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The Negative Impact of Anemia in Outcome from Traumatic Brain Injury

N. Scott Litofsky[1], Simon Martin[1], Jenna Diaz[1], Bin Ge[2], Greg Petroski[2], Douglas C. Miller[3], Stephen L. Barnes[4]

■ BACKGROUND: **Whether anemia complicating traumatic brain injury (TBI) has an impact on patient outcomes is controversial; therefore, recommendations for blood transfusions for such patients are inconsistent. We hypothesized that patient outcome after TBI would be worse in patients with lower hemoglobin levels.**

■ METHODS: **We retrospectively reviewed records of patients with TBI and head Abbreviated Injury Scale >3 with abnormal head computed tomography findings and neurologic injury. The relationships between initial hemoglobin and lowest hemoglobin during hospitalization at threshold values of ≤7, ≤8, ≤9, and ≤10 g/dL were investigated relative to Glasgow Outcome Score at last follow-up not exceeding 1 year.**

■ RESULTS: **Of 939 patients meeting inclusion criteria, initial and lowest hemoglobin concentrations were significant predictors of poor outcome ($P < 0.0001$). For each 1 g/dL higher hemoglobin value, the likelihood of a good outcome increased by 33%. More severe levels of initial anemia were associated with lower Glasgow Coma Scale, greater head Abbreviated Injury Scale, and greater Injury Severity Score ($P < 0.0001$). Female patients had worse outcome than male patients only for initial hemoglobin between 7 and 8 g/dL ($P < 0.05$). Blood transfusion was associated with poorer outcome at hemoglobin levels ≤9 and ≤10 g/dL ($P < 0.05$), but not at lower hemoglobin thresholds.**

■ CONCLUSIONS: **Patient outcome after TBI is worse in patients with lower hemoglobin. Initial hemoglobin and lowest hemoglobin after admission are independently associated with poor outcome. Our data support consideration of blood transfusion when hemoglobin is ≤8 g/dl.**

INTRODUCTION

Acute blood loss anemia occurs in approximately 50% of hospitalized patients with traumatic brain injury (TBI) related to surgical procedures and/or co-existing other injuries.[1-3] Blood transfusion management recommendations in the setting of TBI vary greatly[4] without specific scientifically derived transfusion thresholds[2,3,5-11] and with few data to guide practice.[3,12,13] Generally neurosurgeons prefer to correct TBI-associated anemia with liberal transfusion thresholds[4] related to concerns regarding brain metabolism, reduced brain oxygen tension[11] and energy crisis[14] with resultant poorer neurologic outcomes.[11,15]

Experimental animal models have shown increased apoptosis and impaired oxygen extraction in the brain after TBI with hemodilutional anemia, suggesting selective vulnerability to the combination of anemia and TBI.[16] Other animal models have shown decreased hematocrit contributing to increased intracranial pressure, suggesting that anemia-induced cellular damage increases cerebral edema after TBI.[17] With these potential direct associations between anemia and secondary brain injury and worse outcome,[1,2,9,10,17-22] many neurosurgeons correct hemoglobin of less than 10 g/dL in the setting of TBI by blood transfusion.[23]

The converse arguments for strict transfusion thresholds derive in substantial part from Hebert et al.,[24] who showed no differences in patient outcomes in the intensive care unit setting whether transfused to keep hemoglobin between 7 and 9 g/dL or between 10 and 12 g/dL (albeit not specifically in patients

Key words
- Anemia
- Glasgow Outcome Score
- Hemoglobin
- Injury Severity Score
- Traumatic brain injury

Abbreviations and Acronyms
AIS: Abbreviated Injury Scale
CT: Computed tomography
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
ISS: Injury Severity Scale
TBI: Traumatic brain injury

From the [1]Division of Neurological Surgery, [2]Office of Medical Research, [3]Department of Pathology, and [4]Division of Acute Care Surgery, University of Missouri School of Medicine, Columbia, Missouri, USA

To whom correspondence should be addressed: N. Scott Litofsky, M.D. [E-mail: litofskyn@health.missouri.edu]

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who had suffered TBI). Because blood transfusion has been shown to have negative side effects[1,8,10,19,20,22,25-29] and has been associated either with poorer outcome after trauma[8,13,28-31] or at least no better outcome,[6,25,32-34] many refrain from providing blood transfusion unless hemoglobin decreases to less than 7 g/dL.[32]

The studies on the effects of anemia or transfusion after TBI have had many methodologic differences. The thresholds for a diagnosis of "anemia" or as trigger for transfusion varied between studies. The timing in the patient's course of hemoglobin measurement also varies. Outcome measures differed between studies; some reported only mortality and did not consider neurologic impact. Many involved small numbers of patients. Therefore, the primary aim of our study was to investigate the impact on both survival and neurologic status of low hemoglobin in patients with TBI, considering several different sampling times and a number of different threshold values in a large patient population. We hypothesized that outcomes of patients who suffer TBI with concomitant low levels of hemoglobin would be worse than those with greater levels of hemoglobin. Secondary aims included investigating the impact of patient sex and blood transfusion on outcome of patients with low hemoglobin after TBI.

METHODS

This study met the requirements of the Institutional Review Board of University of Missouri for medical research (IRB# 1208451) with waiver of consent.

Data Collection

Patients admitted to the University of Missouri Hospital, an American College of Surgeons-verified Level I trauma center, from January 1, 2009, through June 15, 2013, were entered prospectively into the center's Trauma Registry (Digital Innovations, Forest Hill, Maryland, USA). Patients with head Abbreviated Injury Scale (AIS) $\geq$3 were identified retrospectively from the Registry for data collection, including date of admission, age, sex, admission Injury Severity Score (ISS), admission head AIS, and initial Glasgow Coma Scale (GCS) score. Patient names, visit numbers, and medical record numbers were cross-referenced to the electronic medical record (Powerchart; Cerner, Kansas City, Missouri, USA) to obtain computed tomography (CT) scan findings, mechanism of injury, operations performed, and discharge disposition. Outcome was classified with a Glasgow Outcome Scale (GOS) score at last follow-up visit documented up to 1 year after injury, based on the clinical descriptions provided, similar to scenario-based validation of the Glasgow Outcome Scale-Extended described by Ekegren et al.[35] This time frame was selected to give patients the best opportunity for maximal improvement after injury. All determinations were made by the same author (S.M.); the senior author (N.S.L.) audited a sample of the determinations and reviewed determinations in question. For purposes of statistical analysis, GOS scores of 4 and 5 (moderate disability and good recovery) were grouped together as "good outcome" whereas "poor outcome" was defined as GOS of 1, 2, or 3 (death, persistent vegetative state, and severe disability). Daily hemoglobin measurements and transfusions received were also collected from Powerchart.

Inclusion/Exclusion Criteria

Patients with head AIS $\geq$3 and findings consistent with TBI on CT scan (intracranial hemorrhage, skull fracture, or cerebral edema) were included for further analyses, whether with isolated TBI or polytrauma. Patients with penetrating trauma, no evidence of TBI on head CT scan, or normal neurologic examination findings were excluded.

Patient Management

Patients were managed via the use of Brain Trauma Foundation guidelines.[36] Intracranial pressure was monitored in patients with GCS $\leq$8. Cerebrospinal fluid drainage, mannitol, hypertonic saline, sedation, and paralysis were used to control refractory intracranial pressure in conjunction with decompressive surgery when indicated.

Hemoglobin Levels

Hemoglobin concentration data for each patient were collected via a search of Powerchart conducted by Cerner. The first hemoglobin during the trauma admission and the lowest hemoglobin each day after admission were recorded. Normal laboratory values for hemoglobin were defined as 13.5—17.5 g/dL for male and 12.0—16.0 g/dL for female patients. In the strictest sense of the term, patients with hemoglobin levels less than normal had anemia. Data were analyzed with the following threshold cutoffs: $\leq$7.0 g/dL, $\leq$8.0 g/dL, $\leq$9.0 g/dL, and $\leq$10.0 g/dL. These cutoffs were selected on the basis of criteria used in the literature and therefore were not mathematically derived by logistic regression. Although most authors have investigated the relationships of $\leq$7.0 g/dL[11,16,21,24,29] and/or $\leq$10.0 g/dL,[6,15,21,32,37-39] others have used $\leq$8.0 g/dL[25,37,40] or $\leq$9.0 g/dL.[11,15,28,37]

Blood Transfusion

Transfusions of red blood cells were recorded. No specific transfusion protocol was in place; the decision to transfuse was at attending physician discretion when augmentation of oxygen delivery or active hemorrhage indicated a need for increased circulating erythrocytes.

Data Analysis

Descriptive statistics characterized the patient population and the outcome variables of interest. Means and SDs were computed in summarizing the numerical variables and frequency and percent was computed in summarizing the categorical variables. The χ^2 test (or Fisher exact test) was used to compare categorical variables, and the Wilcoxon rank sum test was used to compare the numerical variables because of lack of the support for the normal assumption. Age was treated as a continuous variable. Significance was accepted at $P < 0.05$.

The relationship between level of anemia and outcome was investigated in 3 different ways. First, hemoglobin on admission was compared with outcome by a parsimonious logistic regression model with outcome as the dependent and hemoglobin as the independent variable. The model adjusted for age, ISS, and GCS. Sensitivity and specificity for poor outcome was then computed for cut-point thresholds of hemoglobin $\leq$7 g/dL, $\leq$8 g/dL, $\leq$9 g/dL, and $\leq$10 g/dL with a Bonferroni adjustment. Second, each patient's lowest hemoglobin (nadir) during hospitalization was