REVIEW

OPEN

Transfusion practices in traumatic brain injury

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Purpose of review
The aim of this review is to summarize the recent studies looking at the effects of anemia and red blood cell transfusion in critically-ill patients with traumatic brain injury (TBI), describe the transfusion practice variations observed worldwide, and outline the ongoing trials evaluating restrictive versus liberal transfusion strategies for TBI.

Recent findings
Anemia is common among critically-ill patients with TBI, it is also thought to exacerbate secondary brain injury, and is associated with an increased risk of poor outcome. Conversely, allogenic red blood cell transfusion carries its own risks and complications, and has been associated with worse outcomes. Globally, there are large reported differences in the hemoglobin threshold used for transfusion after TBI. Observational studies have shown differential results for improvements in cerebral oxygenation and metabolism after red blood cell transfusion in TBI.

Summary
Currently, there is insufficient evidence to make strong recommendations regarding which hemoglobin threshold to use as a transfusion trigger in critically-ill patients with TBI. There is also uncertainty whether the restrictive transfusion strategy used in general critical care can be extrapolated to acutely brain injured patients. Ultimately, the consequences of anemia-induced cerebral injury need to be weighed up against the risks and complications associated with red blood cell transfusion.

Keywords
anemia, hemoglobin, thresholds, transfusion, traumatic brain injury

INTRODUCTION

After the primary injury, the management of patients with traumatic brain injury (TBI) in the prehospital setting, emergency department, ICU, or operating room focuses on the avoidance of secondary brain insults from systemic derangements such as hypotension, hypoxemia, and anemia [1–4]. Impaired oxygen (O_2) delivery to the brain is thought to be an important factor in the development of these secondary brain injuries, and therefore anemia in the acute admission period may decrease oxygen delivery at a time when the traumatized brain is acutely vulnerable to these secondary insults.

The classic approach in the field of neurosurgery has been to transfuse red blood cells (RBCs) in patients with TBI to maintain a hemoglobin (Hb) level greater than 10 g/dl or hematocrit greater than 30% for the theoretical principle of maintaining optimal oxygen carrying capacity [5]. However, more recently clinical practice has moved towards a restrictive transfusion strategy (maintaining Hb concentrations $\geq$7 g/dl) after studies showed liberal transfusion strategies (Hb $\geq$10 g/dl) may be unnecessary, or perhaps even harmful in the general critical care setting [6–8]. Although there is ongoing concern that the high metabolic requirements of the injured brain may render it more susceptible to injury at a lower transfusion trigger, few studies have focused on this important subgroup of critically ill patients, and most have been underpowered to identify a minimally acceptable Hb thresholds [9▪▪,10]. Because of this conflicting evidence, there is an ongoing debate regarding the optimal transfusion threshold in patients with TBI.

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KEY POINTS

- Although anemia is consistently associated with worse outcomes among patients with TBI, transfusion of red blood cells to correct anemia is also association with poor outcomes.
- It remains unclear if the current transfusion threshold of 7 g/dl used in general critical care is valid for acutely brain injured patients.
- However, there is insufficient evidence to make strong recommendations regarding the relative benefit of a liberal over a restrictive transfusion strategy.
- Whether the use of an individualized approach to target an optimal hemoglobin concentration based on physiologic indicators of cerebral ischemia or metabolic crisis improves outcome remains to be elucidated.
- Large pragmatic randomized controlled trials are urgently needed to address whether a liberal or a restrictive transfusion strategy improves neurologic recovery in patients with traumatic brain injury.

The present review will summarize the recent studies looking at the physiological effects of anemia and RBC transfusions (RBCT) in critically-ill patients with TBI, discuss the transfusion practice variations observed worldwide, and review the current evidence and guidelines for transfusion strategies in patients with TBI.

PHYSIOLOGIC EFFECTS OF ANEMIA ON THE BRAIN

Anemia is a common problem in TBI, with up to half of these patients receiving RBCT for Hb levels less than 9 g/dl during their admission to the ICU [11–14]. The cause of this anemia is multifactorial, mechanistically this includes reduced hematopoiesis because of the negative effects of systemic inflammation on erythropoietin production and inability of erythroblasts to incorporate iron, RBC loss due to frequent phlebotomy and reduced RBC survival, and finally hemodilution from intravenous fluid resuscitation and hemorrhage [15,16]. The Hb concentration is a major factor of brain oxygenation as the delivery of O_2 (DO_2) to the brain is the product of the arterial O_2 content (CaO_2) and cerebral blood flow (CBF):

$$DO_2 = CaO_2 \times CBF$$

whereby $CaO_2 = (Hb \times \text{arterial } O_2 \text{ saturation } (SaO_2) \times 1.39) + (0.003 \times \text{partial pressure of } O_2 \ (PaO_2))$ and CBF is determined by cardiac output and cerebral vessel size. In the setting of decreased O_2 content associated with anemia, the activation of compensatory physiological mechanisms to increase CBF can counteract reductions in Hb and subsequent reductions in cerebral DO_2. In response to anemia, cardiac output is increased through the activation of carotid and aortic chemoreceptors leading to a rise in heart rate and left ventricular stroke volume to augment CBF [17]. Furthermore, dilation of cerebral arterioles (i.e. cerebral vasodilation) occurs because of an increased production of nitric oxide (NO) by endothelial cells, perivascular astrocytes, and neurons to improve CBF and preserve O_2 delivery [18,19]. Other contributory mechanisms include an increase in cerebral tissue O_2 extraction and a reduction in blood viscosity, which increases venous return and decreases systemic vascular resistance to improve microvascular perfusion [20]. In healthy individuals, these compensatory mechanisms maintain cerebral tissue oxygenation until a critical Hb threshold of approximately 5–6 g/dl is reached, below which the cerebral DO_2 progressively diminishes and tissue hypoxia develops as maximal CBF has been achieved and no further vasodilation can occur. The O_2 extraction fraction then increases to meet metabolic tissue requirements, however altered brain function and symptoms of anemia-induced brain dysfunction will start to manifest at this level [21,22].

Independent of injury severity, many patients with TBI develop impaired cerebral autoregulation [23,24]. The exact cellular mechanisms affecting autoregulation are complex and beyond the scope of this review, but have been well summarized previously [25▪]. The loss of autoregulation can impair the brain's compensatory mechanism to progressively vasodilate in the setting of anemia and reduced CaO_2. Moreover, xenon-enhanced computed tomography studies have shown that global reductions in CBF are present within hours following TBI, further impairing the brain's ability to compensate [26]. Subsequently, maximal CBF may be reached at higher Hb thresholds around 9 g/dl, and the compromised cerebrovascular reserve may be insufficient to maintain adequate DO_2 below this Hb level resulting in anemia-induced brain dysfunction and possible injury at higher Hb levels [12,27]. TBI may also be associated with hemodynamic instability because of hemorrhage or neurogenic heart failure, both of which can limit the ability to increase cardiac output to compensate for the reduced CaO_2 [28].

EFFECTS OF ANEMIA AND RED BLOOD CELL TRANSFUSIONS ON TRAUMATIC BRAIN INJURY OUTCOMES

The association between anemia and poor outcomes in patients with TBI is an inconsistent finding. Understanding that anemia is considered a marker

of 'illness-severity' in critically ill patients and included as a variable in ICU risk prediction models [29,30], it is understandable that several observational studies have shown an association between anemia and poor outcomes in patients with TBI [11,31–34]. However, other studies evaluating anemia and TBI outcomes have not demonstrated a consistent risk of harm [12,35–40]. The methodological limitations restricting comparisons between these observational studies include: the inconsistent definitions of anemia and TBI severity; variable timing of Hb measurements; lack of consideration of Hb exposure during the acute admission period; different outcome measures; and residual confounding from factors that are associated with both anemia and outcome. Several studies have explored Hb exposure over time rather than admission values only, incorporating methods including repeated Hb concentrations, mean Hb concentration during the first 7 days, and time-weighted or area under the curve (AUC) exposure [11,13,32]. A recent study observed that both the percentage of time that the Hb at least 9 g/l and AUC was associated with favorable 6-month neurological outcomes based on the Glasgow outcome scale (GOSe), independent of RBCT administration [13].

However, the potential benefits of RBCT to avoid anemia and reduce cerebral tissue hypoxia may be opposed by the potentially adverse effects related to this therapy [25▪]. Several studies have shown that RBCT administration in TBI is associated with increased mortality [11,14,34,41,42,43▪▪,44], decreased functional outcomes [39,42,45▪,46], increased ICU length of stay [47], and impaired cerebral autoregulation [48]. Furthermore, compared to a restrictive strategy, a liberal transfusion strategy applying a threshold trigger of 10 g/dl was associated with an increased risk of progressive cerebral hemorrhagic injury [49▪] and thromboembolic events [10]. However, evidence from observational studies in patients with TBI is conflicting, with data to support a lack of association between RBCT administration and worse outcome in TBI [9▪▪,32]. One recent randomized clinical trial (RCT), employing a factorial design, compared the effects of erythropoietin and two Hb transfusion thresholds (7 vs. 10 g/dl) on neurological recovery after TBI [10]. Favorable neurological outcome was 43% for the Hb transfusion threshold of 7 g/dl and 33% for 10 g/dl ($P = 0.28$). Nevertheless, the number of patients included in the study was relatively small and the two groups of patients showed mean Hb levels much higher than those associated with the treatment arm in which they were randomized. Moreover, in a recent systematic review, insufficient evidence was found to support a difference in outcomes between higher and lower transfusion thresholds in patients with TBI [9▪▪].

CURRENT GUIDELINES

There is clear clinical and guideline agreement that Hb less than 7 g/dl in critically ill patients with TBI requires RBCT [50▪,51,52,53▪]. However, the exact threshold between 7 and 10 g/dl remains a contentious issue. Recent data from a randomized controlled trial (RCT) [10] and meta-analysis [9▪▪] found no difference in neurological outcome between the restrictive and liberal transfusion strategies, but the overall quality of the evidence was low. With both anemia and transfusions associated with worse outcomes in TBI, and a current lack of studies powered to assess outcomes for RBCT and brain injury patients, wide variability in clinical recommendations exist. Current clinical practice guidelines from trauma and critical care specialties recommend a target Hb of 7–9 g/dl [51,53▪]. The recent guidelines from the American Society of Anesthesiologists support the use of restrictive transfusion strategies, Hb less than 8 g/dl and hematocrit values less than 25%, to reduce the administration of RBCs without increasing the risk of poor outcome or neurological and cardiopulmonary complications [54]. The British Committee for Standards in Haematology similarly recommends a target threshold of 7–9 g/dl for patients with TBI, but for patients with evidence of cerebral ischemia, the Hb target increases to more than 9 g/dl [51]. Interestingly, the recently updated Brain Trauma Foundation Guidelines makes no comment on RBCT thresholds for severe TBI [55▪]. The American Association of Blood Banks (AABB) recommended in their recently published clinical practice guidelines that the use of restrictive transfusion threshold is well tolerated in most clinical settings, however highlighted that good practice should always review the Hb concentration, the overall clinical context, and alternative therapies when considering individualized transfusion decisions [50▪].

GLOBAL VARIATIONS IN RED BLOOD CELL TRANSFUSIONS THRESHOLDS

A recent international survey conducted within five critical care medicine societies looked at RBC transfusion threshold practices for patients with acute brain injury [56▪▪]. More than half the clinicians (54%) reported a general Hb threshold of 7–8 g/dl to initiate RBCT in their ICUs for acutely brain injured patients. However, many respondents did not administer RBCT at a fixed Hb threshold, but rather adjusted the transfusion trigger based on additional factors. Half of the

respondents stated they would use a different transfusion threshold specifically for TBI patients: 22% would use 7 g/dl, 28% would use 8 g/dl, 23% would use 9 g/dl, and 27% would use at least 10 g/dl or other. These Hb thresholds were increased by respondents if certain noncerebral factors including coronary artery disease, active bleeding and low mixed venous O_2 saturation were present. Although noncerebral factors influenced Hb thresholds more than cerebral factors, respondents working in North America and ICUs run by neurosurgeons more frequently reported using cerebral factors with brain tissue oxygenation ($PbtO_2$ < 15 mmHg) the most commonly used trigger. Other factors influencing transfusion policies included continental location, respondent's base specialty and experience, with respondents from Africa/Asia and Oceania using a lower threshold for transfusion than in Europe. The most liberal strategies were reported by anesthesiologists, and physicians with less than 5 years practice compared with those with more than 25 years. Seventy-two percentage of respondents stated a potential increase in DO_2 to ischemic regions as a reason to change the RBCT threshold, potential increases in cerebral oxygenation, cardiac output, and volume expansion were also reported but to a lesser degree. The main reasons reported for limiting transfusions were the concerns over the risk of transfusion-related acute lung injury (TRALI; 57%), risk of infection (56%), and altered immune response (43%). Interestingly, over 60% of respondents thought an RCT comparing a liberal to a restrictive transfusion strategy in acute brain injury was necessary, and 41% respondents thought this trial should compare a restrictive strategy with a neuromonitoring-guided strategy. This variability in transfusion thresholds is also noted in a recent survey looking at the blood transfusion practices among European neurotrauma centers participating in the Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI) study [57▪▪]. In 66 centers from 20 countries across Europe and Israel, half of the centers reported their general ICU protocol defined a Hb target level. In TBI patients, only 10 centers (16%) indicated the use of a Hb threshold between 7 and 8 g/dl. The remainder of the centers used higher thresholds: 25% reported between 8 and 9 g/dl; 31% between 9 and 10 g/dl; and 28% more than 10 g/dl.

MULTIMODAL NEUROMONITORING AND PRECISION MEDICINE PARADIGM

In the growing age of precision medicine and the introduction of multimodal neuromonitoring, novel approaches to assess individualized Hb thresholds have started to emerge in the literature. A recent study demonstrated that anemia alone does not appear to be detrimental among patients with severe TBI, however a combination of low $PbtO_2$ (<20 mmHg) and anemia (defined as <9 g/dl) was associated with poor neurological outcome [12], suggesting that unfavorable outcomes from anemia may be more likely to occur during times of brain tissue hypoxia, impaired autoregulation, or low cerebral blood flow states. Another retrospective study looking at cerebral autoregulation during RBCT administration in TBI found that RBC therapy was associated with worsening cerebrovascular pressure reactivity (PRx), as assessed by a moving correlation coefficient between mean arterial pressure and intracranial pressure (ICP) [47]. Interestingly, for patients with a mean $PbtO_2$ more than 20 mmHg pretransfusion, the PRx increased significantly after a RBCT indicating worsening cerebral autoregulation, but did not change in patients with $PbtO_2$ less than 20 mmHg. The recently published Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II (BOOST II) study evaluated the safety and feasibility of a neurocritical care management protocol to improve $PbtO_2$ levels [58▪]. Tiered interventions included RBCT titrated to a Hb goal of more than 10 g/dl for $PbtO_2$ levels less than 20 mmHg, although the number of RBCT administered was not reported for either group. This management protocol based on $PbtO_2$ and ICP monitoring significantly reduced the proportion of time with brain tissue hypoxia compared to ICP-only management protocol. There was a trend towards lower mortality and better functional outcomes, but the study was not powered for clinical efficacy [58▪].

A recent consensus statement from the International Microdialysis Forum for the clinical use of cerebral microdialysis (CMD) [59] found one study that used CMD to examine Hb thresholds associated with increased risk of cerebral metabolic dysfunction in poor-grade patients with subarachnoid hemorrhage (SAH) [60], but no studies exist for TBI patients [59]. However, CMD has been used in TBI research to examine cerebral perfusion pressure augmentation [61–63] and neuroprognostication [64–66]. In addition to invasive monitoring, near-infrared spectroscopy has been trialed as a means of noninvasively assessing cerebral tissue oxygenation saturation ($SctO_2$). Unfortunately, there is conflicting evidence on reliability of this modality to detect clinically meaningful changes in $SctO_2$ pretransfusion and post-transfusion [67▪,68▪], and therefore further data is required before its routine use can be recommended.

A 'one size fits all' approach and the use of an arbitrary Hb threshold may not be the optimal approach for transfusion triggers in patients with TBI. No RCT has specifically tested whether a

protocol-based restrictive transfusion strategy is more effective or safer than an personalized titrated care approach. Applying the precision medicine paradigm to patient-level physiological data, the optimal transfusion threshold likely varies between patients and also within the same patient over time. Titration of RBC therapy may be best individualized based on the initial physiological responsiveness to RBCT to predict benefit or harm [69], considering factors such as cerebral tissue hypoxia, cerebral autoregulation and metabolic state. However, the detection of organ dysfunction with multimodal neuromonitoring does not necessarily correlate with organ injury and irreversible loss of function. Nonetheless, evidence of organ dysfunction may reflect limitations or insufficient compensatory mechanisms that may predispose to cerebral tissue injury and death. Future RCTs should integrate methods to evaluate relevant physiologic parameters to compare transfusion threshold strategies, thereby reflecting the mechanism through which RBCT affects outcome, providing a rationale for initiating or continuing RBCT, and possibly better informing decisions to transfuse.

STORAGE OF RED BLOOD CELLS

Prior to transfusion, several complex biochemical, metabolic, and structural alterations may occur as a result of RBC storage *ex vivo*. The changes to erythrocytes includes: a decrease in 2,3 diphosphoglycerate [70] and adenosine triphosphate [71]; generation of reactive oxygen species [71]; irreversible membrane changes [72]; and several other changes summarized in a recent review [73]. These storage-related changes, collectively known as the 'storage lesion', may alter RBC function thereby reducing their oxygen delivery capacity, and decrease ATP-mediated hypoxic vasodilation [73,74]. There has been concern regarding the contribution of storage lesions to the incidence of transfusion-associated complications and poor outcomes [73], a meta-analysis found that transfusion of older RBCs was associated with an increase in the risk of death, but the methodological limitations of the studies included and heterogeneity prevented definitive conclusions [75]. Recently, the Age of Transfused Blood in Critically Ill Adults (ABLE) trial, along with two other trials [76,77], addressed the effects of RBC storage duration on transfusion outcomes. The ABLE study enrolled critically ill adults randomized to receive either RBC of less than 8 days storage or standard-issued RBC (mean 22.0 ± 8.4 days). They found no difference in 90-day mortality between the groups, however only around 9% of the study population were trauma patients with brain injury [78]. These trials found no advantage to the use of fresher-than-usual blood for critically ill adults, patients undergoing cardiac surgery, and premature infants [76,77,79]. However, these studies were not powered to examine subgroups, such as acutely brain injured patients, and do not address storage for 35–42 days [80]. Furthermore, a recent international survey reported that 30% of respondents would examine the RBC storage duration before transfusion, but only 37% would go on to limit the administration of 'older' RBCs [56▪▪].

FUTURE DIRECTIONS FOR TRANSFUSION THRESHOLDS

Randomized trials evaluating the optimal transfusion threshold for traumatic brain injured patients are currently ongoing, the results of which will greatly increase the body and quality of evidence in this area and improve the current strength of recommendations for transfusions practices in TBI. The TRAIN trial (ClinicalTrials.gov NCT02968654), endorsed by the European Society of Intensive Care Medicine (ESCIM), is randomizing acutely brain injured patients (TBI, SAH, and intracerebral hemorrhage), Glasgow Coma Score (GCS) of <12, and Hb level $<=9$ g/dl in the first 10 days of admission to either a restrictive approach targeting Hb more than 7 g/dl or liberal strategy targeting Hb more than 9 g/dl. The primary outcome for the study is neurological intact survival at 180 days, evaluated by the GOSe, with an a-priori analysis stratified by underlying brain injury type. Recruitment started in 2016 with planned enrollment of 4610 patients (including 2000 patients with TBI) over the next 4 years, powered to detect a reduction in the primary outcome (GOSe 1–5) from 50 to 45% in one of the two arms. The HEMOTION trial (NCT03260478) in Canada is currently randomizing patients with blunt patients with TBI with a GCS at least 12 and Hb level at least 10 g/dl to a transfusion threshold of 7 or 10 g/dl. The primary outcome is neurological outcome assessed by the GOSe at 6 months and is scheduled to be completed in 2021 with a planned sample size of 712 patients. Along with the SaHARA study (NCT02483351) for transfusion thresholds in SAH [81▪], these trials should provide reliable evidence to better understand the balance between the risks associated with anemia and RBCT in acutely brain injured patients, and will address the uncertainty of whether higher transfusion thresholds improve outcomes in this patient population.

CONCLUSION

Anemia remains a common problem in the ICU for patients with moderate and severe TBI. Physicians

must always balance the risk of possible anemia-associated cerebral injury with the risk of harm from allogeneic transfusions. Currently, the evidence is lacking to recommend a liberal over a restrictive transfusion strategy in this critical care patient population. An individualized approach, guided by data from neuromonitoring if available, may be considered to target physiological endpoints other than Hb targets, such as cerebral tissue hypoxia or metabolic crisis. However, this physiology-driven approach has yet to be validated in either well designed multicentre observational studies or large RCTs. The results of two large randomized controlled trials are eagerly awaited to inform future guideline development and decision-making at the bedside for transfusion practices in patients with TBI.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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Recommendations from the American Association of Blood Banks on the target Hb level for RBCT among hospitalized adult patients who are hemodynamically stable, and the length of time RBCs should be stored prior to transfusion. A restrictive transfusion threshold is safe in most clinical settings. The restrictive transfusion threshold of 7 g/dl is likely comparable with 8 g/dl, but these recommendations do not apply to patients with acute coronary syndrome, severe thrombocytopenia, and chronic transfusion–dependent anemia due to insufficient evidence. No mention of Hb targets for acutely brain injured patients.

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The fourth edition of the pan-European, multidisciplinary Task Force guidelines on management of major bleeding and coagulopathy following trauma. Includes representatives of six relevant European professional societies, they recommend a target Hb of 7 to 9 g/dl (Grade 1C).

54. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. Anesthesiology 2015; 122:241–275.

55. ■ Carney N, Totten AM, O'reilly C, *et al.* Guidelines for the management of severe traumatic brain injury. Neurosurgery 2017; 80:6–15.

The fourth edition of the guidelines for the management of severe TBI from the Brain Trauma Foundation. Evidence-based recommendations to clarify what aspects of practice currently can be supported by evidence. Importantly, no recommendations made for transfusion thresholds in severe TBI.

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An international web-based survey to investigate the RBCT practices used for acute brain injury. Eight hundred and sixty-eight responses from five critical care medicine societies of ICU physicians. Hb threshold used for RBCT was <8 g/dl in half of the ICU clinicians who responded. However, more than 50% of physicians used higher Hb thresholds in certain conditions. Systemic and cerebral factors were reported as influencing the need for higher Hb thresholds.

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A survey of 66 European neurotrauma centers participating in the CENTER-TBI that aimed to describe the current approaches to RBCT and coagulation management, and quantify variability between European ICUs. Twenty-six centers (41%) indicated an Hb target between 7 and 9 g/dl and 38 centers (59%) >9 g/dl. Overall, shows a lack of consensus between European ICUs on blood transfusion and coagulation management.

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