



POINT OF VIEW

Optimal hemoglobin levels in the neurocritical patient: Are we there yet?



Niveles óptimos de hemoglobina en el paciente neurocrítico: ¿hemos llegado ya?

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"The superficial changes
The deep also changes
The way of thinking changes
Everything in this world changes"

Julio Numhauser

Introduction

Oxygen (O₂) is essential for cell survival, hence, its levels and delivery to tissues are of critical importance.¹ Oxygen is transported in the bloodstream driven by cardiac output in two ways: a) dissolved (5%) and b) bound to its carrier protein (95%), hemoglobin (Hb). On the other hand, O₂ transfer to the tissues depends on saturation and the O₂/Hb dissociation curve.¹

Anemia, as defined by the World Health Organization (WHO), is highly prevalent in critically ill patients, with an estimated 60% presenting with Hb levels < 12 g/dl at admission.² The etiology of anemia is multifactorial, ranging from objectifiable blood losses to the inherent physiology of the erythrocyte, which undergoes a series of changes in its structure, metabolism and production that predispose to the development of anemia³ (Fig. 1).

Transfusion of whole blood or packed red blood cells is one of the most classic tools when seeking to optimize O₂ transport (TO₂). However, there is still disagreement about when, how much and what the goals of transfusion should be, especially when considering the risks and benefits of this practice.^{4,5}

Hemoglobin and transfusion in the critically ill patient

Reviewing and knowing the past allows us to better understand the present and build the future. In this context, Shoemaker marked the starting point by noting that mortality in high-risk postoperative patients increased when

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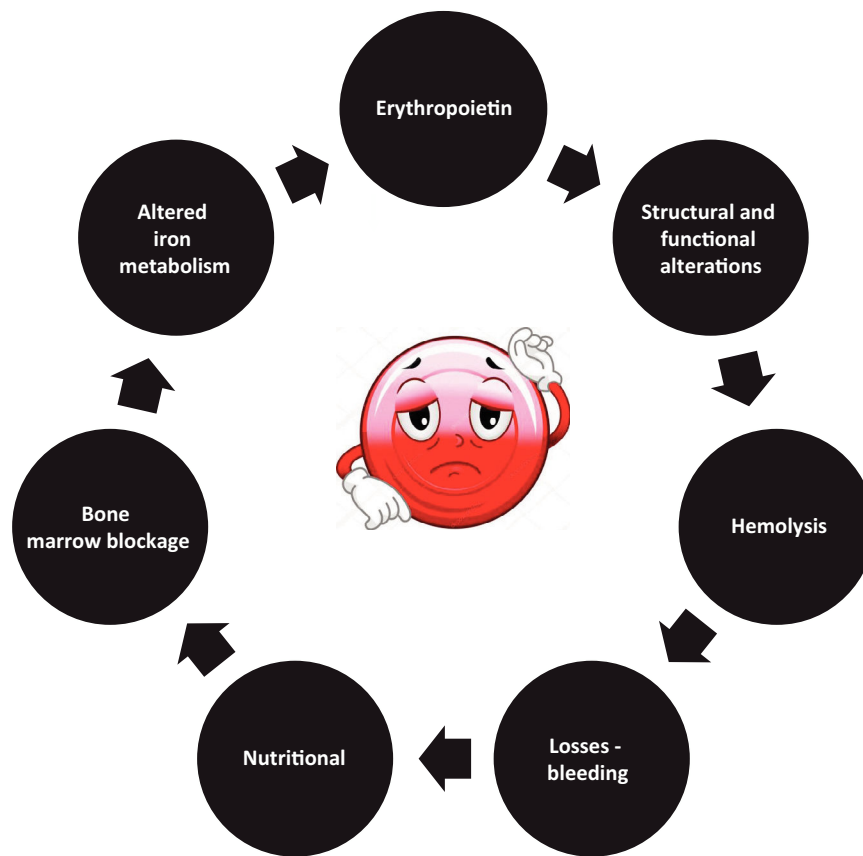


Figure 1 Pathophysiology of anemia in the critically ill patient.

the hematocrit levels were below 32%, especially when the cardiovascular reserves were compromised.⁶ In these individuals, erythrocyte transfusion was significantly associated with improved O_2 transport and consumption (VO_2).⁶ Subsequently, the concepts of tissue hypoxia and oxygen debt resurfaced as a consequence of the analysis of hemodynamic variables in these patients.⁷ As a result, various resuscitation strategies based on optimizing TO_2 and VO_2 were developed, including the transfusion of packed red blood cells with Hb levels > 10 g/dL.⁸ This strategy was abandoned after later studies showed more risks than benefits.⁹

In 1998, the results of the TRICC, a Canadian multicenter, prospective and controlled trial, were published. This study included critically ill patients with Hb levels < 9 g/dL in the first 72 h of admission, with the transfusion of packed red blood cells when Hb < 7 g/dL (restrictive group) versus another group (liberal group) that was transfused when Hb < 10 g/dL.¹⁰ Lower mortality was observed in the restrictive group in individuals < 55 years of age ($p = 0.02$) and when the APACHE II score was < 20 ($p = 0.03$), with the exception of those subjects with impaired cardiac function ($p = 0.69$)¹⁰ – with similar data being reproduced in the TRISS study.¹¹

One of the fundamental aspects to be highlighted in both of the above studies is that patients with acute brain injury were not represented, which is why this population subgroup is excluded from the restrictive transfusion strategy in the recommendations of the European Society of Intensive Care Medicine.¹²

Hemoglobin and transfusion in acute brain injury

Physiological rationale for maintaining adequate hemoglobin levels

Under physiological conditions, the brain consumes 20–25% of the body's total O_2 and glucose, due to its incessant activity. In the context of injury, the brain, lacking reserves of energy substrates, becomes vulnerable to energy deficits and increases its demand.¹³ In this sense, any alteration in the O_2 supply chain (including Hb) could cause cerebral tissue hypoxia – one of the detrimental mechanisms of secondary brain damage.¹⁴

Regarding the pathophysiology of Hb-related tissue hypoxia, the following causes stand out: (a) anemic: this occurs when the Hb levels are insufficient to transport O_2 consistent with the cellular demands (each gram of Hb transports 1.34 mL of O_2); (b) high affinity: triggered by physiological imbalances that shift the O_2 dissociation curve to the left, making cellular delivery difficult (hypothermia, hypocapnia, metabolic alkalosis, 2,3-diphosphoglycerate deficiency in transfusions of blood that has been stored for long periods); and (c) poor quality Hb, characterized by an inability to transport O_2 (carboxyhemoglobin, methemoglobin).^{14,15}

Table 1 Characteristics of the HEMOTION and TRAIN studies.

	HEMOTION ³⁰	TRAIN ³¹
Design	Multicenter, prospective, randomized and controlled	Multicenter, prospective, randomized and controlled. Phase 3. Open-label
Population	TBI moderate, severe (GCS: 3–12) and Hb ≤ 10 g/dl	TBI; SAH; ICH (GCS ≤ 13) and Hb ≤ 9 g/dl
Number of patients	736	820
Randomization	Liberal group (n = 369) ● Transfusion = Hb ≤ 10 g/dl Restrictive group (n = 367) ● Transfusion = Hb ≤ 7 g/dl	Liberal group (n = 397) ● Transfusion = Hb < 9 g/dl Restrictive group (n = 423) ● Transfusion = Hb < 7 g/dl
Mean Hb level (g/dl) at randomization	9.1 in both groups	8.5 in both groups
Average admission-randomization time	55 h liberal group 56 h restrictive group	3 days
Intervention	Leukocyte-depleted packed red cells within 3 h of randomization	Erythrocyte concentration at randomization
ICP monitoring (%)	56.1 liberal group vs. 63.5 restrictive group	Liberal group 70.6 vs. 69.1 restrictive group
Cerebral oxygenation monitoring (%)	4.6 liberal group vs. 6.3 restrictive group	Not specified
Primary outcomes	GOS-E 180 days post-admission. Unfavorable results 68.4% (liberal) vs. 73.5% (restrictive) Adjusted absolute difference 5.4% (95%CI: - 2.9–13.7)a Findings remain consistent in the subgroups analysis	GOS-E 180 days post-admission Unfavorable results 62.6% (liberal) vs. 72.6% (restrictive) Adjusted RR 0.86 (95%CI: 0.79–0.9; p = 0.002) Consistent findings in the subgroups analysis
Secondary outcomes	No significant differences in mortality in the ICU (17.1 vs. 15.3%), hospital (23 vs. 21.5%), or at 6 months (26.8 vs. 26.3%) No significant difference in functional independence or other functional outcome measure	Cerebral ischemic events (at least 1) 8.8% (liberal) vs. 13.5% (restrictive) RR (liberal) 0.65 (95%CI: 0.44–0.97), suggesting lower risk
Limitations	Absence of double-blinding No data on cerebral tissue hypoxia are provided aSample size calculated to detect 10% difference between groups with unfavorable results Although 5.4% was the difference in favor of the liberal strategy, it is clinically significant Differences in baseline characteristics between groups. Adjusting for differences, there may be an absolute reduction in the risk of unfavorable outcomes of 13.7% for the liberal group Statistical analysis with a frequentist approach Absence of Bayesian analysis	Absence of double-blinding Heterogeneous population with different histories and pathophysiology No data referred to transfusion prior to randomization recorded Limited sample power for detecting differences between subgroups Non-conventional definition of unfavorable outcomes GOS-E dichotomization Double adjustment of sample size during study conduction No data on withdrawal of support or non-resuscitation instructions Absence of Bayesian analysis

GCS: Glasgow Coma Scale; GOS-E: Glasgow Outcome Scale-Extended; Hb: hemoglobin; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; CI: confidence interval; ICP: intracranial pressure; RR: relative risk; TBI: traumatic brain injury; ICU: intensive care unit.

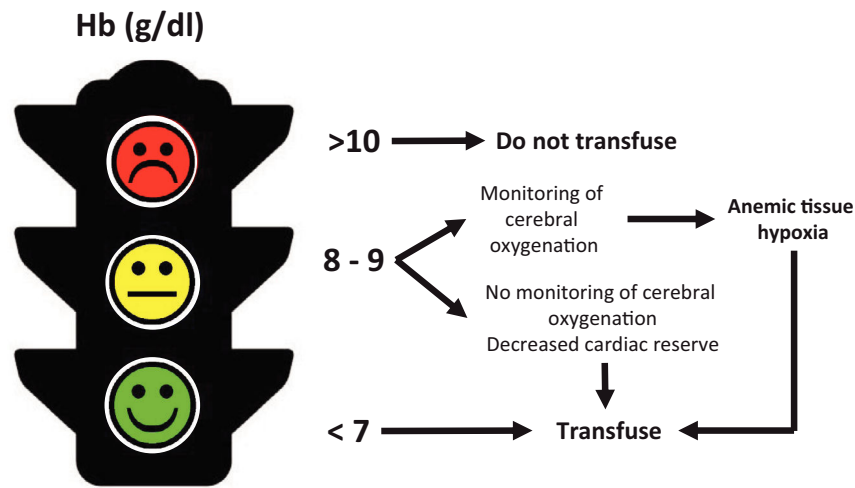


Figure 2 Authors' recommendations according to current evidence.

Preliminary clinical evidence: when uncertainty is the only certainty

The optimal Hb level in acute brain injury is not clear. Both the presence of anemia and the transfusion procedure have been associated with increased complications, mortality and poorer functional outcomes.^{16–20}

The most robust clinical evidence highlights the limitations and methodological problems of the studies analyzed and concludes that the available information is uncertain, confusing and inconclusive regarding the effect of the liberal versus the restrictive transfusion strategy on mortality and the functional outcomes.^{21–26}

Recent trials: Is there light at the end of the tunnel?

The answer is "*train in motion*", an allegorical phrase referring to TRAIN and HEMOTION, two recent studies that have attempted to clarify some of the existing doubts.^{27,28} The main characteristics, results, strengths and weaknesses of these two studies are summarized in Table 1. The conclusions are similar and point to a "*paradigm shift*", establishing that the liberal strategy aimed at maintaining Hb > 9 g/dl is associated with better functional outcomes.^{27,28}

Transfusion target: magic number?

Transfusion carries benefits and risks that should be carefully weighed. Transfusion should be a cost-effective and well-considered intervention; however, the use of Hb concentration alone as a guide to indicate transfusion is inadequate and even dangerous, as it may limit or lead to unnecessary transfusions. When to transfuse remains an empirical and arbitrary decision. How to monitor transfusion effectiveness is a topic that is rarely discussed (Fig. 2).

Physiological studies using positron emission tomography (PET) have shown that transfusion with Hb levels < 10 g/dl increases arterial O₂ content and decreases cellu-

lar O₂ extraction, while cerebral blood flow and metabolism remain unchanged.^{29,30}

Transfusion of packed red blood cells (not stored for prolonged periods) improves invasive cerebral oxygenation (PtiO₂) only in the presence of tissue hypoxia^{31,32}; however, its effects on cerebral metabolism are variable or null.^{33–35}

Non-invasive monitoring of cerebral oxygenation with near-infrared spectroscopy (NIRS) has not yet been able to detect an effect of red blood cell transfusion.^{36,37}

Finally, how do we monitor the quality of the Hb delivered? Undoubtedly, it is not just "a number to be achieved", so we should rethink this aspect and systematically include the assessment of basic physiological variables that allow us to determine whether or not the patient's Hb and the Hb delivered are suitable for delivering oxygen to the tissues.

Conclusion and authors' opinion

Anemia is a prevalent secondary adverse factor associated with acute brain injury. Its deleterious role lies in the fact that it compromises cerebral TO₂, which may induce tissue hypoxia. The transfusion procedure (with leukocyte-depleted fresh red blood cells) requires a prior risk-benefit assessment. Based on recent evidence, it seems prudent to maintain the Hb levels at around 10 g/dl. However, when we transfuse, we must demonstrate its efficacy, and this is not done simply by analyzing "a number".

We believe it essential to maintain basic physiologic variables that ensure adequate oxygen transport and delivery to tissues, especially in settings where advanced neuromonitoring resources are lacking or limited. When both invasive and non-invasive techniques are available to assess cerebral oxygenation, we believe it is necessary to use them as an additional, but not the only, element in determining the transfusion strategy.

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