

*Blood is crucial for life. The “holy” equation of oxygen delivery (DO<sub>2</sub>) explains us that blood (in this term: hemoglobin) is one of the three main components of “vitality”. So why should I stop myself of increasing the Hb, and maximise the DO<sub>2</sub> in this way? ..... a lot of things.*

*There are numerous “guidelines” and “recommendations” about the rules of blood transfusion. Almost none of them work well: The blood transfusion is still a matter of “instinct”, even in developed countries. Now we have the “Patient Blood Management”: What is its difference to other “guidelines”?*

*Maybe the clinician should make a calculation/estimation before “each and every” transfusion whether this would lead to an increase in oxygenation, instead of following the guidelines. But is this feasible?*

*Aryeh Shander is the Godfather of “Patient Blood Management”; and Can Ince is “the” researcher of tissue oxygenation.*

**Nüzhet Mert Şentürk**  
Editor

## Blood Transfusions Correct Anemia and Improve Tissue Oxygenation in Surgical and Critically ill Patients

### Can Ince<sup>1,2</sup>

<sup>1</sup>Department of Intensive Care, Erasmus Medical Center, Rotterdam, The Netherlands

<sup>2</sup>Department of Translational Physiology, Academic Medical Center, Amsterdam, The Netherlands

Anemia is a wide spread condition world-wide associated with increased loss of quality of life, organ failure and mortality. Its causes are multifactorial including iron deficiency, heart and renal failure, COPD, malignancies, various infectious and inflammatory diseases, and blood loss such as occurs in trauma and GI bleeding. The underlying reason why anemia is considered to be life threatening and responsible for organ injury and loss of quality of life is due to the limitation in oxygen delivery to the tissues caused by a reduction in the number of oxygen carrying red blood cells. Anemia can result in shortness of breath, renal and cerebral dysfunction, increased cardiac stress, reduced exercise capacity and physiological reserve. If not corrected adequately it can result in organ failure and even in mortality. The World Health Organization for defining anemia is Hb levels being lower than 13 g/dL for men and 12 g/dL for women. Under such a definition it must be considered that a significant portion of hospitalized patients are anemic either pre-existing or being caused by standard clinical procedures. Often unrecognized in-hospital anemia can be a main contributor organ dysfunction in surgical and intensive care patients (1). Such iatrogenic anemia can be caused by hemodilution due to the routine administration of non-oxygen carrying crystalloids solutions, often in large amounts resulting in a reduced number of circulating oxygen carrying red blood cells.

Although the administration of iron and erythropoiesis-stimulating agent can increase levels of hemoglobin they have been associated with incidence of thrombosis and cancer progression, infection, length of stay, and mortality (2). Allogenic blood transfusions therefore is still the treatment of choice to correct anemia. The value of a Hb trigger to initiate transfusion however has been a source of controversy. Historically the indication for transfusion was dictated by the so-called 10-30 rule (10 grams/d: and/or a Ht of 30% rule) defined by the classic paper of Adams and Lundy (3) who proposed this level for preoperative anemic patients. Later Clark et al. (4) proposed the standard use of this trigger for anemic shock patients and much later Stelling and Zauder (5) provided the scientific basis for these numbers by showing in hemorheology experiments that a Ht of 30% provided the peak oxygen delivery value during hemodilution after which the oxygen carrying capacity of blood declines.

The 10-30 rule for transfusion trigger was questioned by the 1999 study of Hebert et al. (6) opening the way to make anemia more acceptable in the ICU. In this study they compared 7 g/dL to 9 g/dL as a threshold for blood transfusions in critically ill patients and found that patients tolerated 7 g/dL better than 9 g/dL. These findings in combination with studies demonstrating possible adverse effects associated with blood transfusions such as TRA-

#### Address for Correspondence:

Can Ince  
E-mail: c.ince@erasmusmc.nl

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## Blood: Fiend or/and Foe? | INCE vs. SHANDER

LI (transfusion related acute lung injury) and immunomodulation have fueled a restrictive approach to blood transfusions opening the door to a more and more permissive attitude to anemia. Studies highlighting adverse effects of blood storage were mainly conducted in large groups of patients randomizing for so-called fresh blood with aged blood. The study by Koch et al. (7) was such an example where studies were carried out in cardiac surgery patients in which they found that aged blood was associated with a higher mortality than fresh blood. The results of these studies still dominate the literature propagating a negative perception about the efficacy of blood transfusions to treat anemia. However these studies have to be critically assessed because their study design and quality of blood are not applicable to blood products and practice used today. A landmark study carried out by van Hilten et al. (8) in the Netherlands in this context identified non-leuco-reduction as being associated with increased incidence of multiorgan dysfunction, infection and length of hospital stay (8) resulting alongside other studies in the immediate initiation of the EU directive for pre-storage leukoreduction to be required for all banked blood. Both the Koch and Hebert studies are examples where blood was used which was not predominately leuco-depleted blood making their relevance to modern blood transfusion practice not relevant. Such details are key in the interpretation of trials being published in the NEJM today which from a mechanistic and design perspective are poorly reviewed and where the sole publishing criteria seems to be having large number of patients. Consequently trial after trial are currently showing no differences between groups causing confusion and misinterpretation in the field especially in relation blood transfusions. For example another US trial published in the NEJM by Steiner et al. (9) almost identical to the Koch study except that they used leuco-reduced blood, could not reproduce the Koch findings instead finding no difference in outcome when aged red blood cells were transfused in cardiac surgery patients (9). Lacroix et al. (10) also could not reproduce the results in cardiac surgery concerning the age of red blood cells. In fact a large European trial by Holst and co-workers could not even reproduce the earlier 1999 findings by Hebert et al. (6) whereby no differences were found between leaving the take home messages of such large RCT relating to blood transfusions being published in the NEJM in complete disarray.

In contrast however the last decade has seen a large number of trials showing a benefit of choosing a more liberal approach to transfusion over a restrictive approach. Indeed the Sepsis Occurrence in Acutely Ill Patients (SOAP) multicenter trial had shown a better 30 day survival in intensive care patients who had received blood in comparison to those that had not. Similarly Sakr et al. (12) in large (>5000 patient) study showed that critical ill patients who had higher Hb values and/or had had blood transfusions had a lower risk of death in septic patients after non cardiac surgery and especially in elderly patients. Similar findings were also reported in a large Korean study on septic patients by Park et al. (13) who showed better outcome in septic patients who had received blood transfusions. In parallel

similar results have been found in other groups of surgical patients including cardiac surgery and cancer patients showing the benefit of transfusing blood (14, 15). All these findings underscore the general conclusion that avoiding anemia by targeting a conservative (eg 9 g/dL) transfusion trigger is with the current blood received from modern blood banks, a safe procedure of benefit especially for the elderly patient at risk. Such findings indicate that re-evaluation of the transfusion triggers are warranted based on more insight into the physiological basis on how blood transfusion effect tissue perfusion and oxygenation.

Experimental investigations we and others have carried out over the last decade have underscored that fluid resuscitation is ineffective in correcting tissue hypoxia associated with states of shock. This is especially the case for the vulnerable kidney where tissue hypoxia due to microcirculatory lack of red blood cell availability. In several studies in hemorrhagic shock we showed that while correction of systemic hemodynamic variables were accomplished by fluid administration no such parallel improvement in renal microcirculatory oxygenation was found and hyperlactemia and low creatinine clearance persistence (16). Only when blood transfusion was administered was there an improvement in renal tissue oxygenation and a commutant lowering of lactate and an improvement in renal function (17). A recent study we performed in septic rats also showed that while fluid resuscitation only momentarily was effective in improving renal tissue oxygenation and did not resolve renal failure, blood transfusions improved renal tissue oxygenation which persisted in time, and was associated with a recovery in renal function as demonstrated by creatinine clearance and the ratio of renal oxygen consumed per sodium reabsorbed (18). From these and other studies it is clear that the only effective therapy to correct tissue hypoxia is the administration of oxygen carrying red blood cells. Although hemoglobin based oxygen carriers are equally effective in improving tissue oxygenation (19) these are not yet ready for clinical introduction.

We and other have demonstrated that similar improvements in tissue perfusion and oxygenation also occur in patients following blood transfusions. In a clinical study using hand held microscope for measurement of sublingual microcirculation in cardiac surgery patients, we showed that anemia was associated with a low functional capillary density which increased in value following blood transfusion in the sublingual capillary density in cardiac surgery patients (20). In a parallel study in anemic hematologic patients we demonstrated that such a blood transfusion was associated in a parallel improvement in sublingual microcirculatory oxygen availability using sublingual near infra red spectroscopy (21). These studies showed that anemia is associated with microcirculatory reduction in RBC availability resulting in tissue hypoxia. In addition, the studies cited above show that anemia results in organ injury and that blood transfusion and not fluids are the only effective therapy for improving tissue oxygen availability and thereby organ function. These observations lead to the conclusion that based on the current good

# Blood: Fiend or/and Foe? | INCE vs. SHANDER

quality of banked blood and current blood transfusion guidelines still based on outdated literature, requires a re-evaluation of triggers for blood transfusion is needed where a more liberal approach should be considered especially for the elderly patients (22).

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