



## POINT OF VIEW

## Trigger transfusion in severe traumatic brain injury<sup>☆</sup>



### Trigger transfusional en el paciente con traumatismo cráneo-encefálico grave

J.J. Egea-Guerrero<sup>a,\*</sup>, I. García-Sáez<sup>b</sup>, M. Quintana-Díaz<sup>c</sup>

<sup>a</sup> Unidad de Gestión Clínica de Medicina Intensiva, Hospital Universitario Virgen del Rocío, Sevilla, IBIS/CSIC/Universidad de Sevilla, Sevilla, Spain

<sup>b</sup> Servicio de Medicina Intensiva, Hospital Universitario de Donostia, San Sebastián, Guipúzcoa, Spain

<sup>c</sup> Servicio de Medicina Intensiva, Hospital Universitario de La Paz, Idipaz, Madrid, Spain

Received 8 February 2021; accepted 21 March 2021

Available online 21 December 2021

Traditionally, in the management of patients with severe traumatic brain injury (STBI), recommendations focus on keeping intracranial pressure under control. It is surprising to see that there are no specific indications on the management of anemia.<sup>1</sup> From the pathophysiological standpoint, disregarding the levels of hemoglobin (Hb) probably means reaching proper levels of cerebral perfusion pressure, but with a poor quality in tissue oxygenation (Fig. 1). It is unquestionable that, in this context, our clinical practice guidelines should follow the European recommendations on “Patient Blood Management” to minimize blood losses, optimize homeostasis and, therefore, stop, in a multidisciplinary way, the patient from becoming anemic by avoiding unnecessary transfusions.<sup>2</sup>

However, the main problem we face when assessing the medical literature available on STBIs is the heterogeneity of

the studies published that often mix patients with moderate TBIs with authors that use different transfusion thresholds based on the hematocrit or on the levels of hemoglobin (Hb). Also, we should mention that most observational studies published to this date analyze the impact of anemia or the effects of red blood cell transfusion on the prognosis of traumatic brain injury.<sup>3–7</sup>

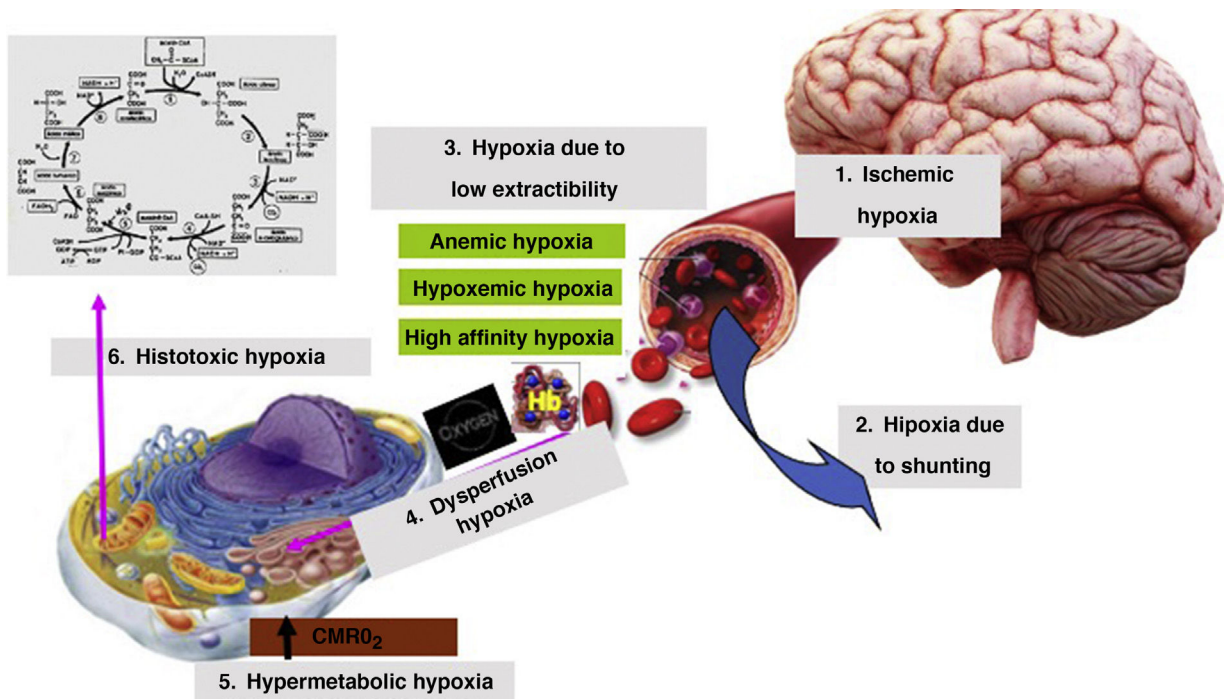
Specifically, certain working groups state that in TBIs, anemia is associated with higher rates of complications and mortality.<sup>3,4</sup> Other studies, however, propose a different hypothesis, claiming that Hb levels >9 g/dL are associated with a better functional prognosis.<sup>5</sup>

Despite of this, we should mention that the solution is not transfusing this subpopulation of neurocritical patients systematically. As a matter of fact, some authors say that the transfusion of red blood cell concentrates is associated with a poor long-term prognosis.<sup>6–8</sup> In this sense, Desjardins et al. working group conducted a systematic review on this matter, but could not draw any definitive conclusions because the study was underpowered due to the lack of homogeneity in the protocols analyzed.<sup>9</sup> However, they claim that blood transfusion was associated with a worse functional prognosis during the management of both moderate and severe TBIs. Nonetheless, a recent retrospective trial identified

<sup>☆</sup> Please cite this article as: Egea-Guerrero JJ, García-Sáez I, Quintana-Díaz M. Trigger transfusional en el paciente con traumatismo cráneo-encefálico grave. *Med Intensiva*. 2022;46:157–160.

\* Corresponding author.

E-mail address: [juanj.egea.sspa@juntadeandalucia.es](mailto:juanj.egea.sspa@juntadeandalucia.es) (J.J. Egea-Guerrero).



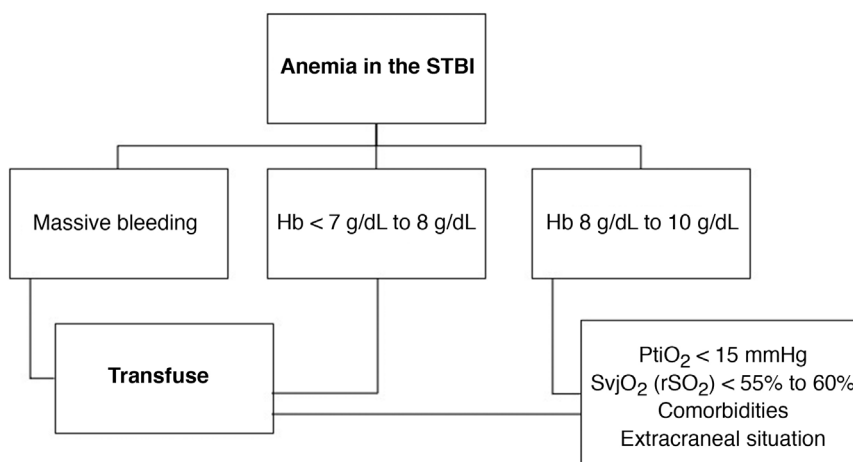
**Figure 1** Possible causes of tissue hypoxia.  $CMRO_2$ , cerebral metabolic rate of oxygen; Hb, hemoglobin.

that a restrictive transfusion approach can be a safe and cost-effective practice.<sup>10</sup>

Despite the interest associated with transfusion strategies during the management of STBI, the number of clinical trials available to this date is still scarce. We should mention the *post-hoc* analysis conducted by McIntyre et al. back in 2006. In this study, the authors found no morbidity or mortality differences in the transfusion restrictive strategy (7 g/dL to 9 g/dL) compared to the more liberal one (Hb, 10 g/dL to 12 g/dL).<sup>11</sup> However, in spite of design limitations, it is striking to see that the recruitment of patients did not include each patients' specific level of consciousness according to the Glasgow Coma Score (GCS). Also, when the characteristics of the population were analyzed, there were barely any significant personal health records between both arms. Afterwards, the clinical trial conducted by Robertson et al. was published. This trial was approached from 2 different perspectives in terms of both the transfusion threshold and the possible utility of erythropoietin.<sup>12</sup> Despite the early expectations this trial generated, we can identify several limiting factors. In the first place, the patients underwent a change of protocol due to the administration of erythropoietin, which extended the duration of the trial for another 6 years. Secondly, the patients of each group had Hb levels above the target values. Thirdly, the sample size per group was relatively small. In their results, the authors did not find any differences in terms of survival or prognosis. We should mention that the liberal transfusion group developed more infections, thromboembolic events, and respiratory distress syndrome. The TRAHT pilot study has recently been published. It reveals that the clinical design of the study is feasible. It also anticipates that patients included in the liberal transfusion group had better recoveries and lower

mortality rates. The authors state that optimizing brain oxygenation can be a key factor in their results.<sup>13</sup> In conclusion, we will have to wait for the definitive results not only from this clinical trial but also from the TRAIN and HEMOTION trials before having more evidence available on this regard. However, we should not forget that clinical trials are always based on ideal scenarios since complex patients with comorbidities and previous treatments are not usually recruited in these studies.

At the same time, it is obvious that our management of patients with STBI who may require transfusions cannot be based on a simple figure appearing on the lab result record sheet, especially if there are specialized units with multimodal neuromonitoring systems available capable of providing reliable information from different pathophysiological angles on the actual situation of the brain. In this sense, we found several trials that analyzed the capacity of  $PtiO_2$  to recognize situations of anemia and brain hypoxia that also proved the effects of transfusion on brain oxygenation.<sup>14,15</sup> Also based on the study conducted by Robertson et al. we found a subanalysis oriented to the information obtained from the neuromonitoring of patients with STBI.<sup>12,16</sup> The authors identified that the restrictive strategy group developed more episodes of brain hypoxia when the sensor was placed in healthy areas of the brain. However, no differences were found in the mortality rate described between the restrictive strategy group and the liberal strategy group. Afterwards, Leal-Naval et al. working group conducted an interesting clinical trial in which the transfusion threshold was guided by the Hb levels and the  $rSO_2$ . The authors proved that there was a lower need for transfusions when both triggers were used without identifying any differences between both groups.<sup>17</sup>



**Figure 2** Assessment scheme on the transfusion need during the management of severe traumatic brain injury (STBI). dL, deciliter; g, gram; Hb, hemoglobin; PtiO<sub>2</sub>, brain tissue oxygen pressure; rSO<sub>2</sub>, regional cerebral oxygen saturation.

To this point, we can say that there is not a single clear piece of evidence that tells us when we should transfuse patients with STBI with Hb levels between 8 g/dL and 10 g/dL. The decision-making process to this point is still controversial, and open to discussion. It is obvious that more information is required when it comes to establishing the transfusion indication. In these cases, and taking the aforementioned considerations into account our opinion is that Fig. 2 is a good guideline on how to proceed on this regard. This way we would be profiting from all the information obtained through advanced neuromonitoring when facing this transfusion uncertainty, and once other causes of tissue hypoxia have been ruled out (Fig. 1). Still, we know that not all centers can systematically monitor ICP, PtiO<sub>2</sub>, and rSO<sub>2</sub>.<sup>16,18</sup> Finally, we should be taking into account the patient’s past medical history, as well as the presence of other bleeding traumatic injuries associated with STBI.

In conclusion, we should mention the need to widen our knowledge in this area that deals with the management of patients who sustain STBIs to establish transfusion indications through objective, safe, and efficient criteria.

### Conflicts of interest

None reported

### References

1. Carney N, Totten AM, O’Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*. 2017;80(1):6–15.
2. European Commission: Supporting Patient Blood Management (PBM) in the EU. A Practical implementation guide for hospitals. Luxembourg: Publications Office of the European Union; 2017, <http://dx.doi.org/10.2818/533179> [Accessed February 2021].
3. Sekhon MS, McLean N, Henderson WR, Chittock DR, Griesdale DE. Association of hemoglobin concentration and mortality in critically ill patients with severe traumatic brain injury. *Crit Care*. 2012;16:R128.
4. Carlson AP, Schermer CR, Lu SW. Retrospective evaluation of anemia and transfusion in traumatic brain injury. *J Trauma*. 2006;61:567–71.

5. Griesdale DE, Sekhon MS, Menon DK, Lavinio A, Donnelly J, Robba C, et al. Hemoglobin area and time index above 90 g/L are associated with improved 6-month functional outcomes in patients with severe traumatic brain injury. *Neurocrit Care*. 2015;23:78–84.
6. Warner MA, O’Keeffe T, Bhavsar P, Shringer R, Moore C, Harper C, et al. Transfusions and long-term functional outcomes in traumatic brain injury. *J Neurosurg*. 2010;113:539–46.
7. Elterman J, Brasel K, Brown S, Bulger E, Christenson J, Kerby JD, et al. Transfusion of red blood cells in patients with a prehospital Glasgow Coma Scale score of 8 or less and no evidence of shock is associated with worse outcomes. *J Trauma Acute Care Surg*. 2013;75:8–14.
8. Leal-Noval SR, Muñoz-Serrano Á, Arellano-Orden V, Cayuela A, Muñoz-Gómez M, Recio A, et al. Effects of red blood cell transfusion on long-term disability of patients with traumatic brain injury. *Neurocrit Care*. 2016;24:371–80.
9. Desjardins P, Turgeon AF, Tremblay MH, Lauzier F, Zarychanski R, Boutin A, et al. Hemoglobin levels and transfusions in neurocritically ill patients: a systematic review of comparative studies. *Crit Care*. 2012;16:R54.
10. Ngwenya LB, Suen CG, Tarapore PE, Manley GT, Huang MC. Safety and cost efficiency of a restrictive transfusion protocol in patients with traumatic brain injury. *J Neurosurg*. 2018;128:1530–7.
11. McIntyre LA, Fergusson DA, Hutchison JS, Pagliarello G, Marshall JC, Yetisir E, et al. Effect of a liberal versus restrictive transfusion strategy on mortality in patients with moderate to severe head injury. *Neurocrit Care*. 2006;5:4–9.
12. Robertson CS, Hannay HJ, Yamal JM, Gopinath S, Goodman JC, Tillee BC, et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial. *JAMA*. 2014;312:36–47.
13. Gobatto ALN, Link MA, Solla DJ, Bassi E, Tierno PF, Paiva W, et al. Transfusion requirements after head trauma: a randomized feasibility controlled trial. *Crit Care*. 2019;23:89.
14. Yamal JM, Hannay HJ, Gopinath S, Aisiku IP, Benoit JS, Robertson CS. Glasgow outcome scale measures and impact on analysis and results of a randomized clinical trial of severe traumatic brain injury. *J Neurotrauma*. 2019;36:2484–92.
15. Leal-Noval SR, Rincón-Ferrari MD, Marín-Niebla A, Cayuela A, Arellano-Orden V, Marín-Caballeros A, et al. Transfusion of erythrocyte concentrates produces a variable increment on cerebral oxygenation in patients with severe traumatic

- brain injury: a preliminary study. *Intensive Care Med.* 2006;32:1733-40.
16. Yamal JM, Rubin ML, Benoit JS, Tilley BC, Gopinath S, Hannay HJ, et al. Effect of hemoglobin transfusion threshold on cerebral hemodynamics and oxygenation. *J Neurotrauma.* 2015;32:1239-45.
  17. Leal-Noval SR, Arellano-Orden V, Muñoz-Gómez M, Cayuela A, Marín-Caballos A, Rincón-Ferrari MD, et al. Red blood cell transfusion guided by near infrared spectroscopy in neurocritically ill patients with moderate or severe anemia: a randomized, controlled trial. *J Neurotrauma.* 2017;34:2553-9.
  18. Llopart-Pou JA, Barea-Mendoza JA, Sánchez-Casado M, González-Robledo J, Mayor-García DM, Montserrat-Ortiz N, et al. Neuromonitoring in the severe traumatic brain injury. Spanish Trauma ICU Registry (RETRAUCI). *Neurocirugía (Astur).* 2020;31:1-6.