

## The Problem of Anemia Associated with Traumatic Brain Injury

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### Abstract

Anemia following traumatic brain injury (TBI) is frequently encountered. A number of studies have shown negative effects on outcome with hemoglobin levels below 9 g/dL but no consensus has been reached in regards to what level of hemoglobin warrants blood transfusion. Some neurosurgical texts recommend transfusion for hemoglobin <10 g/dL despite lack of clear guidelines. While transfusion should theoretically prevent secondary insults from hypoxia, it may also increase morbidity and mortality. We discuss the factors creating confusion in the literature and offer an outline of prospective trial to determine the impact of anemia and transfusion on patient with moderate-to-severe TBI.

**Keywords:** Traumatic brain injury; Anemia; Hemoglobin; Outcome; Commentary; Trial; Transfusion

### The Problem

Anemia (low hemoglobin) commonly occurs after traumatic brain injury (TBI); for instance, in the recent series, 17.4% of patients with head abbreviated injury score (AIS) >3 presented with hemoglobin <10 g/dL, and 45.0% had hemoglobin at or below that level during the first week after injury [1]. One classic neurosurgical text suggests transfusion for those with hemoglobin levels less than 10 g/dL [2]. However, studies like the TRICC trial have influenced critical-care providers to refrain from transfusion in critically-ill patients with Hb >7 g/dL due to higher mortality rates [3]. However, patients with TBI comprise only 6% of this study population, making it difficult to generalize these results TBI patients.

The recent paper also showed that low levels of hemoglobin are associated with worse patient outcomes, which supports results by others [4-11]. These results are contrasted by other studies showing no adverse effects of low hemoglobin in TBI [12-16]. One of the main treatment goals in TBI is the prevention of secondary insults such as hypo-perfusion, hypoxia, and elevated intracranial pressure (ICP) [17-22]. Transfusion should theoretically prevent some of these insults; however, changes that occur in stored red blood cells (RBCs) may limit potential beneficial effects [4,23-25]. The results of transfusion in TBI patients are mixed, as summarized in a recent review by Travers et al. [26].

### The Solution

The bottom line is that the current body of knowledge regarding anemia and transfusion in TBI patients is highly variable and conflicting. The solution to that problem is fairly obvious. We recommend further investigation in the form of a prospective trial, ideally a randomized-controlled trial, in the hospital and post-hospital settings to investigate the potential benefits of blood transfusion on outcome after TBI. A number of factors need to be considered in the

design of such a trial. Fortunately, we have the guidance of several studies to define the necessary terms of the investigation. These include hemoglobin transfusion thresholds for comparison, which types of head injured patients to include, what outcome measures to use, how many patients need to be studied, and other confounding comorbidities.

### Hemoglobin transfusion thresholds

While the data in Litofsky et al. [1] suggested a transfusion benefit at transfusion for hemoglobin <8 g/dL based on no transfusion harm at those levels, other studies have reached different conclusions. Hemoglobin levels <7 g/dl and <9 g/dL have also been identified as showing differences. Because in Litofsky et al. [1] we showed that the impact of anemia was more profound at lower hemoglobin levels and graded as hemoglobin levels increased, it is reasonable to investigate potential transfusion benefit at several different levels.

### Outcome measures

A second key factor in designing a prospective trial is determining the outcome measures. There are many ways to scale and analyze patients during the post-acute period to allow comparisons. The GOS has been a mainstay of studies for outcome after neurologic injury. The GOSE was created to assist in TBI-outcome data as it extends the categories to be more sensitive to change [27]. A more recent outcome scale, the Neurologic Outcome Scale for TBI (NOS-TBI), has 23 items which can be administered by non-physicians in 15 minutes and can be used to stratify patients for outcomes research [28,29]. Finally, neuropsychological testing is an individualized form of cognitive and psychologic assessment which allows for in-depth testing of multiple functional areas which may be impaired in otherwise high-functioning individuals [30,31].

The measurement of patient function throughout rehabilitation can also have value in studies in TBI. Traditionally an inpatient rehabilitation scale, the Functional Independence Measure (FIM) assesses 18 categories of motor and cognitive function and allows serial testing to follow patient progress [32]. The Functional Assessment

Measure (FAM) serves as an adjunct by including behavior, community interaction, and communication [33]. In the setting of anemia, which may limit participation in rehabilitation due to fatigue, the Borg Rating of Perceived Exertion (RPE) can be utilized to subjectively to gauge the perceived effort of rehabilitation.

Fatigue itself has many scales that have been utilized in studies on TBI patients. The Visual Analog Scale for Fatigue is a simple measure that can quantify fatigue on a likert scale [34,35]. The Fatigue Severity Scale (FSS) encompasses multiple domains of function that can be impacted by fatigue, and The Barrow Neurological Institute (BNI) Fatigue Scale assesses 10 items of alertness and daily energy impact on function [36,37].

In an attempt to develop better assessment scales unlimited by location or rehabilitation, the Improving Medicare Post-Acute Care Transformation Act of 2014 (IMPACT Act of 2014) created the Continuity Assessment Record and Evaluation (CARE) Tool to assess the patient's medical, functional, cognitive, and social support across all settings [38-40]. This data set, while at present is exhaustive to administer, may provide valuable data in future studies as it becomes more ubiquitous in post-acute care.

### Study population

The majority of TBI patients are male, so most patients included in series examining the impact of anemia and transfusion on TBI outcome are male. Gender differences in trauma have been demonstrated with mixed outcomes [41-43]. In fact, our own study showed females had worse outcomes than males at more severe levels of anemia [1]. This has been partially attributed to different sex hormones and physiologic responses [44-47]. Distinguishing the two populations in anemia and transfusion may reveal important gender-related differences in the treatment and recovery in the setting of TBI.

### Number of patients

Many of the studies included in our review used small sample sizes. Of note, the only randomized-control trial reviewed had just 50 patients in each of the four arms and the subpopulation of TBI patients from the TRICC trial included 67 patients [20,48]. Determining the appropriate sample size is crucial to ensuring the validity of a prospective study, particularly if measurable differences in outcome are small or variability within groups (standard deviations) are large.

### Confounders

Another factor generally not considered is whether patients had accompanying physiological perturbations of hypotension and/or tachycardia. Brain Trauma Foundation Guidelines clearly indicate the adverse effects of systolic blood pressure less than 90 mm Hg [49]. Many trauma surgeons who follow restrictive transfusion protocols will transfuse patients with higher hemoglobin levels if the patient remains hypotensive or tachycardic [50]. Similarly, other patient factors may play a role in the decision to transfuse. For example, those with cardiovascular disease may not tolerate low levels of hemoglobin [51]. Anemia in these patients may increase morbidity and mortality and may increase the threshold for transfusion [52,53]. In addition, age may contribute to a patient's response to treatment. For instance, Acker et al. [54] found that pediatric patients with TBI who received transfusions were significantly more likely to have worse outcomes and morbidities such as UTI and bacteremia than those who did not. However, no further studies stratify risk of transfusion in patients with

TBI based on age or in conjunction with other significant comorbidities.

The severity of the TBI most also be considered in the population studied. Given that some outcome measures are likely to be subtle, it is probably best to limit a trial to those with moderate and severe TBI. While excluding patients with mild TBI will limit the numbers of patients available, one can probably assume that the differences in outcome should be larger with patients with more severe injury and therefore easier to detect.

Patients with confounding co-morbidities may impact the results. Those with coagulopathy or severe systemic injuries may continue to have decreasing hemoglobin levels despite correction with transfusion. These patients may be best to exclude if we wish to have the cleanest comparison of transfusion benefit.

### A Proposal

Given the lack of clear guidelines in anemia and transfusion in TBI and the gaps in the literature as outlined above, we would propose a trial as follows:

#### Location

The study would occur at an American College of Surgeons-verified Level 1 Trauma center. Ideally, multiple centers be will be needed to participate in this trial, as will be indicated below.

#### Patient inclusion

Adult patients age  $\geq 18$  with isolated blunt head trauma as verified by CT scan on arrival with moderate-to-severe TBI as defined by GCS (moderate: GCS 9-12; severe: GCS 3-8). Patients with penetrating head or multi-system trauma, normal neurological exams, negative head CT, or known coagulopathy or other hematologic disorders would be excluded from the study.

#### Anemia definition and transfusion

Hemoglobin levels would be measured on arrival and daily while in the ICU setting. Anemia would be defined at three different levels – hemoglobin  $<7$  g/dL, hemoglobin  $<8$  g/dL and hemoglobin  $<9$  g/dL with the patient population to receive RBC transfusion to maintain hemoglobin at the various levels.

#### Outcome measurement

Several primary outcome measures would be assessed at discharge, 6 months, and 1 year. To be able to place the results of the study in context with previous studies, GOS would be assessed. Since the GOS is likely not sensitive enough to detect potentially significant differences in outcome, the NOS-TBI would also be administered because of its relative ease. Neuropsychologic testing, using the processing speed section of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS – IV) at hospital discharge, 6 months and 1-year would also be obtained. Neuropsychologic testing should include multiple categories such as verbal learning and memory, visual memory, visual-constructional ability, verbal fluency, motor speed, attention, fine motor coordination, and global adjustment to activities of daily living, but processing speed is the only factor to be able to discriminate between patients with moderate to severe injury and others. Lastly, to assess the impact of fatigue on recovery, the Visual Analog Scale for

Fatigue (VAS-f) will be determined at discharge for the hospital, discharge from rehab, and a 6 months. Secondary outcomes include in-house mortality, transfusion reactions, ventilator days, infection rate, ARDS, pulmonary embolus, DVTs, hospital length-of-stay, and discharge disposition from the hospital and from rehabilitation.

### Patient factors

Patient-specific information should include gender and comorbidities. In addition, physiologic deviations such as hypotension and tachycardia should be recorded. Exclusion of patients with Abbreviated Injury Score of > 9 for non-head site should minimize physiological perturbation effects.

### Number of patients

Determining the number of patients for the study is fairly straightforward. Calculations can be based on a power of 0.8 (beta) and probability of 0.05 (alpha). If one assumes a 10% difference in measured outcome between groups (not overly ambitious), and takes data from published TBI studies utilizing the outcome measure for the calculations, the following results for patient numbers are obtained:

- Glasgow Outcome Scale – 1542 patients per group (54% good outcome of hemoglobin < 7 g/dL, 59% good outcome for hemoglobin < 8 g/dL, and 61% good outcome for hemoglobin < 9 g/dL) [1].
- NOS-TBI – 1542 patients per group (mean 12.7, standard deviation 13.1) [29].
- VAS-fatigue – 959 patients per group (mean 27.4, standard deviation 21.1) [35].
- WAIS-IV (processing speed) – 27 patients per group (mean 86.2, standard deviation 10.8, 105 assumed difference) or 95 patients per group (5% assumed difference) [31].

From this analysis, using three different transfusion thresholds with multiple outcome measures, probably 4500 patients will be necessary to detect significant differences. Thus, the sample population required to find significant differences at the various transfusion thresholds proposed is likely the major limitation for accomplishing the study.

### Conclusion

We believe that a prospective or randomized-control trial can provide the data necessary to adequately assess the effects of anemia and transfusion on outcome in the setting of moderate-to-severe TBI. Multiple centers would need to participate in this trial to have an appropriate sample population to satisfactorily answer the questions posed.

### Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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