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The effects of iron deficiency on blood transfusion requirements in traumatic brain injury.

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Abstract

Introduction: Traumatic brain injury (TBI) is the leading cause of preventable death in trauma patients. TBI often need blood transfusion, iron deficiency (ID) is known as the first cause of anemia worldwide, but no known predictors of transfusion requirements are available at intensive care unit (ICU). The aims of this study were to investigate ID relationship with blood transfusion requirements in TBI patients at ICU.

Methods: One hundred forty-two patients with severe TBI, as defined by Glasgow Coma Scale (GCS) scores <8 with an expected ICU length of stay ≥ 48 hours were admitted to the general ICU were enrolled in the prospective observational study between April 1, 2013, and December 31, 2015. Patients were divided into 2 groups according to their baseline iron status: iron- deficient (ID) and non-ID (normal iron profile) cohorts. Demographic features, laboratory values, blood transfusions, and length of ICU stay were recorded.

Results: A total of 134 patients were included in this analysis. The mean Glasgow coma score at baseline was 6 ± 5 and Injury Severity Score (ISS) 18.5 ± 4.5. ID with TBI patients, which was diagnosed in 65 patients (48.5%), compared with non-ID patients, with higher ISS but no difference in admission GCS score or APACHE II scores. ID was associated with a greater use of blood transfusions (5 and 2 U/ patient, respectively; p=.0001). The median length of ICU stay after TBI was longer among the ID versus the non-ID group (25 and 17 days per patient, respectively; p=.0001).

Conclusion: We found that ID was highly prevalent at ICU admission patients with TBI and that it was associated with higher blood transfusion requirements. Therefore, ID may be a prognostic factor for the blood transfusion requirements in TBI at ICU.

Keywords: Iron deficiency, Blood transfusion, Traumatic brain injury.

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Introduction

Traumatic brain injury (TBI) is a major cause of death and disability, with large direct and indirect costs to society [1]. A study found that 89% of severe TBI patients (GCS ≤ 8) developed at least one organ system dysfunction, with 35% progressing to organ failure [2]. Multiple organ traumas (MOT) with concomitant TBI has been shown to increase rates of infection, length of hospital stay, and ventilator use in ICU patients [3].

Anemia is a common condition in critically ill patients and results in a high requirement for blood transfusions associated with poor outcomes [4]. Iron deficiency (ID) is known as the first cause of anemia worldwide and prevalence of ID at ICU admission is around 25 to 40% [5]. Blood losses are particularly problem during ICU stay when transfusions are required, leading to iron losses and is known to be significant during an ICU stay [6].

However, effects of ID on transfusion requirements at TBI are unknown and, to the best of our knowledge, there are no data available. The main objective of this prospective observational study was to investigate ID relationship with blood transfusion requirements in TBI patients at ICU.

Methods

After approval by the Ethics Committee of the Inonu University in Malatya (acceptance number: 2015/214), and written informed consent was obtained from the patients, a prospective observational study was undertaken consisting of 142 consecutive adult TBI patients between April 1, 2013, and December 31, 2015. All patients admitted to our 15-bed ICU. Eligibility criteria included a GCS score, assessed after

resuscitation, of 8 or less (on a scale from 3 to 15, with lower scores indicating a reduced level of consciousness), as assessed on the basis of computed tomography [CT], at least one reactive pupil, a body weight of 45 to 135 kg, initiation of treatment within 8 hours after injury. Exclusion criteria were: Patients were excluded if they had a GCS score of 3 and bilaterally fixed and dilated pupils, a life expectancy of less than 24 hours, prolonged or uncorrectable hypoxemia (partial pressure of arterial oxygen, <60 mm Hg), hypotension (systolic blood pressure, <90 mm Hg) at the time of randomization, spinal cord injury, pregnancy, only an isolated epidural hematoma, or coma that was suspected to be due primarily to other causes, prescription of erythropoietin, iron, or blood product transfusions during the previous month. Patients with evidence of iron overload (both serum ferritin of ≥ 250 ng/mL and transferrin saturation of ≥ 50%) were also excluded. Because all the potential participants were unconscious at the time of study entry, written informed consent was obtained from a legally acceptable representative before randomization.

Brain injury management

Brain-injured patients with a GCS ≤ 8 were intubated and were mechanically ventilated. Patients were sedated with either midazolam (0.2 to 0.5 mg.kg−1.h^{-1}) or propofol (1 to 5 mg.kg^{-1}.h^{-1}) and continuous infusion of fentanyl (2 to 5 μg.kg^{-1}.h^{-1}). Management of patients was consistent with the guidelines of the Brain Trauma Foundation [7]. Subsequently, intracerebral pressure (ICP) monitoring was performed in patients with GCS ≤ 8 and with an abnormal brain computed tomography (CT) scan or whenever deemed appropriate by the attending intensives, using either an intraparenchymental device or a ventriculostomy in the presence of hydrocephalus [8]. Cerebral perfusion pressure (CPP) was maintained in the range of 60 to 70 mmHg with continuous infusion of norepinephrine when needed [7]. To prevent secondary brain insults, the following standards of care were also applied: normoxia ($PaO_2 \geq 80$ mmHg), normocapnia ($35 \leq PCO_2 \leq 45$ mmHg), body temperature between 36°C and 38°C and maintenance of a serum osmolality ranging between 280 and 320 mOsm.kg^{-1} [9].

Intracranial hypertensive episodes defined by an ICP ≥ 20 mmHg were treated by boli of sedatives and a bolus of mannitol (0.5 g.kg^{-1}). Mannitol was used in the setting of plasma osmolality ≤ 320 mosm.kg^{-1}. In the case of refractory intracranial hypertension (ICP ≥ 20 mmHg for more than 15 minutes despite usual first-line treatment), barbiturates (sodium thiopental) were added with an intravenous bolus of 2 to 3 mg.kg^{-1} followed by a continuous infusion of 2 to 3 mg.kg^{-1}.h^{-1}. Sedation was stopped whenever the control of ICP was deemed appropriate [7].

Data collection

Data derived from medical charts were collected for all consenting patients, including age, gender, APACHE II score for the first 24 hours following ICU admission, GCS at presentation to emergency department. Significant comorbidities were also recorded. Factors that could interfere with iron metabolism, nutritional state or with neuromuscular weakness were recorded: iron administration, blood transfusion, corticosteroids, vasopressor use, parenteral nutrition, renal replacement therapy and length of mechanical ventilation. Major complications, such as hemorrhage, ICU-acquired infection or acute renal failure and outcome variables were also collected.

Biological variables

Blood samples were obtained on the day of ICU admission, and the following parameters were analyzed: Hemoglobin (Hb) concentration (g/L), serum iron concentration (mmol/L), transferrin saturation (TSAT) (%), ferritin concentration (mg/L), soluble serum transferrin receptor concentration (mg/L), high-sensitivity C-reactive protein (CRP) concentration (mg/L). Samples were centrifuged, and the plasma was stored. All hematologic variables were measured using an automated analyzer (Beckman-Coulter/LH780, USA). Serum iron and transferrin saturation levels were measured using commercially available kits (Abbott, Milano, Italy), and ferritin concentration was determined using nephelometry on an Immune Light 2000 (Siemens Company, USA). High-sensitivity CRP was measured using immunonephelometry on the automated analyzer. Normal values of iron profile variables are shown in Table 1.

Table 1: Iron Parameters on ICU Admission TBI patients.

Variable	Normal ranges	ID (n=65)	Non-ID (n=69)	P value
Hb (g/dL)	13.5-17.5	7.4 ± 1.6	12.5 ± 3.4	0.008
Serum iron (mmol/L)	12-35	36 ± 10.2	156 ± 24.7	0.009
TSAT (%)	20-50	23 ± 1.5	43 ± 3.1	0.876
Serum ferritin (mg/L)	30-300	35 ± 13	221 ± 34	0.001
Soluble serum transferrin receptor (mg/L)	0.83-1.76	0.75 ± 0.5	0.82 ± 0.3	0.376
C- reactive protein (mg/L)	<10	4.2 ± 0.5	3.9 ± 0.2	0.349

Variables are expressed as mean ± SD) and percentage, n (%). ID, iron-deficient; non-ID, normal iron profile; Hb, hemoglobin, TSAT, transferrin saturation.

Definitions of iron deficiency

Anemia was defined as Hb concentration of <130 g/L in men and <120 g/L in women, in accordance with the World Health Organization criteria. Using this approach, ID was defined as either a serum ferritin level of <80 μg/L or a ferritin level of 80-150 μg/L combined with either a transferrin saturation (TSI) (serum iron per total iron binding capacity) of <20 % or a CRP level of <5 mg/L [6].

Blood transfusion

The protocol for transfusion in our ICU uses restrictive criteria: stable patients are transfused only when hemoglobin reaches 7 g/dL, whereas patients in septic shock or with acute cardiac conditions are transfused when hemoglobin reaches 9 g/dL [7].

Primary endpoint

The primary endpoint of this prospective study was the blood transfusion requirements in TBI patients.

Statistical analyses

Power analysis indicated that a minimum of 64 patients were required in each group based on type I error α of 0.05; type II error β of 0.20; difference of 5.8, standard deviations (SD) of group I of 4.4 and SD of group II of 1.7, respectively. Normality distribution of our data was confirmed using the Kolmogorov-Smirnov test. All variables between 2 groups were compared using the Mann-Whitney U test, and the distribution of gender with respect to the groups was analyzed using Yates' corrected chi-square test. A value of $P<0.05$ was considered to be statistically significant. All values are presented as means ± SD or number (%).

Results

Patient characteristics

A total of 142 consecutive ICU patients who fulfilled the inclusion criteria were considered for this study. Eight patients were excluded for the following reasons: 4 patients were diagnosed with bilaterally fixed and dilated pupils; 2 patients a life expectancy of less than 24 hours; 2 patients only an isolated epidural hematoma. Ultimately, 134 adult TBI patients ICU admission were included in the study. Clinical and demographic data for the 134 patients are presented in Table 2.

Table 2: TBI Patients' Characteristics.

Variable	ID (n=65)	Non-ID (n=69)	P value
Age (year)	34 ± 6	33 ± 8	0.853
Sex male/female	36/29	40/29	0.321
Body mass index (kg/m^2)	26 ± 8	25 ± 5	0.234
Cause of injury-no. (%)			
Motor vehicle or motorcycle accident	30 (46%)	34 (49%)	0.687
Fall	25 (38%)	26 (37%)	0.632
Sports or recreation accident or other event	10 (16%)	19 (14%)	0.234
Glasgow Coma Scale score-no. (%)			
Overall score			
3	5 (8%)	4 (6%)	0.317
4-6	31 (48%)	35 (48%)	0.245
	29 (34%)		
7 or 8	19 ± 2	30 (36%)	0.278
APACHE II (score)		17 ± 3	0.383

Variables are expressed as mean ± SD or percentage, n (%). ID, iron-deficient; non-ID, normal iron profile; ICU= intensive care unit; APACHE II=Acute Physiology and Chronic Health Evaluation

ID, Hb levels, and transfusion rates

Table 1 presents the remaining 134 patients were divided into 2 groups according to their baseline iron status: iron-deficient (ID; n=65; 48.5%) and non-ID (normal iron profile; n=69; 51.5%). The mean Glasgow coma score at baseline was 6 ± 5 and Injury Severity Score (ISS) 18.5 ± 4.5. Median Hb concentration on ICU admission was 9.6 (7.4 to 12.5) g/dL. At ICU admission ID patients was associated with low hemoglobin levels (P=01, Table 1). The median number of transfused blood units was associated with a higher transfusion rate in the ID group than in the non-ID group (5 and 2 U/patient, respectively; P =0.0001, Table 3). The median ICU length of stay was longer among the ID than the non-ID group (25 and 17 days/patient, respectively; P=0.0001, Table 3). ID with TBI patients, compared with non-ID patients, with higher ISS but no difference in admission GCS score or APACHE II scores. There were no significant differences regarding the day-28 neurological outcome, in-ICU and hospitality death, the number of ventilation-free days (Table 3).

Table 3. *Outcome Variables.*

Variable	ID (n=65)	Non-ID (n=69)	P value
Blood transfused units (n)	5 ± 2	2 ± 1	0.001
ICU length of stay (days)	25 ± 4	17 ± 3	0.001
ICU mortality (n)	5 ± 3	6 ± 2	0.231
Hospital mortality (n)	5 ± 2	7 ± 3	0.321

Data are presented as means ± SD

ID: iron deficiency; non-ID: no iron deficiency; ICU: intensive care unit

Discussion

In this prospective observational study, we found that ID was highly prevalent at ICU admission patients with TBI (48.5%) and that it was associated with higher blood transfusion requirements. To the best of our knowledge, this is the first report of the clinical relationship between ID and transfusion in ICU admission with TBI patients.

Patients with severe TBI commonly develop anemia. For patients with neurological injury, anemia is one potential cause of secondary injury which may worsen neurological outcomes. In addition, blood transfusion is commonly used in the treatment of anemia. For a long period, hemoglobin of 10.0 g/dL was the threshold for transfusion [10]. In a landmark multicenter Canadian trial, Hebert and colleagues randomized 838 critically ill patients to either a liberal protocol where transfusions were administered to maintain hemoglobin levels above 9 g/dl or a restricted strategy where hemoglobin levels were kept between 7 and 9 g/dl [11]. Overall, the 30-day mortality rate was 19 % in the restricted group and 23 % in the liberal transfusion group, with a significant difference in outcome among younger patients. Therefore, it could be concluded that limiting the use of blood products should lead to improvements in patient outcome. In a recent large multicentre study the mean Hb among TBI patients who remained in hospital longer than 24 days after ICU admissions was 96–98 g/L [12]. In our study, 52% of patients who had hemoglobin <10.0 g/dL received blood transfusion. The threshold for blood transfusion was frequently higher than 7.0 g/dL, which may be attributed to the presence of shock and the attempt to improve oxygen delivery and reduce secondary brain insult.

Maintaining a haemoglobin concentration of high has long been a management strategy to improve cerebral oxygenation in TBI patients. Low Hb level is a frequent finding among TBI patients and may result in secondary cerebral ischemia through a variety of different mechanisms, including impaired cerebrovascular regulation, reduced cerebral oxygen delivery and tissue hypoxia. As such, Hb <9 g/dl has been associated with poor outcome in several studies on TBI patients and correction of anemia by giving blood transfusions may represent a valuable therapeutic option in this setting [13]. Nevertheless, the effects of blood transfusions moderately anemic TBI patients remain controversial. In studies of anemic TBI patients, transfusion does improve brain oxygenation in some patients [14]. Other potentially beneficial effects of maintaining a higher hemoglobin concentration are to avoid increased ICP induced by anemia, and to provide a higher blood pressure and therefore better cerebral perfusion pressure [15]. Moreover, in some observational studies on TBI patients, blood transfusions were associated with a number of complications, including an increased risk for infections, and with poor outcome [16]. Thus, considering this “blood transfusion anemia paradox”, the optimal Hb level to trigger TBI patients has not been defined yet [17]. Determining who and when to transfuse this patients population is thus a challenge and recent years have seen continuing debate and discussion regarding the optimal transfusion, ‘trigger’.

Although blood transfusion can be lifesaving in extreme circumstances, in the absence of life threatening haemorrhage, the indications for transfusion are somewhat controversial. Blood transfusions have well-recognized problems, including the need to type and cross match, and the potential transmission of diseases, or the development of transfusion-related complications (such as transfusion-related acute lung injury or transfusion associated circulatory overload) and immunosuppression [18]. Studies have shown that for most critically ill patients, there is no advantage to maintaining a higher haemoglobin concentration [19].

ID is a common cause of anaemia in society and admission hospitality. In this study, the prevalence of ID is relatively high. Indeed, because of the blood losses regularly observed in TBI patients, one could have expected a higher prevalence of ID. Thus, we choose to use an ID definition that has already been used in an intervention study and that is commonly accepted in surgery patients [6]. There are few studies of the epidemiology of anaemia admission TBI patients. Accordingly, reduction of ID and ID-related anaemia during the TBI admission is likely to be beneficial. There is a consensus in the literature that reducing anemia rates and reducing the number of blood transfusions are 2 important goals of perioperative care [20]. This study focused on admission iron data, and the goal was to maintain Hb levels between 70 and 90 g/L. We showed that higher rates of transfusion are required for ID patients compared to non-ID patients. More importantly, this study identified ID as an important prognostic factor for predicting transfusion requirements in TBI admission patients.

Our study has several limitations. First, we did not measure inflammatory markers on admission Therefore; the biochemical parameters we used for diagnosis not only are markers for ID but also can indicate activation of acute-phase responses. A second important limitation is that, because this is an observational study, and, therefore, multiple adjustments for all comorbidities could not have been performed. Finally, this study had performed in a relatively small sample of patients and monocentric. Future studies should be carried out with larger numbers of patients to verify our results.

In conclusion, ID is common in patients admitted to the TBI patients at ICU. Moreover, we found that ID may be a prognostic factor for higher blood transfusion requirements with TBI at patients ICU admission. We believe that it is important to avoid transfusion during at ICU stay when possible with TBI. ID anemia may be able to be used to identify patients who should receive transfusion and the number of blood units required. Our findings may have implications for blood transfusion management strategies in TBI patients.

Conflict of Interest Statement:

Authors declare that there is no conflict of interest

Authors contributions

Durak MA and MS Aydogan: Providing conception, drafting of the article and supervision. Gurbuz S: Revising it critically for important intellectual content.

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