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ORIGINAL

Anemia and brain oxygen after severe traumatic brain injury

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Abstract *Purpose:* To investigate the relationship between hemoglobin (Hgb) and brain tissue oxygen tension ($PbtO_2$) after severe traumatic brain injury (TBI) and to examine its impact on outcome. *Methods:* This was a retrospective analysis of a prospective cohort of severe TBI patients whose $PbtO_2$ was monitored. The relationship between Hgb—categorized into four quartiles (≤9; 9–10; 10.1–11; >11 g/dl)—and $PbtO_2$ was analyzed using mixed-effects models. Anemia with compromised $PbtO_2$ was defined as episodes of Hgb ≤ 9 g/dl with simultaneous $PbtO_2 < 20$ mmHg. Outcome was assessed at 30 days using the Glasgow outcome score (GOS), dichotomized as favorable (GOS 4–5) vs. unfavorable (GOS 1–3). *Results:* We analyzed 474 simultaneous Hgb and $PbtO_2$ samples from 80 patients (mean age 44 ± 20 years, median GCS 4 (3–7)). Using Hgb > 11 g/dl as the reference level, and controlling for important physiologic covariates (CPP, PaO_2, $PaCO_2$), Hgb ≤ 9 g/dl was the only Hgb level that was associated with lower $PbtO_2$ (coefficient −6.53 (95 % CI −9.13; −3.94), $p < 0.001$). Anemia with simultaneous $PbtO_2 < 20$ mmHg, but not anemia alone, increased the risk of unfavorable outcome (odds ratio 6.24 (95 % CI 1.61; 24.22), $p = 0.008$), controlling for age, GCS, Marshall CT grade, and APACHE II score. *Conclusions:* In this cohort of severe TBI patients whose $PbtO_2$ was monitored, a Hgb level no greater than 9 g/dl was associated with compromised $PbtO_2$. Anemia with simultaneous compromised $PbtO_2$, but not anemia alone, was a risk factor for unfavorable outcome, irrespective of injury severity.

Keywords Hemoglobin · Brain tissue oxygen tension · Anemia · Traumatic brain injury · Cerebral oxygenation · Clinical study · Humans · Outcome · Brain oxygen · Brain injury

Introduction

Anemia is frequent after traumatic brain injury (TBI), occurring in up to 50 % of patients [1, 2]. Normally, dilation of cerebral arterioles augments cerebral blood flow (CBF) and preserves oxygen delivery in the setting of decreased oxygen content associated with anemia [3], therefore symptoms of anemia-induced brain dysfunction become manifest only when hemoglobin (Hgb) is less than 7 g/dl [4, 5]. In conditions of impaired cerebral autoregulation, such as occurs after TBI, compensatory mechanisms may be insufficient to maintain adequate CBF and anemia-induced brain injury may occur at higher Hgb thresholds, e.g., <9–10 g/dl [6]. In animal models of TBI, anemia reduces cerebral oxygenation [4, 7] and aggravates secondary brain injury [7–9]. Anemia also may worsen outcome [10, 11], although the relationship between anemia and TBI prognosis is still controversial [12]. Furthermore, correction of anemia with red blood cell transfusion, particularly when using Hgb targets greater than 10 g/dl, may in turn be associated with increased morbidity [13–15]. Guidelines recommend that anemia should not be the only factor used to decide whether to administer transfusions [16]; however, there are no established physiological markers to guide decision-making in TBI patients with anemia.

In animals, brain tissue oxygen tension ($PbtO_2$) is a good marker of anemia-induced brain injury [4, 7] and correction of anemia with transfusion [17] is associated with $PbtO_2$ increase and attenuation of compromised $PbtO_2$ and injury. Monitoring of $PbtO_2$ is an established tool to measure cerebral oxygenation in brain-injured patients [18] and is increasingly used in neurocritical care [19]. Cerebral perfusion pressure (CPP) and CBF are important physiologic determinants of $PbtO_2$ [20, 21]. Other factors include PaO_2 and $PaCO_2$ [22]. Low $PbtO_2$ is associated with poor outcome after TBI [23–25]. $PbtO_2$ might thus provide information about the physiological impact of anemia after severe TBI.

The objective of this study was to investigate the relationship between hemoglobin and $PbtO_2$ in patients with severe TBI and to examine its impact on outcome.

Materials and methods

Patients

Subjects were part of a prospective database (the brain oxygen monitoring outcome (BOMO) study) that describes patients with severe TBI treated in the neurointensive care unit at the Hospital of the University of Pennsylvania, Philadelphia [23]. Approval for the study was obtained from the institutional review board. Patients included in this study had (1) non-penetrating TBI and (2) both $PbtO_2$ and intracranial pressure (ICP) monitoring. Patients were excluded who (1) had fixed and dilated pupils at admission, (2) had less than 24 h of intracranial monitoring, (3) had $PbtO_2 = 0$ mmHg for longer than 3 h, (4) were declared brain dead within 48 h of initiation of monitoring. For the purpose of this study only patients who had at least 24 h of valid $PbtO_2$ and Hgb sampling were analyzed.

Intracranial monitoring

Intracranial pressure (Camino®, Integra Neurosciences, Plainsboro, NJ) and $PbtO_2$ (Licox®, Integra Neurosciences) were monitored as part of standard patient care [23, 26]. Monitors were inserted at the bedside into the frontal lobe and secured with a triple-lumen bolt. In all patients, monitors were placed into white matter that appeared normal on the admission head CT. When there was no asymmetry in brain pathology on CT, the probes were placed in the right frontal region. If the patient had undergone a craniotomy, the probes were placed on the same side as the injury if the craniotomy flap permitted. Non-contrast head CT scan was performed in all patients within 24 h of admission to confirm correct placement of the various monitors, e.g., not in a contusion or infarct. Probe function was confirmed by an oxygen challenge (FiO_2 1.0 for 2 min). To allow for probe equilibration, data from the first 3 h after ICP and $PbtO_2$ monitor insertion were discarded. Each patient also had an arterial catheter for mean arterial pressure (MAP) recording and calculation of CPP (MAP−ICP).

General clinical management

All patients were managed according to a protocol based on published recommendations for severe TBI care [27]. This included early evacuation of traumatic hematomas, pressure-limited ventilation to maintain $PaCO_2$ between 30 and 40 mmHg and $SaO_2 > 93$ %, sedation using propofol during the first 24 h followed by sedation and analgesia using lorazepam, morphine, or fentanyl, bed rest with head elevation initially of at least 30°, euvolemia using 0.9 % normal saline, and anticonvulsant prophylaxis with phenytoin for 1 week. Goals of therapy included maintaining ICP < 20 mmHg and CPP > 60 mmHg.

Elevated ICP (>20 mmHg for longer than 2 min) was initially treated with head of bed elevation, sedation, and analgesia. If ICP remained greater than 20 mmHg for longer than 10 min despite these measures, osmotherapy was administered with mannitol (0.5–1 g/kg, 25 % solution). Thereafter, cerebrospinal fluid was drained using

an external ventricular drain particularly if there was hydrocephalus. Second-tier therapies for refractory intracranial hypertension included optimized hyperventilation ($PaCO_2$ 30–35 mmHg), decompressive craniectomy, or pharmacological coma (with propofol or pentobarbital).

Management of brain oxygen

Patients received "cause-directed therapy" to maintain $PbtO_2 \geq 20$ mmHg according to our local protocol and as previously described [23, 26]. When $PbtO_2$ was low in the setting of ICP > 20 mmHg, measures were taken to lower ICP as described above. If ICP < 20 mmHg or lowering ICP failed to raise $PbtO_2$ then CPP was increased with phenylephrine. If the cause of low $PbtO_2$ was systemic hypoxemia then pulmonary function was optimized (by increasing FiO_2 and/or positive end-expiratory pressure). If excess metabolic demand was suspected (e.g., pain, agitation, fever, or seizures) then analgesic, sedative, or antiepileptic medications were administered. If these measures failed and hemoglobin was less than 10 g/dl a blood transfusion was administered.

Blood transfusion

Hemoglobin concentration was measured at least twice per day and the decision to transfuse blood was based on the discretion of the clinician in charge and the patient's clinical status when Hgb was 7–10 g/dl. Blood transfusion was given if hemoglobin was less than 7 g/dl. Blood gas concentrations (including PaO_2 and $PaCO_2$) were measured simultaneously with Hgb concentration.

Outcome assessment

A neurointensivist and a neurocritical nurse independently assessed short-term outcome at 30 days using the Glasgow outcome score (GOS), dichotomized as favorable (GOS 4 = moderate disability or 5 = good recovery) or unfavorable (GOS 1 = death, 2 = vegetative state, and 3 = severe disability requiring long-term rehabilitation).

Data collection and processing

Clinical and radiological variables included age, admission Glasgow coma scale (GCS), APACHE II score, and Marshall CT grade [28, 29]. Marshall CT grade was determined by consensus of a neurointensivist, a neuroradiologist, and a non-ICU neurologist who were blinded to patient outcome. Data were retrieved electronically via the computerized clinical information system. $PbtO_2$, ICP, and CPP were monitored continuously at the bedside (component monitoring system M1046-9090C, Hewlett Packard, Andover, MA) and also were recorded usually every 15 min and at least every 30 min in ICU records. For $PbtO_2$ data, artifacts (e.g., periods related to disconnection of monitoring devices, 1.0 FiO_2 during respiratory therapy), and data points outside of physiological ranges were manually excluded. For each patient, every consecutive hemoglobin sample was matched to simultaneous pressure data: matching was performed by calculating the mean value for $PbtO_2$, ICP, and CPP recorded over the 3 h preceding the Hgb sampling. Levels of Hgb were categorized into four separate quartiles: >11, 10.1–11, 9.1–10, and ≤9 g/dl. Anemia was defined as the presence of at least one episode of Hgb ≤ 9 g/dl, according to current transfusion practices and Hgb targets for transfusion in neurocritical care [1, 11, 30–32]. Compromised brain oxygen was defined as the presence of at least one episode of $PbtO_2 < 20$ mmHg for at least 15 min, according to our threshold for therapeutic intervention and the actual definition of moderate brain hypoxia [33] or compromised brain oxygen [34]. Anemia with compromised $PbtO_2$ was defined as the simultaneous occurrence of episodes with Hgb ≤ 9 g/dl and $PbtO_2 < 20$ mmHg.

Statistical analysis

Longitudinal data analysis was performed to account for repeated measures of physiological variables across different patients over time. Repeated measures of Hgb and of $PbtO_2$ were analyzed using a mixed-effects multilevel regression model, with mean $PbtO_2$ values nested into the patients and Hgb levels (categorized into four quartiles: ≤9, 9.1–10, 10.1–11, >11 g/dl, using >11 g/dl as the level of reference), CPP, PaO_2, $PaCO_2$, age, Marshall CT grade, admission GCS, APACHE II score (without GCS) as covariates. To examine the risk factors for unfavorable outcome at 30 days a logistic regression was used with age, Marshall CT grade, admission GCS, APACHE II score (without GCS), anemia, compromised $PbtO_2$, and anemia with simultaneous compromised $PbtO_2$. Data analysis was performed using STATA 12.0 (College station, Texas, 77845, USA). Significance was defined as $p \leq 0.05$.

Results

Patient characteristics

Eighty patients hospitalized over a 4-year period were studied (Table 1). Thirty-one patients managed during the same time period were excluded because of penetrating TBI ($n = 10$), ICP and $PbtO_2$ monitoring for less than

Table 1 Patient clinical characteristics

Variable	Value
Patient number	80
Age (years)	44 ± 20
Female/male (%)	18/62 (22.5 %)
Median admission GCS	4 (IQR 3–7)
Marshall CT grade	
II	18 (22 %)
III	26 (33 %)
IV	3 (4 %)
V	33 (41 %)
APACHE II score	19 ± 5
Glasgow outcome score (GOS)	
Good outcome GOS (4–5)	49 (61 %)
Poor outcome GOS (1–3)	31 (39 %)

Data are presented as mean ± SD or median (interquartile range, IQR)

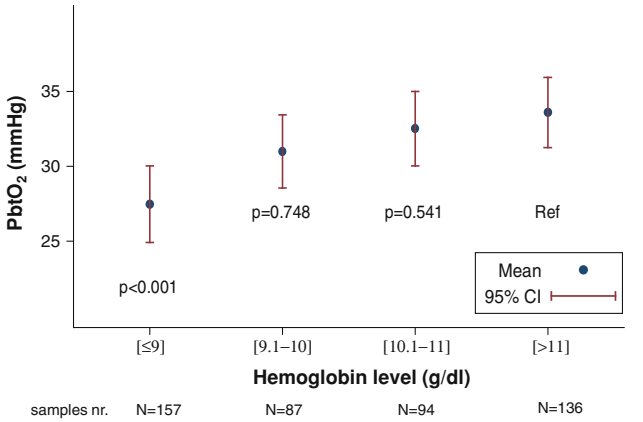

Fig. 1 For each quartile of hemoglobin, mean (95 % CI) values of $PbtO_2$ were calculated with mixed-effects models, accounting for subject variability over time

24 h ($n = 8$), $PbtO_2 = 0$ mmHg with a confirmed diagnosis of brain death within 48 h of the start of intracranial monitoring ($n = 8$), and incomplete $PbtO_2$ data ($n = 5$). An additional 23 patients were excluded from the present analysis because of lack of data on Hgb or blood gas analysis.

Relationship between hemoglobin and $PbtO_2$

Monitoring of $PbtO_2$ started on average 16 h after TBI and lasted for 5 ± 3 days. A total of 474 hemoglobin samples were analyzed. Median hemoglobin concentration was 10 g/dl (range 6.4–15.2 g/dl). Anemia (Hgb ≤ 9 g/dl) was observed in 154 samples (33 %). The median number of Hgb samples per patient was four (IQR 2–6). The majority of Hgb samples were between 9 and 11 g/dl: 13 % of samples were <8 g/dl, 2.5 % were <7 g/dl, 13 % were >12 g/dl, and 4 % were >13 g/dl. Categorization of Hgb into four quartiles (≤9, 9.1–10, 10.1–11, >11 g/dl) provided optimal distribution of Hgb samples.

Using a mixed-effects model, estimated mean (95 % CI) $PbtO_2$ values were calculated for each Hgb level (Fig. 1): compared to Hgb > 11 g/dl (reference level), mean $PbtO_2$ was lower when Hgb level was ≤9 g/dl ($p < 0.001$), whereas no significant differences in mean $PbtO_2$ were found at higher Hgb levels. Association of Hgb with $PbtO_2$ was further examined after adjusting for CPP, PaO_2, and $PaCO_2$ (Table 2) and for outcome predictors (age, admission GCS, Marshall CT grade, APACHE II score): compared to Hgb > 11 g/dl, Hgb ≤ 9 g/dl was the only Hgb level that was associated with lower $PbtO_2$ values (coefficient −6.53 (95 % CI −9.13; −3.94), $p < 0.001$). A positive linear relationship between $PbtO_2$ and CPP also was found (coefficient 0.12 (95 % CI 0.04; 0.20), $p = 0.003$), i.e., for each 10 mmHg decrease of CPP the $PbtO_2$ was 1.2 mmHg lower.

Table 2 Multivariate associations between the different hemoglobin levels and mean $PbtO_2$

Variable	Coefficient	95% CI	Adjusted *p* value
Hemoglobin level (g/dl)			
>11	Reference	Reference	Reference
10.1–11	−0.65	−3.40; 2.09	0.641
9.1–10	0.14	−3.13; 2.85	0.929
≤9	−6.53	−9.13; −3.94	<0.001
Cerebral perfusion pressure	0.12	0.04; 0.20	0.003
PaO_2	0.0002	−0.01; 0.01	0.971
$PaCO_2$	0.10	−0.03; 0.22	0.120
Age	−0.02	−0.13; 0.08	0.692
Admission GCS	0.37	−0.16; 0.89	0.168
Marshall CT grade	−0.16	−1.71; 1.39	0.839
APACHE II score	−0.23	−0.79; 0.32	0.409
Intercept	21.40		

Mixed-effects multilevel model was used to examine the relationship between mean $PbtO_2$ and different hemoglobin levels, with values of $PbtO_2$ nested into patients and quartiles of hemoglobin, cerebral perfusion pressure, PaO_2, $PaCO_2$, age, admission GCS, Marshall CT grade, and APACHE II score entered as covariates. Compared to hemoglobin >11 g/dl (reference level), a hemoglobin level ≤9 g/dl was associated with lower $PbtO_2$ levels. A decrease in cerebral perfusion pressure was also associated with a reduction of $PbtO_2$. All the other covariates did not contribute significantly to the model

Relationships between unfavorable outcome and anemia, compromised $PbtO_2$, and anemia with simultaneous compromised $PbtO_2$

Fifty-three patients (51 %) had anemia and 64 (80 %) had brain hypoxia. Thirty patients had anemia with compromised $PbtO_2$ (38 %), i.e., they had at least one episode with simultaneous Hgb ≤ 9 g/dl and $PbtO_2 < 20$ mmHg. Patients without simultaneous anemia and compromised $PbtO_2$ ($n = 50$; 62 %) were distributed as followed: six had no anemia and no compromised $PbtO_2$, ten had anemia alone without compromised $PbtO_2$, 21 had

Table 3 Relationship between anemia with simultaneous compromised $PbtO_2$ and unfavorable outcome

Variable	Odds ratio	95% CI	*p*
Anemia (Hgb $\leq$ 9 g/dl) and simultaneous brain hypoxia ($PbtO_2 < 20$ mmHg)	6.24	1.61; 24.22	0.008
Admission GCS	0.80	0.65; 1.00	0.045
Marshall CT grade	1.69	0.98; 2.93	0.059
APACHE II score	1.27	1.02; 1.58	0.030
Age	1.01	0.97; 1.04	0.758

Logistic regression was used to examine the association between anemia with simultaneous brain hypoxia and unfavorable outcome (defined as a GCS 1–3 at 30 days), adjusting for age, admission GCS, Marshall CT grade, and APACHE II score. The presence of anemia with simultaneous brain hypoxia increased the risk of unfavorable outcome by 6.24. Sensitivity of the model was 74 %, specificity 86 %, and the area under the ROC curve 0.88

compromised $PbtO_2$ alone without anemia, and 13 had anemia and compromised $PbtO_2$ that did not occur simultaneously. After adjusting for age, admission GCS, Marshall CT grade, and APACHE II score, anemia with simultaneous compromised $PbtO_2$ increased the risk of unfavorable outcome (adjusted odds ratio 6.24 (95 % CI 1.61; 24.22), $p = 0.008$) (Table 3). Sensitivity of the model was 74 %, specificity 86 %, and area under the ROC curve 0.88.

When the number of red blood cell transfusions received (complete data available on 57/80 patients) was added as a covariate to the model, the association between anemia with simultaneous compromised $PbtO_2$ and 30-day outcome remained significant (adjusted odds ratio 8.50 (95 % CI 1.22; 59.49), $p = 0.031$).

Entering anemia and compromised $PbtO_2$ separately as two variables in the model instead of anemia with simultaneous compromised $PbtO_2$ shows no impact of having Hgb $\leq$ 9 vs. $>$ 9 g/dl on unfavorable outcome (adjusted OR 0.89 (95 % CI 0.23; 3.51), $p = 0.867$), whereas having at least one episode of $PbtO_2 < 20$ mmHg vs. no compromised $PbtO_2$ increased the risk of unfavorable outcome (adjusted OR 9.42, 95 % CI (1.49–59.63), $p = 0.017$).

Discussion

In our cohort of 80 severe TBI patients whose intraparenchymal $PbtO_2$ was monitored, we found a significant relationship between Hgb and $PbtO_2$, whereby an Hgb level $\leq$9 g/dl was strongly associated with lower mean $PbtO_2$ values. Also, anemia (defined as Hgb $\leq$ 9 g/dl) and simultaneous compromised $PbtO_2$ (defined as $PbtO_2 < 20$ mmHg), but not anemia alone, was associated with a higher risk of unfavorable outcome, irrespective of cerebral and systemic injury, and even after controlling for the amount of blood that was transfused.

Relationship between hemoglobin and brain oxygen

Studies in TBI patients have used variable thresholds (8–11 g/dl) to define anemia [1, 2], but an optimal threshold for the definition of anemia in this setting is still unknown. From a physiological standpoint, the lowest Hgb threshold can be defined as the Hgb level below which oxygen delivery is impaired and cerebral hypoxic injury begins to occur. Mathematical modeling in animals suggests that oxygen uptake in the ischemic brain progressively decreases when hemoglobin concentration is less than 10 g/dl [6]. Here, we found mean $PbtO_2$ values were lower when hemoglobin was no greater than 9 g/dl. After adjusting for important determinants of cerebral oxygenation (CPP, PaO_2, and $PaCO_2$) and outcome (age, GCS, Marshall CT grade, APACHE II score), Hgb $\leq$ 9 g/dl was the only Hgb level that was associated with significantly lower $PbtO_2$. This Hgb threshold is in line with the definition of anemia utilized by the largest TBI prognostic database (the MRC CRASH trial, including more than 8,500 patients) [32] and with the current Hgb targets for blood transfusion in neurocritical care [1, 11, 30, 31].

Impact of anemia with compromised $PbtO_2$ on unfavorable outcome

Anemia is observed in approximately 50 % of TBI patients [2]. Whether anemia is associated with poor outcome after TBI is still controversial: some studies found that anemia during the ICU stay was associated with worse prognosis [10, 11], but another did not [12]. A possible explanation for these controversial findings is that the vulnerability of the brain to anemia may differ across TBI patients. An important mechanism by which anemia may contribute to secondary cerebral damage is by reducing oxygen transport capacity and $PbtO_2$ [9]. Consistent with this are the findings of increased expression of hypoxia-related molecules (erythropoietin, endothelial derived factors, neuronal nitric oxide synthase) [8], providing mechanistic evidence of anemia-induced tissue hypoxia. Here, we show that the simultaneous occurrence of anemia and compromised $PbtO_2$ was associated with worse outcome at 30 days. In contrast, we found no association between anemia alone and outcome. This is an important and novel finding that suggests that anemia per se may not be detrimental, but it may aggravate prognosis when it is simultaneously associated with compromised $PbtO_2$. Importantly, when adjusting for the number of units of blood transfused, the association of anemia and simultaneous compromised $PbtO_2$ with outcome remained statistically significant, suggesting that

anemia with compromised $PbtO_2$ per se, independent of transfusions, was a risk factor for unfavorable outcome.

Potential clinical implications of our study

Understanding the mechanisms involved in anemia-induced cerebral injury will contribute to the development of optimal therapy for anemic TBI patients. An important issue is a clearer definition of transfusion triggers based on individual physiological endpoints rather than generalized hemoglobin thresholds: this may reduce transfusion-related morbidity and attenuate anemia-induced cerebral insults, i.e., balance the potential risks associated with anemia and transfusion [16]. Our findings suggest that $PbtO_2$ may be a useful physiological target to manage anemia in patients with severe TBI.

Study limitations

There are several potential limitations to our study. First, although data were extracted prospectively, analysis was retrospective. However statistical analysis was performed by an independent statistician (Katia Iglesias) and blinded to patient outcome. Second, despite a standardized algorithm to manage ICP/CPP/$PbtO_2$ being applied to all subjects, the study was performed at a single institution and included a limited sample size and a selected group of severe TBI patients who underwent $PbtO_2$ monitoring. Our findings cannot be generalized to a wider TBI population: larger studies are needed to confirm our findings. All patients received cause-directed therapy to maintain $PbtO_2 > 20$ mmHg: therefore it is possible that patients with anemia and low $PbtO_2$ were those who were unresponsive to interventions to 'correct' compromised $PbtO_2$ and that it was this failure of $PbtO_2$ to respond to interventions that drove this outcome. This is a potential confounder. Third, Hgb values were matched to values of $PbtO_2$, CPP, and blood gas analysis obtained during the 3 h previous to Hgb sampling. Although somewhat arbitrary we found this interval appropriate, particularly because we did not account for concomitant therapeutic interventions that may substantially alter many of the variables measured. Increasing this interval further (e.g., up to 12 h) could have introduced confounding factors. On the other hand, the relationship between hemoglobin, $PbtO_2$, and outcome may have been underestimated. Another important issue is whether the covariation between $PbtO_2$, Hgb, and outcome are interlinked due to other reasons: owing to the nature of the study, this cannot be determined. Furthermore, given the limited number of samples with Hgb < 8 and < 7 g/dl, the relevance of the proportion of patients with Hgb thresholds lower than 9 g/dl is unclear. Fourth, only outcome at 30 days was obtained: although this time point may be sufficient to differentiate outcomes of general ICU patients, it may not be sufficient time to reflect long-term recovery. Thus we cannot speculate as to whether anemia with compromised $PbtO_2$ is associated with worse long-term prognosis. Fifth, the $PbtO_2$ monitor measures regional $PbtO_2$: clinical studies suggest that regional $PbtO_2$ still may be a good indicator of global brain oxygenation, particularly when the probe is located in uninjured brain [35] as in the present study. Since the $PbtO_2$ probes were placed in normal-appearing brain tissue on admission CT, and not around areas of contusions or lesions, it may underestimate the extent of brain hypoxia, at least in patients with focal injuries and hematomas [33]. Sixth, the precise causes of anemia-related brain hypoxia in our TBI cohort are not defined. Mixed-effects models, however, indicate that low CPP was an important cause of reduced $PbtO_2$. Finally, logistic regression model performed on the subset of patients in whom complete data on blood transfusions were available ($n = 57/80$) showed that the impact of anemia with compromised $PbtO_2$ was independent of the units of blood transfused. Although this result was derived from a rather limited number of patients, it reinforces the main conclusions of the study.

Conclusions

In this cohort study of severe TBI patients whose brain oxygen was monitored, patients with hemoglobin levels no greater than 9 g/dl were more likely to have lower mean $PbtO_2$ values, irrespective of other important physiologic cofactors, including cerebral perfusion pressure, PaO_2, and $PaCO_2$. Anemia with simultaneous compromised $PbtO_2$, but not anemia alone, increased the risk of unfavorable 30-day outcome after severe TBI. Our findings suggest that anemia-associated compromised $PbtO_2$ may aggravate TBI prognosis and support the concept that $PbtO_2$ may be a helpful physiologic target for the management of anemia after severe head injury.

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Conflicts of interest Eileen Maloney-Wilensky and Peter D. Le Roux are members of Integra Lifesciences Speaker's Bureau. Integra Lifesciences, however, had no involvement of any kind in the present study.

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