Physiopathology of anemia and transfusion thresholds in isolated head injury

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BACKGROUND: Blood transfusion strategies among patients with critical illness are currently supported by the Transfusion Restriction In Critical Care trial findings. This study found that a restrictive transfusion protocol (i.e., transfusion at hemoglobin levels of \( \leq 7 \) g/dL) to maintain blood hemoglobin concentration between 7 g/dL and 9 g/dL) was not associated with any significant differences in mortality when compared maintaining transfusion targets between 10 g/dL and 12 g/dL. The subgroup analysis on patients with head injury had similar findings, but neurological outcomes were not able to be assessed. As such, there is little evidence for generalizing lower hemoglobin concentration triggers for transfusion to patients with head injury, especially during their acute phase.

Although the implementation and extrapolation of the Transfusion Restriction In Critical Care trial has been widely observed throughout critical care units, there has been a varied approach to blood transfusion in patients with acute head injury. This mainly depends on individual clinician opinions and the authority-delegated lead clinician while the patient is on the intensive care unit. Blood transfusions have been associated with increased mortality and morbidity, impaired oxygen delivery for the use of old blood, immune reactions, bloodstream infections, and transfusion errors. Ischemia and vasoconstriction are the result of impaired nitric oxide metabolism or tissue hypoxia from 2,3-diphosphoglycerate depletion, the latter impairing hemoglobin oxygen binding. While blood transfusions have shown to be associated with poor neurological outcome following head injury, confounding factors include concomitant injuries for patients with multiple injuries or the need for neurosurgical intervention. Hypoxia and hypotension however are markers of poor outcome in the acute management after head injury evidenced by the fact that a common histologic finding among patients who die of head injury is ischemic neuronal damage, which may explain the raised lactate-oxygen index in the jugular venous blood of many patients.

A retrospective review found that anemia for patients with head injury significantly increased morbidity and mortality. Moreover, several animal studies have shown that maintenance of a high transfusion threshold is associated with a significant increase in survival and better neurological outcomes. Induced anemia after head injury leads to cerebral ischemia in cases where cerebral autoregulation is impaired and in the ipsilateral side to cerebral contusions. Studies have shown that “secondary injury” occurs at a hematocrit level of 20%, consistent with blood hemoglobin concentrations between 6 g/dL and 7 g/dL, which is close to current transfusion thresholds. Blood transfusions have been shown to increase brain tissue oxygenation (\( \text{PTi}_O_2 \)) in a significant number of patients with head injury, independent of their cerebral perfusion pressure (CPP). These changes are more evident among patients with baseline low \( \text{PTi}_O_2 \) suggesting that patients with anemia and low \( \text{PTi}_O_2 \) may be those who benefit the most from blood transfusions.

The previously mentioned disparity between a general approach to anemia in the patient with critical illness and pathophysiologic events specifically in neurotrauma patients...
Monetary (with microdialysis or PTiO2 monitoring) and neuro-
logical outcomes in neurotrauma patients. However, critical
levels of PTiO2 of 15 mm Hg have been shown to be correlated
with increased incidence of stroke and mortality. Cerebral is-
chemia is associated with an elevated lactate-pyruvate ratio and
raised tissue concentrations of glutamate and glycerol. These
observations suggest that transfusion thresholds for patients
with head injury may be better determined by physiologic
markers of cerebral ischemia and hypoperfusion rather than as-
suming a common threshold of transfusion.

This study reviews the physiopathologic components of
cerebral microcirculation with their diagnostic or therapeutic
value and their response to blood transfusions during the clinical
management of acute head injury. It also demonstrates the exis-
ting reasons for the lack of consensus regarding the optimal
hemoglobin level in this population.

MATERIALS AND METHODS

Search Strategy
An OVID literature search was used using PubMed
(between 1960 and November 1, 2011), MEDLINE (between
1960 and November 1, 2011), EMBASE (between 1980 and
November 1, 2011), Cochrane Reviews (from 1960 and No-

vember 1, 2011), and WEB of Science (between 1960 and
November 1, 2011) databases for anemia and blood transfu-
sion in head injury. In addition, a MeSH search was used, using
the following key words as headings: traumatic brain injury
OR head injury OR head trauma AND blood transfusion OR
hemoglobin levels OR anemia. The combination of searches
reduced the PubMed and MEDLINE retrieved articles from
136,754 to 74 and reduced EMBASE retrieved articles from
7,446 to 6, while the Web of Science identified 20 articles. The
Cochrane database located 47 from 6,967 articles, using for
searches involving head injury or anemia or traumatic brain
injury of transfusion in title, abstract, or keyword searches;
however, none of these studies were specifically focused on
blood transfusion and neurological outcomes in head injury.
All searches were filtered selecting only for articles using either
human adult populations (>18 years) or animal experimental
models and written in the English language. Review articles,
case reports, and clinical studies were all included.

Selection of Studies
The following conditions lead to the review of 23 studies:

- Studies using neurological outcome as the main end point
  when comparing transfusion thresholds
- Studies using cerebral oximetry as main end point when
  comparing transfusion thresholds
  and
- Studies in which the main variables where at least two
different levels of hemoglobin
- Studies in which definition of anemia is clearly stated as
  the lowest hemoglobin or the lowest hematocrit before
  transfusion.

The Relevance of Cerebral Microcirculation and
Cerebral Hemodynamics During the Acute Phase
of Head Injury

Several components of cerebral blood flow (CBF) are
dynamic, particularly during the acute phase after head injury.
The following dynamic components determine the physiopath-
ology and outcome in head injury.

Impairment of Cerebral Autoregulation

Perfusion heterogeneity and significant reductions in
CBF has been described after head injury. Ischemic thresholds
due to perfusion–metabolic demand mismatch as well as areas
of established hypoperfusion and subsequent hyperemia all
contribute to the formation of posttraumatic cerebral infarction.
Impaired cerebral autoregulation is regarded as the principal
mechanism of such posttraumatic cerebral perfusion mismatch.12
Cerebral autoregulation appears more efficient in its response
to systemic hypertension than hypotension.13 In this setting, auto-
regulation becomes an essential determinant of tissue perfusion
in the areas within the ischemic penumbra, specifically when there
is concurrent anemia or hemodilution because CBF is impaired
in normovolemic anemia.13

Perfusion Mismatch

CBF is reduced in the hyperacute phase of head injury. This
occurs along with a reduction in cerebral oxygen con-
sumption and without an increase in arteriovenous oxygen dif-
ference, consistent with a decreased cerebral metabolism or
mitochondrial dysfunction.14 However, during the acute phase
of head injury, regional reductions in CBF may also lead to an
increase in arteriovenous oxygen difference, when ongoing ce-
rebral metabolism results in a greater oxygen extraction ratio.

In animal studies, despite varied mechanisms of tra-
matic head injury, CBF is reduced with altered cerebral perfusion
distribution. The fluid percussion models have showed reduc-
tions of 40% to 50% in CBF during the first hour after head
injury,15 with similar effects shown with controlled cortical im-
 pact16 and impact acceleration models.17

Inflammatory Changes

Head injury causes elevated inflammatory markers in
plasma, cerebral tissue, and cerebrospinal fluid (CSF). In
humans and experimental models, an increase in tumor ne-
crosis factor α, interleukin 6, and interleukin 1 in both plasma
and CSF18 occur within hours after the initial injury along with
an increase in blood-brain barrier permeability to small and
large molecules.19 Leukocyte aggregation and margination as
well as complement activation20 have been demonstrated. The
permeability of the blood-brain barrier may be enhanced in
areas of leukocyte margination and cerebral vasodilation as well
as by microglial and astrocyte induced up-regulation of endo-
theilial nitric oxide synthetase (eNOS) and inducible nitric oxide
synthetase (iNOS).21

Pressure-Oxygen Dependency

In normal conditions, there is a linear correlation between
arterial PO2 and brain tissue PO2 (PTiO2).22 Oxygen is con-
sumed continuously by the cerebral tissue creating a gradient

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of PT\textsubscript{2} between the capillaries and distal tissue. A critical PT\textsubscript{2} before cerebral tissue infarction is established has been described at PT\textsubscript{2} values of 20 mm Hg being independent of CBF.\textsuperscript{23} The driving pressure of oxygen inside neuronal mitochondria is jeopardized in the setting of a low PT\textsubscript{2}, astrocytic and tissue swelling, suggesting that higher PT\textsubscript{2} may be necessary to ensure cellular gradients during the acute phase of head injury.\textsuperscript{24} The rate of oxygen diffusion is directly proportional to the gas tension gradients between the vessels and the mitochondria.\textsuperscript{25} This may explain the development of cerebral hypoxia after severe head injury, even when CPP is maintained at more than 60 mm Hg. An increase in oxygen tension using hyperbaric hyperoxia in animal models showed reduction in the inflammatory response and improved functional outcomes.\textsuperscript{26} Among human studies, hyperbaric hyperoxia for patients with severe head injury have shown a significant reduction in mortality in the group treated with hyperoxia.\textsuperscript{27} Moreover, the exposure to hyperbaric oxygen demonstrated a rise in cerebral oxygen consumption, suggesting that hyperbaric conditions significantly increases cerebral aerobic metabolism in patients with head injury.\textsuperscript{28} This rationale supports the hypothesis that patients with head injury managed with a PT\textsubscript{2} of more than 20 mm Hg may reduce mortality.\textsuperscript{29}

Determinants of Cerebral Microcirculation, During the Acute Phase of Head Injury

The ability of blood to flow through vessels of varied caliber, in particular through the microcirculatory network, depends on factors such as cell membrane characteristics, cell geometry, and blood viscosity.\textsuperscript{30} While cell membrane properties cannot be directly manipulated, it is possible to alter blood viscosity to improve the microcirculation dynamics. Plasma shows a linear relationship between shear stress (the force parallel to the direction of the flow per unit area of fluid sheared) and shear rate (velocity gradient between adjacent layers of the flow in laminar conditions). This allows the maintenance of a constant viscosity under laminar flow. High shear rates are typical of arterial blood flows, while low shear rates are mainly present in venous blood flow.\textsuperscript{31} However, as blood is a non-Newtonian fluid, blood viscosity varies with temperature, shear stress, and shear rate. In this setting, blood viscosity increases exponentially at low shear rates, mainly owing to the tendency of large molecules such as fibrinogen to aggregate. At high shear rates, blood viscosity is reduced owing to an increase in deformation of red blood cell (RBC) shape and alignment of their longer axes parallel to the direction of flow.\textsuperscript{32}

Hematocrit

Hematocrit is directly related to viscosity in particular during low flow states. This is because when shear rates are reduced, viscosity rises exponentially, RBC deformability becomes impaired, and RBC aggregation occurs.\textsuperscript{30} This jeopardizes perfusion through the microcirculation. This phenomenon is worsened as the RBC diameter (8 \mu m) exceeds the diameter of capillaries.\textsuperscript{33} However, at extreme values of hematocrit, the relationship between hematocrit and viscosity is no longer linear.\textsuperscript{34}

During the acute phase of head injury, fluid resuscitation or implementation of restrictive transfusion thresholds, may lead to normovolemic hemodilution and a reduction in blood viscosity, leading to improved blood rheology. However, the concomitant reduction in carried oxygen content added to post-traumatic tissue swelling and perfusion heterogeneities may increase the risk of cerebral infarction by a reduction on PT\textsubscript{2}.\textsuperscript{35} Although anemia initially reduces blood viscosity, it also induces vasoconstriction thereby reducing CBF, shear stress, and functional capillary density.\textsuperscript{36} The variable interdependence between hematocrit and viscosity raises the hypothesis that establishing a viscosity threshold as an indicator for blood transfusion, could optimize transfusion practices and oxygen delivery and perhaps improve cerebral microcirculation.\textsuperscript{37}

RBC Deformability

Cell deformability ensures the circulation of RBC across blood vessels despite their greater cross-sectional area compared with that of the capillaries. RBC deformability is ensured by its biconcave RBC structure because the cell membrane is larger than that needed to enclose its own volume.\textsuperscript{38} In addition, the flexibility of the RBC membrane, which is an energy needing process; the membrane area-to-volume ratio;\textsuperscript{39} the permeability of the RBC membrane, allowing loss of intracellular water to decrease even further its volume;\textsuperscript{40} and the viscoelastic properties of the RBC membrane for which the state and structure of the intracellular hemoglobin is pivotal\textsuperscript{41} all are required to ensure adequate RBC deformability.

Hemoglobin Concentration in Plasma

Oxygen delivery to tissues has traditionally been taught to depend on the oxygen carrying capacity of blood, with hematocrit level of 30% defined as optimal when the hemoglobin function is normal.\textsuperscript{42} While hematocrit level less than 30% has been associated with better neurological outcomes in head trauma,\textsuperscript{43} severe hemodilution to hematocrit near 10% is associated with vasodilation of carotid arteries and a proportionate increase in CBF to maintain oxygen delivery.\textsuperscript{44} At hematocrit levels lower than 10%, tissue oxygen consumption becomes supply dependant with resulting anaerobic metabolism and ischemia.\textsuperscript{45} Such severe hemodilution results in reduced capillary density, leukocyte adhesion, tissue acidosis, and inflammatory changes within the cerebral microcirculation in animal models.\textsuperscript{46} The degree of anemia interplays with blood viscosity and the cerebral vasodilatory response. However, modest anemia increases CBF by reducing blood viscosity\textsuperscript{47} and triggering a vasodilatory response. Experimental models have demonstrated that when the hematocrit level is reduced to less than 15%, such vasodilatory response is dampened leading to reduced oxygen delivery.\textsuperscript{48} The previously mentioned dual or nonlinear response of viscosity to extreme values of hematocrit is due to the many determinants affecting viscosity such as temperature, cellular aggregation, and blood cell deformability.\textsuperscript{49}

Among healthy humans, critical anemia is defined by hemoglobin levels of less than 6 g/dL (hematocrit level of 15%). In this situation, delivery of oxygen to cerebral tissue is inadequate, leading to the neurological signs such as impaired cognition, decreased memory, and reaction time.\textsuperscript{50} With
hemoglobin concentrations less than 6 g/dL, cerebral vasodilation occurs through the up-regulation of neuronal nitrate oxide, inducible nitric oxide (iNOs) and endothelial nitric oxide (eNOS) through presynaptic β-2 adrenoreceptor activation. These findings are also present in healthy humans at high altitude. Acute anemia is associated with a threefold increase in the incidence of infarction within the contused brain tissue. In addition, minor reductions in cerebral oximetry have been associated with worse neurological outcome in humans. Anemia has shown to be an independent risk for neurological injury in cardiac surgical patients, even at levels of hemoglobin of near 12 g/dL. Poor neurological outcomes are described when hemoglobin levels are maintained to less than 7 g/dL.

Erythropoietin (EPO) synthesized by astrocytes and neurons acts both as a paracrine and autocrine hormone, through receptors localized in neurons, astrocytes, endothelial cells, and smooth muscle. When EPO is activated after anemia, a down-regulation of neuronal apoptosis occurs via multiple mediators. In addition, an increase in angiogenesis and vasodilation occurs within the ischemic penumbra in experimental models. Two clinical trials have shown efficacy of EPO in stroke and in head injury, respectively. In stroke, EPO was associated with better neurological outcomes, while in head injury, EPO was associated with reduction in mortality, independently of its effects on hemoglobin concentration.

**Cerebral Markers Directly Affected During Anemia**

**Cerebral Tissue Partial Pressure of Oxygen, PTO2**

Regional brain oxygenation is represented by the partial pressure of tissue oxygen (PTO2). This monitoring tool has been used in both clinical and experimental settings for more than three decades. However, only recently has PTO2 monitoring been incorporated in clinical guidelines. Normal levels of PTO2 have been described to have a range of 25 mm Hg to 35 mm Hg and are directly influenced by hemoglobin concentration. However, although cerebral oximetry has shown to be correlated with CPP, there is lack of evidence demonstrating better neurological outcomes directly related to an increase in PTO2, the exception being those patients with baseline PTO2 levels of less than 15 mm Hg.

**Jugular Vein Saturation of Oxygen**

For a stable level of hemoglobin, a reduction in SJVO2 reflects either a low content of oxygen (hypoxic states) or an increased cerebral tissue extraction of oxygen (brain injury or ischemia). Conversely, an increased SJVO2 suggests either a total increase (hyperoxic states) or relative increase (hyperemic states) in the blood content of oxygen or a significantly reduced tissue extraction of oxygen (i.e., extensive infarct or brain death). SJVO2 is limited in its utility by being a global monitor of cerebral perfusion and somewhat insensitive in the detection of cerebral ischemia. SJVO2 monitoring has been used as a component of diagnostic algorithms to guide the manipulation of cerebral perfusion in specialized neurotrauma units. In the setting of anemia, a reduction in the values of SJVO2 is directly linked to impaired oxygen carrying capacity; however, in extreme cases, it may also suggest that cerebral ischemia is already established.

**When Anemia Leads to Cerebral Ischemia: Microdialysis Markers**

Analysis of the extracellular fluid (ECF) within the cerebral parenchyma has facilitated the understanding of adaptive changes to ischemia. Extracellular glucose levels decline as lactate levels rise when ischemia is established. This normally occurs at PTO2 levels of less than 20 mm Hg. Increased glucose consumption occurs mainly at the pericontusional zone where tissue swelling is abundant and oxygen gradients are jeopardized. In these situations CO2 production, tissue pH, and temperature decrease in parallel to the rise in lactate concentrations, with these events normally seen within 12 hours following head injury.

Observational clinical studies using microdialysis have demonstrated that the severity of posttraumatic cerebral ischemia correlates with elevated glutamate concentrations in ECF. Increased intracellular calcium, secondary activation of catalytic enzymes, and denaturing of phospholipidic cellular membranes. In addition, reductions in CPP or raised intracranial pressure are associated with increased concentrations of excitatory amino acids in ECF.

**When Anemia Leads to Cerebral Ischemia: Serum Markers**

**Neuron-Specific Enolase**

Neuron-specific enolase (NSE), an intracytoplasmatic enzyme, catalyses the conversion of 2-phosphoglycerate to phosphoenolpyruvate during glycolysis and has been used as a nonspecific marker of neuronal injury as well as neuroendocrine tumors. The peak plasma concentrations of NSE have been correlated to the size of cerebral infarction on computed tomography as well as functional outcome. There are currently no studies correlating levels of NSE with cerebral oximetry.

**Protein SB-100**

Serum SB-100 protein is a calcium-binding protein that has been found to be significantly increased after head injury, being used as a predictor of neurological outcome and as a surrogate of injury severity. This protein is normally located inside the cytosol of astrocytes and Schwann cells, its increase in CSF and blood after head injury reflecting glial damage. Although SB-100 protein is the most studied marker, its sensitivity is affected by the short half-life and the renal dependant clearance.

**Cerebral Markers of Anemia When This Compromises Cerebral Tension of Oxygen**

Several tissue markers of ischemia have been used in research. A reduction in microtubule-associated protein 2 immunostaining has been used as an early marker of ischemia. Microtubule-associated protein 2 is a protein involved in maintaining the integrity of the neuronal cytoskeleton. The tissue area defined by its reduction in staining represents the volume of affected tissue.
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Sample Number</th>
<th>End points</th>
<th>Transfusion Threshold</th>
<th>Definition of Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective cohort</td>
<td>100 patients, only 43 TBI</td>
<td>Dichotomized GOS</td>
<td>Not specified</td>
<td>Hematocrit level &lt; 30%</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>225 patients with TBI</td>
<td>Dichotomized GOS</td>
<td>Not specified</td>
<td>Hematocrit level &lt; 30%</td>
</tr>
<tr>
<td>Retrospective study</td>
<td>62 patients with TBI only</td>
<td>Impact of transfusions in PTiO2</td>
<td>Not specified</td>
<td>Hemoglobin levels &lt; 8 g/dL</td>
</tr>
<tr>
<td>Retrospective study</td>
<td>28 patients with TBI</td>
<td>Lower hematolin LOI</td>
<td>Not specified</td>
<td>Hemoglobin levels &lt; 12 g/dL or hematocrit &lt; 30%</td>
</tr>
<tr>
<td>Prospective single center</td>
<td>102 patients with TBI</td>
<td>GOS at 3 mo</td>
<td>Not specified</td>
<td>Hemoglobin levels &lt; 12 g/dL or hematocrit &lt; 30%</td>
</tr>
<tr>
<td>Retrospective study</td>
<td>57 patients with TBI</td>
<td>Neuropsychological performance</td>
<td>Hemoglobin levels &lt; 12 g/dL or hematocrit &lt; 30%</td>
<td></td>
</tr>
<tr>
<td>Retrospective study</td>
<td>404 patients (196 were patients with TBI)</td>
<td>Anemia and neurological outcome</td>
<td>Not specified</td>
<td>Hemoglobin levels &lt; 10 g/dL</td>
</tr>
<tr>
<td>RCT</td>
<td>100 low-birth-weight patients</td>
<td>Transfusion and neurological outcome</td>
<td>Hematocrit &lt; 30%</td>
<td>Hematocrit &lt; 30%</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>169 patients with TBI</td>
<td>GOS and RLA at hospital discharge</td>
<td>Restrictive strategy threshold: hemoglobin 7 g/dL (aiming to maintain hemoglobin levels at 70-90 g/dL). Liberal strategy threshold: hemoglobin 10 g/dL (aiming to maintain hemoglobin levels at 100-120 g/dL)</td>
<td>Hemoglobin levels of &lt; 7 g/dL for the restrictive strategy or &lt; 100 g/dL for the liberal strategy within 48 h after birth</td>
</tr>
<tr>
<td>Post hoc subgroup analysis</td>
<td>67 patients with TBI</td>
<td>Transfusion and death at 30 d</td>
<td>Restrictive strategy threshold: hemoglobin 7 g/dL (aiming to maintain hemoglobin levels at 70-90 g/dL). Liberal strategy threshold: hemoglobin 10 g/dL (aiming to maintain hemoglobin levels at 100-120 g/dL)</td>
<td>Not specified</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>51 patients with TBI</td>
<td>Transfusion and PTiO2</td>
<td>Hemoglobin levels &lt; 100 g/dL</td>
<td>Not specified</td>
</tr>
<tr>
<td>RCT</td>
<td>451 low-birth-weight patients</td>
<td>Transfusion and neurological outcome or death</td>
<td>Restrictive strategy threshold: hemoglobin 7 g/dL (aiming to maintain hemoglobin levels at 70-90 g/dL). Liberal strategy threshold: hemoglobin 10 g/dL (aiming to maintain hemoglobin levels at 100-120 g/dL)</td>
<td>Hemoglobin levels of &lt; 7 g/dL for the restrictive strategy or &lt; 100 g/dL for the liberal strategy within 48 h after birth</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>3,875 patients with TBI (from 2the IMPACT database)</td>
<td>GOS at 3 and 6 mo</td>
<td>Not specified</td>
<td>Not specified. Range of hemoglobin levels among studies: 6-17 g/dL</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>133 patients with TBI</td>
<td>Dichotomized GOS</td>
<td>Not specified</td>
<td>Hemoglobin levels &lt; 8 g/dL</td>
</tr>
<tr>
<td>RCT</td>
<td>637 low-birth-weight patients</td>
<td>Neurological outcome</td>
<td>Restrictive strategy threshold: hemoglobin 7 g/dL. Liberal strategy threshold: hemoglobin 9.5 g/dL</td>
<td>Hemoglobin levels &lt; 9.5 g/dL for the liberal strategy or &lt; 7 g/dL for the restrictive strategy, within 7 d after ICU admission</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>66 patients with TBI</td>
<td>Transfusion and PTiO2</td>
<td>Hemoglobin levels of &lt; 7 g/dL</td>
<td>Not specified</td>
</tr>
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<td>Retrospective study</td>
<td>1,150 patients with TBI</td>
<td>Transfusion and death or systemic complications</td>
<td>Hemoglobin levels &lt; 9 g/dL for three consecutive measurements within the first 7 d of admission</td>
<td>Not specified</td>
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<td>Retrospective study</td>
<td>788 patients with TBI</td>
<td>Transfusion and death</td>
<td>Not specified</td>
<td>Hematocrit &lt; 36%</td>
</tr>
<tr>
<td>Retrospective study</td>
<td>82 patients with TBI</td>
<td>Transfusion and death</td>
<td>Not specified</td>
<td>Hematocrit &lt; 36%</td>
</tr>
<tr>
<td>Post hoc analysis</td>
<td>3,554 patients with TBI</td>
<td>GOS at 3 and 6 mo</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Retrospective study</td>
<td>27 patients with TBI</td>
<td>Transfusion and PTiO2</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

(Continued on next page)
Overexpression of amyloid precursor protein (APP) has been shown using immunoreactivity staining of cerebral tissue after head trauma. APP is a neuronal protein, synthesized and matured within the cytosol, and is integral to the maintenance of cell membrane integrity. APP accumulates intra-axonally an early and consistent marker of neural injury in both animal and human models.

Immunohistochemical labeling is also able to identify neurofilaments. These are essential proteins for neuronal structure, specifically the axonal skeleton. As neuronal damage is established after injury, the intra-axonal transport of neurofilaments becomes delayed. Neurofilament accumulation represents axonal transport impairment after brain injury owing to both cellular disruption as well as functional impairment after head injury.

Current Practice Regarding Blood Transfusion Strategies in Patients With Head Injury

Currently, there is no evidence that supports the use of restrictive strategies for blood transfusion (acceptance of a hemoglobin level of $7 \, \text{g/dL}$) for patients with head injury. Ethical concerns have been raised concerning trials of transfusion triggers based on differing hemoglobin concentrations where neurological outcome is the end point.

Although some studies have correlated blood transfusion with an increase on the cerebral tension of oxygen, these studies failed to demonstrate a correlation with improved neurological outcome. Only sustained and severe cerebral hypoxia has been correlated with death. Despite the reported effects of anemia, it remains unclear what level of hemoglobin should be targeted as optimal.

Finally, a case can be made for tailoring blood transfusions to individual need based on measures of cerebral hemodynamics and cerebral metabolism. The limitation of this approach is that, although there are few studies assessing the validity of cerebral microdialysis as an integral part of cerebral metabolic multimonitoring, there are no data to date showing a correlation between the introduction of microdialysis data in the therapeutic algorithm and better neurological outcomes.

This review has identified 23 studies, all focused on the effect of anemia or blood transfusions on the neurological outcome after head injury (Table 1). However limitations in these studies include the following:

1. Lack of randomized controlled trials (RCT). Only four RCTs have been identified among 25 studies. Three of them are in preterm low weight neonates. Only one is based on a critically ill population but uses multiple surrogate end points. The study by Zygun et al. used a three-arm randomization of three different blood hemoglobin concentrations (hemoglobin at $<8 \, \text{g/dL}$, hemoglobin at $9 \, \text{g/dL}$, and hemoglobin at $10 \, \text{g/dL}$) for 30 patients with acute head injury. The primary end point was the assessment of cerebral oximetry to ascertain if $\text{PTiO}_2$ was increased posttransfusion. They found a direct correlation between levels of hemoglobin and $\text{PTiO}_2$; however, this did not translate into improved neurological outcomes. A secondary end point was changes in the lactate-pyruvate ratio using microdialysis, but relationship

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</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>30 patients with TBI</td>
<td>Transfusion and $\text{PTiO}_2$</td>
<td>3 different thresholds:</td>
<td>According to assigned group.</td>
</tr>
<tr>
<td>RCT</td>
<td>139 patients with TBI</td>
<td>GOS and FSE at 6 mo</td>
<td>A. Transfused at least 1 U of blood if hemoglobin level was $&lt;10 , \text{g/dL}$.</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

FSE, Functional Status Examination; ICU, intensive care unit; LOI, jugular venous lactate oxygen index; RLA, Rancho Los Amigos score; TBI, traumatic brain injury.
with hemoglobin levels could be demonstrated. There is currently no RCT within the adult population that randomizes different levels of hemoglobin and transfusion thresholds with assessment of neurological outcome.

2. Mixed nature of the study design. Of the 20 studies, 13,8,43,85–95 were retrospective cohort reviews, with 3 being post hoc subgroup analyses,2,93,96 2 prospective observational studies,97,98 and 3 studies prospective observational37,59,99 (Table 1). With no RCT reported of acute head injury in adults, lack of Class 1 to 2 evidence limits current recommendations.

3. Limited size of the specific population. The sample sizes among these studies vary between 2895 and 3,875 patients.95 Many of these studies incorporate not only head injury but also patients with multiple injuries, for whom it is already known that morbidity and mortality are significantly increased with blood transfusions.43,83,86,90,91,93,96 The confounding effect of trauma severity and blood transfusion requirements complicates interpretation.

4. Different definitions of anemia and absence of uniformity within the transfusion thresholds among studies. Of the 25 studies, 11 had not recorded the level of hemoglobin at which blood transfusion was mandated.43,85,86,93,94,97,99 In addition, the transfusion threshold of hemoglobin varied greatly as shown in Table 1.

5. Variable study endpoints. Primary end points have included neurological outcomes largely defined using the Glasgow Outcome Scale (GOS) and33,80–83,86–88,92–94,96,97 death,2,8,89–91 cerebral oximetry with the level of hemoglobin at which blood transfusion was mandated.43,85,86,93,94,97,99

In addition, the transfusion threshold of hemoglobin varied greatly as shown in Table 1.

6. Limited size of the specific population. The sample sizes among these studies vary between 2895 and 3,875 patients.95 Many of these studies incorporate not only head injury but also patients with multiple injuries, for whom it is already known that morbidity and mortality are significantly increased with blood transfusions.43,83,86,90,91,93,96

The first systematic review ever performed focused on the completeness of this study. All authors have similarly contributed to the search, writing, design, and completeness of this study.

REFERENCES


