A neuro-centric perspective on the correlation between hemoglobin levels and neurological outcomes in traumatic brain injury patients, with literature review

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Introduction:

There has been a general consensus regarding maintaining a transfusion threshold of 7g/dL for the treatment of anemia. This level has been chosen because it is known that hemoglobin levels below 5 or 6g/dL are likely to induce tissue hypoxia. However, one main goal of neurocritical care is to prevent secondary neurological injury, of which hypoxia can be a preventable etiology. The incidence of anemia after severe traumatic brain injury (TBI) has been found to be as high as 88%. Thus, functional outcomes could in theory be improved with higher hemoglobin thresholds (10 g/dL). We present a review of hemoglobin transfusion thresholds and neurological outcomes to serve as a preliminary stepping stone to future research in this area.
Methods:

We reviewed reports that investigated transfusions of packed RBC (pRBC) in neurotrauma patients. We included adult patients (18yo and older) with severe TBI (GCS < 8), and we only included studies which looked at neurological outcomes and compared two transfusion thresholds based on hemoglobin level. Thirty-five studies met our criteria. We organized the data based on hemoglobin cutoffs of 7, 8, 9, and 10g/dL. Combined R values were calculated using R 3.5.1, using an alpha level of 0.05. Meta-analyses were performed with combined p-values.
**Results:**

We found that all ascending combinations of Hg levels led to combined P values of < 0.01. We conclude that regardless of the transfusion level provided, complications such as mortality, hospital days, and pneumonia rates do not show considerable differences across various ranges of hemoglobin transfusion levels above 7g/dL. Given the lack of conclusive differences in these rates across the 35 studies examined, we believe a stronger emphasis should be placed on neurological functional outcome rather than overall outcomes.

There is little controversy at this time regarding transfusion thresholds in the non-neurologically injured patient, in whom the risk/benefit ratio favors a threshold of 7g/dL, while thresholds in the
8-10g/dL range have been shown to have more adverse outcomes (typically due to transfusion reactions)\textsuperscript{46}, and thresholds between 5-7g/dL have similar outcomes\textsuperscript{47}. However, neurocritically ill patients, with their unique needs, are quite underrepresented in the vast majority of populations studied, thus prompting controversy.

It is well known that nervous tissue requires a strict amount of oxygen, and physiologic autoregulatory mechanisms are well established to monitor and control oxygen delivery to nervous tissue. Autoregulatory mechanisms fail during injury to the nervous system. Anemic patients with an uninjured brain can tolerate low hemoglobin levels due largely in part to the autoregulatory mechanisms present to increase cerebral blood flow and ultimately oxygen delivery to the
brain. In patients with any brain injury, autoregulatory mechanisms are impaired, and these patients will have lowered cerebral blood flow, and low hemoglobin levels have been correlated with increased neurological morbidity and increased brain ischemia[48, 49].

In physiology, the hemoglobin level that maximizes the amount of oxygen delivered per unit brain tissue is around 10 g/dL, where blood rheological properties allow for more oxygen delivered per cardiac cycle per unit brain tissue, measured in 100g brain tissue[19]. Below this hemoglobin level, the oxygen content of the blood decreases, whereas above his level blood viscosity limits blood flow and thus oxygen delivery. While it has been shown that the transfusion of RBCs increases brain tissue oxygenation in patients with TBI[51], the
neuroprotective implication of this is poorly understood. More so, attempts to correlate the improved hemoglobin levels with improved outcomes has led to the opposite findings. Transfusions seem to consistently correlate with poorer patient outcomes, typically measured as hospital stay, ICU stay, ventilator days, organ system failures, mortality, and other similar metrics. However, attempts to correlate transfusions and hemoglobin levels in TBI with specifically neurological outcomes are lacking, hence prompting the review included in our paper.
Discussion:

The results of our review demonstrate the two key points that intrigued us into writing this paper. The first is that transfusions at any level above 7g/dL are associated with poorer overall outcomes for TBI patients. The second is that very few of the studies actually looked at functional neurological outcomes. A few of these were prospective randomized trials, so the most likely confounding factor in these results is that patients who needed transfusions were more likely to have poorer outcomes inherently because they were sicker to begin with. The bottom line is that better studies are needed in TBI patients to assess whether a higher hemoglobin transfusion threshold actually benefits neurological recovery.
Summary Points:

- Physiologically, the ideal hemoglobin level to maximize oxygen delivery to brain tissue is 10g/dL
- Clinically, red blood cell transfusions above 7g/dL have been correlated with worse outcomes due to transfusion reactions
- Few studies (especially high quality studies) exist to show whether maintaining a threshold higher than 7g/dL actually improves neurological outcomes, and we need these studies
Works Cited:


