a blood transfusion in the observational European SOAP study. In the transfusion group a higher 30-day survival rate was noticed. (12) In the FOCUS study of Carson et al. on high risk elderly patients with underlying cardiovascular disease subjected to the hip surgery, a liberal RBCs transfusion strategy (Hgb ≥ 100 g/L), in comparison to restrictive strategy (Hgb ≤ 80 g/L or symptomatic anaemia), did not affect mortality or reduce inability to walk independently on a 60-day follow-up, nor did it affect in-hospital morbidity. The study results did not support the hypotheses that a blood transfusion induces long-term immunosuppression that is severe enough to increase the mortality rate by more than 20-25%. (13) On a study population of 73,067 patients with a non-ST segment elevation myocardial infarction subjected to cardiac catheterisation, Hanna et al. reported that lower Hgb

concentrations were associated with more extensive coronary artery disease, less use of revascularisation, evidence-based therapies and a higher in-hospital mortality (7% increase for each 1g/dL decrease in Hgb lower than 15 g/dL). (14) According to the Eastern Association for the Surgery of Trauma and the American College of Critical Care Medicine of the Society of Critical Care Medicine, RBCs transfusions are clearly indicated for the treatment of hemorrhagic shock, particularly in patients who have reached critical DO<sub>2</sub>. The efficacy of RBCs transfusions in haemodynamically stable trauma and critically ill patients with anaemia has not been demonstrated in most clinical settings. RBCs transfusions should be considered in patients on mechanical ventilation, trauma patients after their initial stabilisation and in patients with stable cardiac disease below a Hgb level of 7 g/dL, which is equally effective as transfusions below a Hgb level of 10 g/dL. In patients with acute coronary syndrome (ACS), RBCs administration may have positive effects at Hgb levels below 8 g/dL. In septic patients, RBCs transfusions must be assessed individually since optimal transfusion triggers in sepsis are not known and there is no clear evidence that transfusion increases tissue oxygenation. In patients at risk for acute lung injury or ARDS, the administration of RBCs should be avoided. RBCs should not be used as a method of weaning patients from mechanical ventilation. In the absence of acute bleeding, transfusions should be given as single units. (9) The transfusion guidelines from the Croatian Medical Association and the Croatian Society for Quality Improvement in Health Care suggest Hgb 7.0 g/dL as a level at which transfusion therapy must be started in critically ill patients. (15) The guidelines of the European Society of Anaesthesiology suggest a Hgb concentration of 7.0 – 9.0 g/dL during active perioperative bleeding. (16) ASA guidelines suggest a Hgb concentration from 6 to 10 g/dL, depending on a patient's clinical status. Transfusions for patients undergoing cardiopulmonary bypass is indicated at a Hgb concentration of 6.0 g/dL. For patients older than 65 and for patients with chronic cardiovascular or respiratory diseases, transfusions are justified at a Hgb concentration of 7.0 g/dL. For stable patients with a Hgb concentration between 7 and 10 g/dL, the benefit of transfusions is unclear. In patients with active bleeding, transfusions are recommended after

a blood loss higher than 1,500 mL or 30% of blood volume. Rapid blood loss without immediate control warrants a blood transfusion. (1) The American STS and SCA guidelines suggest transfusions in cardiac patients at a Hgb concentration of 6 g/dL, as this can be lifesaving. Haemoglobin of 7 g/dL represents a reasonable transfusion threshold in most cardiac postoperative patients. Transfusions for Hgb levels above 10 g/dL is not suggested. (6) Because of insufficient primary compensatory mechanisms, damaged ventricular function and oxygen transport, most guidelines recommend higher Hgb concentrations as a transfusion indication in patients with ACS. Also, most transfusion guidelines suggest the use of a clinical assessment in combination with the Hgb concentration. The problem with such recommendations is that a clinical evaluation may be misleading in severely ill and unstable patients.

#### **GLOBAL OXYGENATION PARAMETERS IN CRITICAL ILLNESS**

Considering the fact that blood loss estimation, intravascular volume and clinical symptoms are not always adequate (and that there is little scientific evidence to point to a specific Hgb/Htc level as an optimal transfusion trigger), many studies tried to establish more convenient parameters. Most studies directed their efforts to global oxygenation parameters, such as oxygen saturation from mixed and central venous blood (SVO<sub>2</sub>, ScVO<sub>2</sub>), DO<sub>2</sub>, oxygen consumption (VO<sub>2</sub>) and ERO<sub>2</sub>. SVO<sub>2</sub> indicates the relation between global VO<sub>2</sub> and DO<sub>2</sub>. Tissue dysoxia, indicated by decreased VO<sub>2</sub> depending on DO<sub>2</sub>, usually becomes evident at SVO<sub>2</sub> levels of 40-50%. If ERO<sub>2</sub> is disturbed, tissue dysoxia may be evident at higher SVO<sub>2</sub> levels. SVO<sub>2</sub> depends on Hgb concentrations, CO, VO<sub>2</sub> and arterial oxygen saturations (SaO<sub>2</sub>). It should be a key factor in determining the amount of blood loss a critically ill patient can tolerate. (17) Studies on animal models with acute, normovolemic haemodilution, demonstrated that a Hgb concentration of 4 g/dL represents the level when VO<sub>2</sub> starts to decline, which corresponds to SVO<sub>2</sub> of 44% and ERO<sub>2</sub> of 57%. (18, 19) Most investigators used SVO<sub>2</sub> and calculated ERO<sub>2</sub> as transfusion indicators. Keeping in mind the risks from pulmonary artery catheterisation, the use of these parameters in everyday clinical prac-

tice may be difficult. (20-26) Considering the fact that most critically ill patients in medical or surgical ICUs do not have a pulmonary artery catheter inserted, or it is inserted for a short period of time, a question can be raised whether ScVO<sub>2</sub> and ScVO<sub>2</sub> derived ERO<sub>2</sub> may be used as relevant transfusion indicators. SVO<sub>2</sub> reflects the relation between DO<sub>2</sub> and VO<sub>2</sub> in the upper and lower parts of the body and the heart. ScVO<sub>2</sub> reflects the balance between DO<sub>2</sub> and VO<sub>2</sub> in the cranial part of the body and the brain. Although in normal conditions and healthy individuals SVO<sub>2</sub> is higher than ScVO<sub>2</sub> (2-5%), this relation may change in shock of any aetiology, severe sepsis, cardiac decompensation, head injury, etc. In these conditions (due to a blood flow redistribution in the upper parts of the body, decreased splanchnic and renal circulation and increased ERO<sub>2</sub>) ScVO<sub>2</sub> may outmatch SVO<sub>2</sub> by up to 20%. (27-31) The use of individual ScVO<sub>2</sub> and ERO<sub>2</sub> values as transfusion indicators in these conditions is questionable. In the most common situations in the ICU, when SaO<sub>2</sub> is near 100%, ERO<sub>2</sub> may be calculated from the SaO<sub>2</sub> and SVO<sub>2</sub> difference, without a need for VO<sub>2</sub> and DO<sub>2</sub> measurements. (31, 33, 34) When anaemia results in DO<sub>2</sub> reduction, ERO<sub>2</sub> of 50% represents an indirect indicator of tissue oxygen deficit and may be used as a transfusion trigger. (24) Studies that compared ScVO<sub>2</sub> and SVO<sub>2</sub> in various clinical situations have still not provided reliable answers on the question of whether or not both of these parameters can be used for the purpose of triggering transfusion therapy. As a result of blood flow redistribution, regional impairment of tissue oxygenation and microcirculation in critically ill patients, the various outcomes of these studies are often inconclusive. Therapeutic procedures in the ICU (oxygenotherapy, assisted ventilation, administration of fluids, inotropes, anaesthetics, analgetics, sedatives etc.) additionally contribute to a disproportionality between ScVO<sub>2</sub> and SVO<sub>2</sub>. (28, 29, 30) Although ScVO<sub>2</sub> and SVO<sub>2</sub> do not correlate completely, in the 2012 Surviving Sepsis Campaign Guidelines, both of these values are considered equivalent, and targets of 70% and 65% respectively are recommended in the beginning of septic resuscitation. (35) In a study by Rivers et al., ScVO<sub>2</sub> was used during early goal-directed therapeutic interventions to restore a balance between DO<sub>2</sub> and VO<sub>2</sub> in patients with severe sepsis and

septic shock. (36) On animals, and later on high risk critical patients, Reinhart et al. demonstrated a good correlation between ScVO<sub>2</sub> and SVO<sub>2</sub> in conditions such as bleeding, fluid resuscitation, hypoxia, normoxia and hyperoxia. According to the authors, ScVO<sub>2</sub> may confidently predict acute changes in VO<sub>2</sub>/DO<sub>2</sub> relations, i.e. monitor trends in DO<sub>2</sub> and VO<sub>2</sub>. (31, 37) Sekkat et al. and Dueck et al. had similar conclusions on cardiac and neurosurgical patients. They found significant differences in the numerical ScVO<sub>2</sub> and SVO<sub>2</sub> values, but also they found trends between these parameters that correspond to various haemodynamic conditions which can be used in clinical decision making. (38, 39) In a study on 53 surgical and medical patients, Chawla et al. concluded that ScVO<sub>2</sub> was not a reliable substitute for SVO<sub>2</sub>, and that calculating VO<sub>2</sub> in this way may cause serious errors. (40) In a study on 20 patients in hemorrhagic or septic shock, Ho et al. demonstrated that changes in ScVO<sub>2</sub> and SVO<sub>2</sub> do not accompany each other and that this distinction increases when SVO<sub>2</sub> falls below 70%. (41) In a study on 20 patients, Lorentzen et al. found that ScVO<sub>2</sub> and SVO<sub>2</sub> were not comparable in patients undergoing aortic valve replacement. In patients subjected to coronary artery bypass graft (CABG) procedures, ScVO<sub>2</sub> may be used as a SVO<sub>2</sub> substitute, although absolute values were not completely the same. Lower SaO<sub>2</sub> (<92%), reduced Hgb levels and low CO, increased this disproportion. (42) Elsherbeny et al. found that there is poor agreement between ScVO<sub>2</sub> and SVO<sub>2</sub> regardless of type of surgery, changes in CO and type of pharmacological support. ScVO<sub>2</sub> values above 70% could reliably predict normal SVO<sub>2</sub>, but ScVO<sub>2</sub> values below 70% could not reliably predict inadequate SVO<sub>2</sub>. (43)

### **GLOBAL OXYGENATION PARAMETERS AS INDICATORS FOR BLOOD TRANSFUSION**

In a study by Paone et al. on 100 cardiovascular patients, SVO<sub>2</sub> of 55% was used as a transfusion trigger. The study results showed that blood transfusions were significantly reduced in comparison to the amount of blood that would be transfused if traditional triggers were used. (20) On 60 high risk, surgical, haemodynamically stable patients, Adamczyk et al. assessed the ScVO<sub>2</sub> value for a decision for blood

transfusions in comparison to the criteria of the French guidelines for blood transfusions in critically ill patients, which is based on a consensus by the French Society of Intensive Care Medicine (SLRF). The French guidelines suggest administration of RBCs according to Hgb levels and the associated clinical state of the patient (10 g/dL – ACS, 9 g/dL – ischemic heart disease, stable heart failure, 8 g/dL > 75 years, severe sepsis, 7 g/dL – other critically ill patients). In the study, patients were retrospectively divided into two groups based on ScVO<sub>2</sub> values (< or >70%) prior to transfusion therapy. Each group was additionally divided in two subgroups, depending on whether SLRF criteria were matched. Although the transfusions significantly increased Hgb levels in all patients, ScVO<sub>2</sub> was significantly increased only in patients with pretransfusion levels below 70%. Thirteen patients of 20 that were transfused contrary to SLRF recommendations had an ScVO<sub>2</sub> < 70%, and regarding the VO<sub>2</sub>/DO<sub>2</sub> relationship they seemed to benefit from the blood transfusion. 54.5% of the patients that received a blood transfusion according to the SLRF criteria had an ScVO<sub>2</sub> ≥ 70%, which implies that the VO<sub>2</sub>/DO<sub>2</sub> relation had been adequate and that the patients were transfused in excess. (21) Considering physiologic and pathophysiologic mechanisms for the oxygen exchange at the cellular and tissue levels, ERO<sub>2</sub> could be used as the best indicator for transfusion therapy. (22-26, 44, 45) A reduction in ERO<sub>2</sub> following the administration of RBCs should point out that a blood transfusion was justified. Bashir et al. compared cerebral and peripheral oxygen saturation in patients subjected to autologous blood transfusions during abdominal aortic aneurysm repair. In the post-transfusion group of patients with decreased ERO<sub>2</sub>, a statistically significant increase in cerebral oxygen saturation, Hgb concentration, oxygen partial pressure and SVO<sub>2</sub> was noticed. (44) On an animal model, Wilkerson et al. tried to determine whether global ERO<sub>2</sub> reflects disturbed myocardial metabolism during acute, normovolemic anaemia. The left ventricular metabolism (arterial-coronary sinus lactate) was compared to ERO<sub>2</sub>. The authors concluded that ERO<sub>2</sub> could be a valid indicator of myocardial metabolism in anaemia and that significant myocardial lactate production starts when global ERO<sub>2</sub> exceeds 50%, which may serve as an indication for a blood transfusion. (22)

On animals subjected to critical left ascending coronary artery stenosis, Levy et al. demonstrated that cardiac failure occurs at higher Htc levels. In the presence of limited coronary vascular reserve, the whole body ERO<sub>2</sub> greater than 50% may serve as a valid indicator of myocardial metabolism in anaemia, and may be a useful guide to transfusion therapy. (23) In the study of Orlov et al. on patients subjected to cardiopulmonary bypass (CPB) procedures, the post-transfusion ERO<sub>2</sub> values did not change in patients with normal pre-transfusion ERO<sub>2</sub> values. In patients with elevated pre-transfusion ERO<sub>2</sub> values, a significant reduction in ERO<sub>2</sub> levels was noticed after the transfusion. The authors concluded that incorporating ERO<sub>2</sub> into the decision on transfusion therapy could substantially reduce post-cardiac surgery RBCs transfusions. (24) Seghal et al. tried to determine whether transfusion practices would have been different if an ERO<sub>2</sub> ≥ 45% had been used as a transfusion trigger on patients subjected to CABG procedures. The authors concluded that the use of ERO<sub>2</sub> in transfusion algorithms could reduce allogeneic blood transfusion. (25) In a study by O'Farrell et al. on patients subjected to complex cardiac surgical procedures, a decrease in ERO<sub>2</sub> was noticed two hours after the administration of RBCs if the baseline ERO<sub>2</sub> was elevated. The study suggests that increased ERO<sub>2</sub> may be a better transfusion trigger than decreased Hgb concentrations and that using ERO<sub>2</sub> in everyday clinical practice may reduce unnecessary blood transfusions. In the study, 40% of transfusions would have been avoided if elevated ERO<sub>2</sub> was used as the transfusion trigger instead of Hgb concentrations. (26) On 58 patients admitted to the general ICU, Mung'ayi et al. tried to determine the relation between RBCs transfusions and ERO<sub>2</sub>, using ScVO<sub>2</sub> instead of SVO<sub>2</sub>. The study showed that blood transfusion did not significantly change ERO<sub>2</sub>. Changes in Hgb concentrations did not correlate with ERO<sub>2</sub> changes following blood transfusions. In patients with a higher APACHE score, a statistically significant relation in the change of ERO<sub>2</sub> following blood transfusion was noticed. A subgroup analysis of the patients with pre-transfusion ERO<sub>2</sub> higher than 0.30 yielded a mean reduction in ERO<sub>2</sub> of 0.055. The study results imply that the majority of patients who were transfused, did not physiologically require RBCs, and did not benefit from the increased oxygen content. The

authors' comment on the lack of significant changes in the ERO<sub>2</sub> was that about 60% of the patients had a baseline ERO<sub>2</sub> below 0.30. If ERO<sub>2</sub> of 0.45 had been the transfusion trigger, then only 3 out of 58 patients would have been transfused. (45) Despite the fact that blood transfusions may improve physiologic and even global oxygenation parameters in critically ill patients, blood circulation to individual organs, regional oxygenation and microvascular perfusion may be significantly impaired. (46) This impairment may be expressed particularly when stored RBCs are used. On an animal model, Tsai et al. compared the effects of fresh and stored RBCs on microvascular perfusion and DO<sub>2</sub> after acute isovolemic hemodilution. In comparison to fresh RBCs, stored RBCs reduced microvascular flow and functional capillary density, microvascular oxygen extraction and the tissue oxygen levels. The authors concluded that stored RBCs caused signifi-

cantly malperfused and underoxygenated microvasculature, that was not detectable on the systemic level. (47) Possible future 'physiologic' transfusion triggers will be organ-specific, based on impairment of regional tissue oxygenation. Myocardial tissue oxygenation, estimated by electrocardiographic ST-segment changes, cerebral, abdominal and muscle tissue oxygenation estimated by near infrared spectroscopy or in-vivo optical spectroscopy, regional capnography, neuropsychologic and cognitive function tests and other techniques have already been investigated in a number of transfusion therapy studies. (17, 48, 49, 50)

### CONCLUSION

Well indicated transfusion therapy will improve patients' clinical outcomes and even save lives. The uncritical administration of blood products will impair patients'

primary conditions, cause serious adverse effects and unnecessary financial expenses. Most transfusion guidelines suggest that a combination of Hgb/Htc levels and clinical signs should be used in the decision making process for blood transfusions. The problem with such indications is that clinical evaluation may be misleading in severely ill patients, and Hgb levels that impair oxygen utilisation cannot be easily determined. SVO<sub>2</sub> and ERO<sub>2</sub> are good indicators that show whether a blood transfusion is really necessary. Whenever possible, this is what should be used in everyday clinical practice. In some patients categories in the ICU, ScVO<sub>2</sub> and ERO<sub>2</sub> derived from ScVO<sub>2</sub> could be used as transfusion indicators, provided that clinicians are familiar with the specific differences between ScVO<sub>2</sub> and SVO<sub>2</sub> in normal and critically ill patients.

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