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Outcomes associated with brain tissue oxygen monitoring in patients with severe traumatic brain injury undergoing intracranial pressure monitoring

Haydn Hoffman, MD,[1] Karl Abi-Aad, MD,[2] Katherine M. Bunch, MS,[1] Timothy Beutler, MD,[1,3] Fadar O. Otite, MD,[3] and Lawrence S. Chin, MD[1]

Departments of [1]Neurosurgery, [2]Surgery, and [3]Neurology, State University of New York Upstate Medical University, Syracuse, New York

OBJECTIVE Brain tissue oxygen monitoring combined with intracranial pressure (ICP) monitoring in patients with severe traumatic brain injury (sTBI) may confer better outcomes than ICP monitoring alone. The authors sought to investigate this using a national database.

METHODS The National Trauma Data Bank from 2013 to 2017 was queried to identify patients with sTBI who had an external ventricular drain or intraparenchymal ICP monitor placed. Patients were stratified according to the placement of an intraparenchymal brain tissue oxygen tension ($PbtO_2$) monitor, and a 2:1 propensity score matching pair was used to compare outcomes in patients with and those without $PbtO_2$ monitoring. Sensitivity analyses were performed using the entire cohort, and each model was adjusted for age, sex, Glasgow Coma Scale score, Injury Severity Score, presence of hypotension, insurance, race, and hospital teaching status. The primary outcome of interest was in-hospital mortality, and secondary outcomes included ICU length of stay (LOS) and overall LOS.

RESULTS A total of 3421 patients with sTBI who underwent ICP monitoring were identified. Of these, 155 (4.5%) patients had a $PbtO_2$ monitor placed. Among the propensity score–matched patients, mortality occurred in 35.4% of patients without oxygen monitoring and 23.4% of patients with oxygen monitoring (OR 0.53, 95% CI 0.33–0.85; p = 0.007). The unfavorable discharge rates were 56.3% and 47.4%, respectively, in patients with and those without oxygen monitoring (OR 1.41, 95% CI 0.87–2.30; p = 0.168). There was no difference in overall LOS, but patients with $PbtO_2$ monitoring had a significantly longer ICU LOS and duration of mechanical ventilation. In the sensitivity analysis, $PbtO_2$ monitoring was associated with decreased odds of mortality (OR 0.56, 95% CI 0.37–0.84) but higher odds of unfavorable discharge (OR 1.59, 95% CI 1.06–2.40).

CONCLUSIONS When combined with ICP monitoring, $PbtO_2$ monitoring was associated with lower inpatient mortality for patients with sTBI. This supports the findings of the recent Brain Oxygen Optimization in Severe Traumatic Brain Injury phase 2 (BOOST 2) trial and highlights the importance of the ongoing BOOST3 trial.

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KEYWORDS cerebral oxygen monitoring; severe traumatic brain injury; multimodality monitoring; intracranial pressure

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality, which accounted for 2.8 million emergency department visits, hospitalizations, and deaths in 2013.[1] Severe TBI (sTBI), defined as having a Glasgow Coma Scale (GCS) score ≤ 8, is associated with high rates of mortality and poor functional outcome. Management is aimed at avoiding secondary injury by reducing brain swelling and optimizing cerebral perfusion and oxygenation. Current guidelines by the Brain Trauma Foundation recommend intracranial pressure (ICP) monitoring in patients with sTBI.[2] In addition to ICP monitoring, cerebral oxygen monitoring may provide clinicians with useful data that can guide treatment. Cerebral hypoxia occurs commonly in the early course of sTBI and is an independent predictor of poor outcomes.[3–6] Given the potentially devastating effects of cerebral hypoxia, monitoring of brain tissue oxygen tension ($PbtO_2$) has been proposed for those at high risk of hypoxic injury or those

ABBREVIATIONS ACS = American College of Surgeons; AIS = Abbreviated Injury Scale; BOOST = Brain Oxygen Optimization in Severe Traumatic Brain Injury; EVD = external ventricular drain; FiO_2 = fraction of inspired oxygen; GCS = Glasgow Coma Scale; GOS-E = Glasgow Outcome Scale–Extended; ICP = intracranial pressure; ISS = Injury Severity Score; LOS = length of stay; NTDB = National Trauma Data Bank; $PbtO_2$ = brain tissue oxygen tension; PSM = propensity score matching; sTBI = severe TBI; TBI = traumatic brain injury.

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requiring hyperventilation for ICP management.[7,8] Some authors have observed favorable outcomes with combined $PbtO_2$ and ICP monitoring compared with only the latter,[9–11] but others have not found this to be true.[12–14] Given the heterogeneity of the outcomes, the Brain Trauma Foundation did not provide a recommendation regarding $PbtO_2$ monitoring in the 4th edition of their guidelines.[2]

Many of the studies investigating $PbtO_2$ monitoring to date have been single-institution cohorts with small sample sizes and limited generalizability. To address this, we sought to use a national database to retrospectively compare the outcomes of patients who underwent $PbtO_2$ monitoring in conjunction with ICP monitoring with those who received ICP monitoring alone. These results could inform future efforts to investigate $PbtO_2$ monitoring with randomized clinical trials.

Methods

Description of the Data Set

The National Trauma Data Bank (NTDB) was used for this study. The NTDB is operated by the American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP) and includes trauma registry data from more than 700 facilities in the US. It employs the National Trauma Data Standard, which defines the reporting of specific data elements. Data abstractors are trained to report data in standardized forms, and interrater reliability audits are performed to ensure the consistency of the data.[15,16]

Inclusion Criteria

Patients aged 18 years or older with a head Abbreviated Injury Scale (AIS) score of 3, 4, or 5 who were admitted to an ACS trauma verification level 1 facility between 2013 and 2017 were identified. Those who were treated at an outside hospital before being transferred to the TQIP participating facility were excluded. Patients with GCS scores of 3–8 that were not obtained from examinations limited by pharmacological sedation or neuromuscular blockade were included. We excluded patients with a hospital length of stay (LOS) < 2 days because these patients were more likely to have incurred catastrophic, nonsurvivable injuries. Patients with advanced directives to withhold life-sustaining treatments were also removed. We subsequently identified patients who had an external ventricular drain (EVD) or intraparenchymal ICP monitor (e.g., Camino, Natus Medical Incorporated) placed.

Exposure Variables

The independent variable of interest was placement of an intraparenchymal oxygen monitor (e.g., Integra Licox, Integra LifeSciences Corp.). NTDB collection criteria did not provide constraints on types of $PbtO_2$ monitors to include but did explicitly mention Licox.[17] The Injury Severity Score (ISS) was calculated for each patient using AISs, and the scores were included as a covariate to adjust for overall injury severity. Patients were considered to have an isolated TBI if they did not have a nonhead AIS score ≥ 3. Vital sign abnormalities were defined as any of the following values recorded in the emergency department: hypotension (systolic blood pressure < 90 mm Hg), hypoxia (SpO_2 < 90%), bradycardia (heart rate < 60 beats per minute), and tachycardia (heart rate > 100 beats per minute).

Outcomes

The efficacy outcomes included inpatient mortality and discharge disposition. The latter was included as a surrogate for functional status and defined as favorable (discharged to home with or without organized home health services, a short-term facility, or inpatient rehabilitation) or unfavorable (discharged to an intermediate care facility, skilled nursing facility, or other long-term care facility) as described by Clement et al.[18] Total hospital LOS and ICU LOS were used as safety outcomes because optimization of $PbtO_2$ could necessitate lengthier hospitalizations, which are associated with increased morbidity. Given that treatment of cerebral hypoxemia can be associated with an increased fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure ventilator settings that could affect respiratory status, we also evaluated the duration of mechanical ventilation and the incidence of tracheostomy placement as additional safety outcomes. With the exception of the latter, all outcomes are provided as discrete variables in the NTDB. Tracheostomy was identified with the following ICD-9 procedure codes: 31.1, 31.21, 31.29, and ICD-10 procedure codes: 0B110F4, 0B110Z4, 0B113F4, 0B113Z4, 0B114F4, 0B114Z4.

Statistical Analysis

Univariate analysis was performed with the chi-square test for categorical variables and the Mann-Whitney U-test for nonparametric continuous variables. Propensity score matching (PSM) was used to compare outcomes in patients with (ICP + $PbtO_2$ group) or without (ICP group) $PbtO_2$ monitoring. Logistic regression models were used to develop propensity scores with the following independent variables: age, sex, GCS score, ISS, presence of hypotension, insurance, race, and hospital teaching status. Patients with or without $PbtO_2$ monitor placement were matched using a 2:1 nearest neighbor matching technique with 2 patients in the ICP group for every patient in the ICP + $PbtO_2$ group. The Cochran-Mantel-Haenszel test and the Wilcoxon signed-rank test were used to compare binary and continuous outcomes, respectively, for matched data. Given that the PSM analysis utilized a small subset of the overall cohort, we also performed sensitivity analyses involving the entire cohort. For these, multivariable-adjusted binary logistic and linear regressions were used to compare differences in binary and continuous outcomes, respectively, and each regression was adjusted for age, sex, GCS score, ISS, presence of hypotension, insurance, race, and hospital teaching status. Subgroup analyses were performed for patients undergoing craniotomy, with or without isolated TBI, and with various GCS score thresholds. Statistical analysis was performed using IBM SPSS version 24.0 (IBM Corp.) and R version 4.0.2 (www.r-project.org).

Results

Description of the Cohort

A total of 3421 patients with sTBI who underwent ICP monitoring were identified. The median (IQR) age was

37 years (25–53 years), and the majority of patients were male (77.8%). The median (IQR) ISS was 29 (22–38), and the most common injury mechanism was motor vehicle accident (58.7%), followed by fall (18.2%). The majority of patients (80%) were treated at teaching institutions. Intraparenchymal ICP monitors were slightly more common than EVDs (59.4% and 53.2%, respectively), and a small minority had both placed (12.5%).

There were 155 (4.5%) patients in whom a $PbtO_2$ monitor was placed. Of these, 90 (58.1%) also had an EVD placed, while the remaining patients had ICP measured with intraparenchymal monitors. The median (IQR) number of hours from presentation to cerebral monitor placement was 4.08 hours (2.38–9.55 hours) in the ICP group and 3.95 hours (2.33–7.63 hours) in the ICP + $PbtO_2$ group ($p = 0.496$). The ICP + $PbtO_2$ monitoring and ICP groups differed with respect to race, insurance status, proportion treated at a teaching hospital, and presence of hypotension (Table 1). There was a lower proportion of White patients and a higher proportion of minority (Black, Asian, American Indian, and Pacific Islander combined) patients in the ICP + $PbtO_2$ group. The ICP + $PbtO_2$ group also included more patients with Medicaid and "other/unknown" insurance, as well as fewer patients with private insurance and self-pay status. Fewer patients in the ICP + $PbtO_2$ group were hypotensive or treated at teaching hospitals. PSM generated a separate cohort of 455 patients matched 2:1 in which none of the exposure variables were associated with the treatment group (Table 1).

PSM Analysis

Inpatient mortality occurred in 1106 (32.3%) patients. Of those who died, withdrawal of life-sustaining treatments occurred in 29 (80.6%) patients from the ICP + $PbtO_2$ group and 666 (62.2%) patients in the ICP group ($p = 0.025$). Among those who had care withdrawn, this occurred at a median (IQR) of 7 days (4–12.25 days) and 8 days (5–12 days) after hospitalization for the ICP + $PbtO_2$ and ICP groups, respectively ($p = 0.693$). As shown in Fig. 1, among the propensity score–matched data, mortality occurred in 110 (35.4%) patients in the ICP group and 36 (23.4%) patients in the ICP + $PbtO_2$ group (OR 0.53, 95% CI 0.33–0.85). In the ICP + $PbtO_2$ and ICP groups, 56.3% and 47.4% of patients experienced an unfavorable discharge, respectively (OR 1.41, 95% CI 0.87–2.30). Eighty-five (2.5%) patients in the cohort experienced a stroke during hospitalization, and the incidence of stroke was similar in each propensity score–matched group (OR 0.55, 95% CI 0.15–1.96).

Sensitivity Analysis

In the sensitivity analysis, $PbtO_2$ monitoring was associated with decreased odds of mortality (OR 0.56, 95% CI 0.37–0.84) but higher odds of unfavorable discharge (OR 1.59, 95% CI 1.06–2.40) and no difference in stroke (OR 0.66, 95% CI 0.20–2.16). It was also not associated with total LOS ($p = 0.154$) or ICU LOS ($p = 0.104$).

Subgroup Analysis

As shown in Table 2, the ICP + $PbtO_2$ group had lower mortality in patients with a multisystem injury but not in those with isolated TBI. Patients with multisystem injury in the ICP + $PbtO_2$ group had longer ICU LOS ($p = 0.031$). $PbtO_2$ monitoring was also associated with lower mortality in patients with a GCS of score 6–8, but not in those with a score of 3–5. Those who underwent a craniotomy or craniectomy also experienced lower odds of mortality in the ICP + $PbtO_2$ group.

Safety Analysis

The median (IQR) hospital LOS and ICU LOS in the cohort were 18 days (9–30 days) and 13 days (7–20 days), respectively. Hospital LOS was similar between groups among PSM data (Fig. 2), but ICU LOS was significantly longer in the ICP + $PbtO_2$ group compared with the ICP group (median [IQR] 15 days [8.75–22 days] vs 13 days [9–18.5 days], respectively; $p = 0.032$).

The median (IQR) days of mechanical ventilation in the cohort was 10 days (5–16 days). This was longer in the ICP + $PbtO_2$ group (11.5 days [7–19 days] compared with 9.5 days [5–15 days] for the ICP group) ($p = 0.033$). There was no difference in the incidence of tracheostomy placement (OR 1.28, 95% CI 0.87–1.88).

Discussion

The management of patients with sTBI entails optimization of cerebral physiological parameters including cerebral blood flow and oxygen delivery to brain tissue. ICP is one of the primary measures that is treated in order to avoid secondary injury.[2] $PbtO_2$ monitoring is a newer method that has gained interest because it may have higher sensitivity to detect cellular injury when compared with ICP.[19,20] In a study of 19 patients with subarachnoid hemorrhage and 2394 samples of lactate and pyruvate collected using cerebral microdialysis, Chen et al. found that abnormal ICP and cerebral perfusion pressure had a sensitivity of up to 21.2% for the prediction of cellular metabolic distress.[21] Conversely, $PbtO_2 < 20$ mm Hg was found in 53% of samples exhibiting metabolic distress.[21] Furthermore, several studies have demonstrated that ICP might not always correlate with cellular oxygen consumption; a normal ICP, which would normally indicate adequate cellular oxygenation according to the Krogh model of oxygen transport, may not reflect adequate cerebral oxygenation in the setting of TBI.[22,23] This can be explained by the phenomena of microvascular collapse, perivascular edema, and endothelial swelling resulting from TBI, which significantly limits oxygen diffusion into cells.[19] Capillary oxygen pressure, however, has been shown to correlate better with cellular respiration, and, unlike ICP, which assumes a constant microenvironment exchange, accounts for the dynamic changes at the capillary beds such as distribution of erythrocytes with different oxygen concentrations.[24] There are two types of technology for measuring $PbtO_2$: the optical luminescent and polarographic methods. The former relies on oxygen diffusion on a matrix containing a dye combined with light emission on the matrix. The change in light frequency following dye penetration is then converted to the oxygen partial pressure. The polarographic method relies on a battery with a cathode/anode

TABLE 1. Demographic and injury data in patients with sTBI and an abnormal head CT scan stratified by the presence of cerebral oxygen monitoring

	All Patients w/ sTBI & ICP Monitoring (n = 3421)			PSM Patients (n = 465)		
	ICP	ICP + $PbtO_2$	p Value	ICP	ICP + $PbtO_2$	p Value
Median age (IQR)	37 (25–53)	37 (24–54)	0.752	39 (25–56)	37 (24–54)	0.852
Sex			0.626			0.380
Male	2540 (77.8)	118 (76.1)		247 (79.7)	118 (76.1)	
Female	725 (22.2)	37 (23.9)		63 (20.3)	37 (23.9)	
Race			0.001			0.997
White	2065 (63.2)	95 (61.3)		187 (60.3)	95 (61.3)	
Black	531 (16.3)	21 (13.5)		42 (13.5)	21 (13.5)	
Asian	84 (2.6)	9 (5.8)		20 (6.5)	9 (5.8)	
American Indian	12 (0.4)	0		0	0	
Pacific Islander	7 (0.2)	3 (1.9)		5 (1.6)	3 (1.9)	
Other/unknown	567 (17.4)	27 (17.4)		56 (18.1)	27 (17.4)	
Insurance			0.017			0.996
Medicare	341 (10.4)	12 (7.7)		24 (7.7)	12 (7.7)	
Medicaid	819 (25.1)	42 (27.1)		88 (28.4)	42 (27.1)	
Private	1266 (38.8)	58 (37.4)		109 (35.2)	58 (37.4)	
Self-pay	457 (14.0)	13 (8.4)		28 (9.0)	13 (8.4)	
No charge	4 (0.1)	1 (0.6)		3 (1.0)	1 (0.6)	
Other/unknown	379 (11.6)	29 (18.7)		58 (18.7)	29 (18.7)	
Teaching hospital	2626 (80.4)	112 (72.3)	0.013	216 (69.7)	112 (72.3)	0.565
No. of comorbidities			0.533			0.442
0	1907 (58.4)	97 (63.0)		178 (57.4)	97 (63.0)	
1	769 (23.6)	32 (20.8)		80 (25.8)	32 (20.8)	
2+	587 (18.0)	25 (16.2)		52 (16.8)	25 (16.2)	
Injury mechanism			0.881			0.698
MVC	1916 (58.7)	87 (56.1)		187 (60.3)	87 (56.1)	
Fall	593 (18.2)	31 (20.0)		59 (19.0)	31 (20.0)	
Firearm	129 (3.9)	4 (2.6)		11 (3.5)	4 (2.6)	
Transport/other	125 (3.8)	7 (4.5)		9 (2.9)	7 (4.5)	
Struck by/against	178 (5.5)	8 (5.2)		19 (6.1)	8 (5.2)	
Other/unknown	325 (10.0)	18 (11.6)		25 (8.1)	18 (11.6)	
Hypotension	317 (9.7)	7 (4.5)	0.031	16 (5.2)	7 (4.5)	0.762
Pulse			0.931			0.356
60–99	1,484 (45.6)	73 (47.1)		123 (40.2)	73 (47.1)	
<60	267 (8.2)	12 (7.7)		29 (9.5)	12 (7.7)	
≥100	1,502 (46.2)	70 (45.2)		154 (50.3)	70 (45.2)	
GCS score			0.895			0.197
3–5	2208 (67.6)	104 (67.1)		189 (61.0)	104 (67.1)	
6–8	1058 (32.4)	51 (32.9)		121 (39.0)	51 (32.9)	
Intracranial injury			0.214			0.589
SAH	132 (4.0)	2 (1.3)		6 (1.9)	2 (1.3)	
SDH	213 (6.5)	6 (3.9)		21 (6.8)	6 (3.9)	
EDH	25 (0.8)	0		3 (1.0)	0	
Contusion	319 (9.8)	13 (8.4)		21 (6.8)	13 (8.4)	
Mixed	2430 (74.4)	127 (81.9)		245 (79.0)	127 (81.9)	
Isolated TBI	1245 (38.2)	64 (41.6)	0.396	137 (44.2)	64 (41.6)	0.590
Median ISS (IQR)	29 (22–38)	30 (24–38)	0.169	29 (24–35)	30 (24–38)	0.229

EDH = epidural hematoma; MVC = motor vehicle collision; SAH = subarachnoid hemorrhage; SDH = subdural hematoma.
Values represent the number of patients (%) unless stated otherwise.

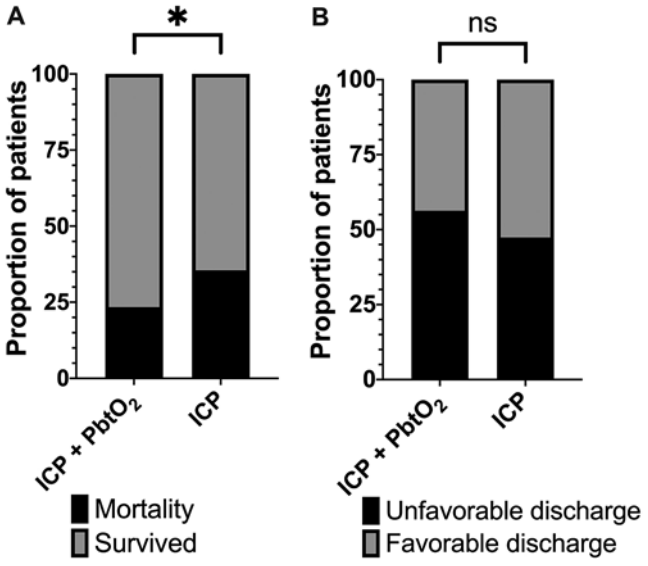

FIG. 1. Comparison of efficacy outcomes. Boxplots showing mortality (**A**) and unfavorable discharge (**B**) among patients with or without cerebral oxygen monitoring. *p < 0.05; ns = not significant.

system that uses oxygen for reduction at the cathode. The generated galvanic current intensity is then converted to the oxygen partial pressure. The latter method is applied in the Licox brain oxygen monitor that was approved by the US FDA in 2001. The Licox monitor can be inserted into the brain in a fashion similar to that of a fiber-optic ICP monitor, approximately 3.5 cm below the dura mater. Although the placement of different types of $PbtO_2$ monitors could have introduced heterogeneity into the cohort, we suspect that the majority of patients had Licox monitors placed based on NTDB collection criteria.[17]

$PbtO_2$ monitoring has primarily been implemented as an adjunct to ICP monitoring. A notable exception was observed in a study by Meixensberger et al. that compared ICP with only $PbtO_2$ monitoring, and no difference in outcome was found.[25] Most subsequent studies evaluating the benefits of cerebral oxygen monitoring compared ICP monitoring alone with ICP and $PbtO_2$ monitoring combined. It remains unclear whether the addition of $PbtO_2$ monitoring improves outcomes. In our study, the $PbtO_2$ + ICP group experienced a significantly lower mortality rate than the ICP group. The sensitivity analysis recapitulated this finding with the entire cohort of 3241 sTBI patients. There are several possible explanations for the mortality benefit in the $PbtO_2$ + ICP group. $PbtO_2$ monitoring could detect impairments in cerebral perfusion before ICP elevations occur. It could also reflect impairments in cerebral autoregulation, which is not informed by ICP monitoring. Alternatively, mortality in the $PbtO_2$ + ICP group could have been artificially reduced by less severe injuries and more aggressive treatment plans. The former seems less likely since the GCS scores and ISSs were similar between the groups, and the latter is inconsistent with the higher rates of withdrawal of care in the $PbtO_2$ + ICP group. The subgroup analysis showed that $PbtO_2$ monitoring was associated with lower mortality in select populations with worse clinical presentations, including patients with multisystem injury and those who required craniotomy or craniectomy. These findings may be explained by the fact that patients with more severe injuries are at higher risk for secondary injury in the form of cerebral hypoxia. This is especially true of patients with coexisting pulmonary injury. Conversely, mortality in patients with lower GCS scores (3–5) was not associated with $PbtO_2$ monitoring. Further research is needed to define subsets that benefit from $PbtO_2$ monitoring the most.

$PbtO_2$ monitoring has historically shown inconsistent mortality benefit. A meta-analysis of 9 studies including 1284 patients showed no difference in mortality between groups.[26] However, patients who received $PbtO_2$ monitoring had a higher rate of favorable outcome at discharge and at 6-month follow-up, defined as either a Glasgow Outcome Scale score of 4–5, Glasgow Outcome Scale–Extended (GOS-E) score of 5–8, or functional independence measure score ≥ 7. When the authors excluded the study by Martini et al., which presented a major source of heterogeneity (attributed to the fact that they did not exclude patients who died directly following the primary insult), the remaining pool of 655 patients experienced a significant

TABLE 2. Multivariable-adjusted subgroup analysis of the association between $PbtO_2$ monitoring and each outcome

	Outcome					
	Mortality		Unfavorable Discharge		p Value	
	OR	95% CI	OR	95% CI	Total LOS	ICU LOS
Injury type						
Isolated TBI	0.82	0.46–1.48	1.77	0.90–3.50	0.442	0.898
Multisystem injury	0.39	0.22–0.69	1.40	0.83–2.37	0.173	0.031*
GCS score						
3–5	0.64	0.40–1.02	1.54	0.92–2.59	0.099	0.314
6–8	0.40	0.17–0.96	1.70	0.87–3.33	0.895	0.178
Craniotomy						
Yes	0.46	0.24–0.87	1.75	0.94–3.25	0.465	0.240
No	0.62	0.36–1.06	1.38	0.78–2.42	0.248	0.246

* Higher ICU LOS in patients with $PbtO_2$ monitoring.

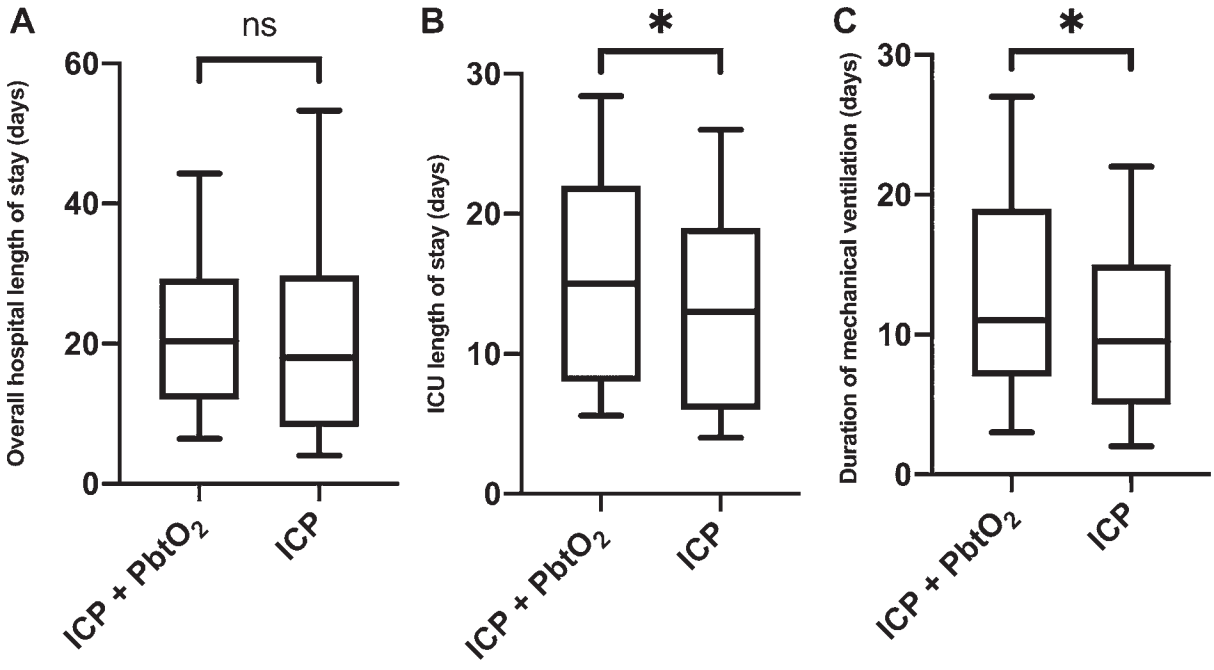

FIG. 2. Comparison of safety outcomes. Boxplots showing the overall hospital LOS (**A**), ICU LOS (**B**), and duration of mechanical ventilation (**C**) among patients with or without cerebral oxygen monitoring. *Whiskers* indicate 10th and 90th percentiles. *p < 0.05; ns = not significant.

mortality reduction with $PbtO_2$ monitoring.[12] These results are in concordance with ours, which also excluded patients with early mortality. Other sources of heterogeneity that complicate direct comparisons of outcomes associated with $PbtO_2$ monitoring include varying $PbtO_2$ thresholds and treatment strategies used to increase cerebral oxygenation. For example, Stiefel et al.[27] treated $PbtO_2$ levels < 25 mm Hg, while Meixensberger et al.[25] permitted levels as low as 10 mm Hg before intervening. Interestingly, Stiefel et al. demonstrated that duration of time with $PbtO_2$ < 25 mm Hg was significantly higher in patients who died.[27] All other studies of the meta-analysis used a threshold of 20 mm Hg, which is consistent with the Neurocritical Care Society consensus statement.[28] The most comprehensive study of optimal $PbtO_2$ thresholds was performed by Hirschi et al.; the authors evaluated 1,380,841 recorded values and compared clinical outcomes with dichotomized $PbtO_2$ ranges.[29] A threshold of 19 mm Hg yielded the largest area under the curve; however, the authors also found significant treatment benefits for values up to 33 mm Hg.

Various strategies for increasing cerebral oxygenation exist. Meixensberger et al. treated low $PbtO_2$ levels by increasing cerebral perfusion pressure, while others have implemented systemic oxygenation strategies.[25] For example, in a randomized controlled trial by Lin et al., low $PbtO_2$ values were treated with 100% FiO_2 for up to 5 hours.[10] For the ongoing Brain Oxygen Optimization in Severe Traumatic Brain Injury phase 3 (BOOST3) trial a 3-tiered management protocol based on ICP and $PbtO_2$ values was developed.[30] Tier 3 interventions included most aggressive treatments such as pentobarbital coma, decompressive craniectomy, induced hypothermia, and neuromuscular blockade. Tier 2 treatment interventions for $PbtO_2$ < 20 mm Hg included blood transfusion for a target hemoglobin ≥ 10 g/dL. While the BOOST 2 trial showed a trend toward lower mortality and improved functional outcomes in the ICP + $PbtO_2$ arm, the study was a phase 2 trial only, powered to detect the feasibility and safety of the proposed treatment protocol. Primary endpoints included differences in duration of hypoxia ($PbtO_2$ < 20 mm Hg) and elevated ICP (> 20 mm Hg) between each group. The ICP + $PbtO_2$ arm experienced reduced hypoxia time, and there were no differences in duration of elevated ICP or adverse events between both arms.[30]

Although mortality was lower in patients with $PbtO_2$ monitoring, there was no difference in discharge disposition. This was unexpected since the BOOST 2 trial identified improved functional outcomes in the treatment arm at the 6-month follow-up. Our findings may be related to the lack of outpatient follow-up, since some patients could experience improvements in their functional statuses after discharge. Furthermore, favorable versus unfavorable discharge is a relatively insensitive measure of functional outcome compared with the GOS-E score that was used in BOOST 2. There was no difference in the incidence of stroke between the 2 groups in our study, which may be related to the manner in which this outcome was coded in NTDB. Strokes were defined as neurological deficits absent on admission and did not necessitate MRI findings of ischemia.[17] Therefore, a variety of neurological events not influenced by cerebral hypoxia could have contributed to this outcome, such as expansion of a hematoma or hydrocephalus.

Few authors have examined the safety of interventions for treating cerebral hypoxia. We did not find any difference in overall LOS; however, there was significantly

longer ICU LOS and duration of ventilation in the ICP + $PbtO_2$ group. The longer times in the ICU and on mechanical ventilation in the ICP + $PbtO_2$ group could be adverse effects from the treatments for cerebral hypoxia. For example, sustained administration of high FiO_2 can lead to barotrauma, transfusion can cause lung injury, and excessive fluid boluses can lead to pulmonary edema. Since we did not have information regarding how cerebral hypoxia was treated in the cohort, we are unable to draw a conclusion regarding $PbtO_2$ treatment and these outcomes, but it is an important association that should be investigated in future studies. Alternatively, the ICP group could have been more severely injured and therefore died earlier, but since the presenting GCS score and ISS did not differ between the groups, we suspect that this is less likely.

Our study is limited by its retrospective nature, which introduced the possibility of confounding. We attempted to address this with PSM, but this technique is only as effective as the variables used to develop the propensity scores, and it is possible that we did not account for an important confounder. The two groups differed with respect to race, insurance, hypotension, and teaching hospital status before PSM. Prior studies have failed to show an association between race and mortality in patients with TBI.[31,32] The greater proportion of Medicaid insured patients and the presence of fewer privately insured patients in the ICP + $PbtO_2$ group could have contributed to less favorable outcomes,[32] while the lower incidence of hypotension would have had the opposite effect. The combined effect of these differences is uncertain, but none of these variables were significantly different after PSM was performed. Although the inclusion of data from multiple institutions increased the generalizability of the results, it introduced heterogeneity in several parameters that we were not able to account for with NTDB data. These include probe location (affected vs unaffected hemisphere), $PbtO_2$ treatment threshold, different $PbtO_2$ monitors, strategies for treating cerebral hypoxia, and selection criteria for monitor placement. Information regarding indications for $PbtO_2$ monitor placement was not available. Additionally, it is possible that in some patients, $PbtO_2$ measurements were disregarded or their accuracy was not ensured with a 100% FiO_2 test, although we suspect that inclusion of only ACS trauma verification level 1 facilities minimized this. Finally, NTDB does not provide data regarding neurological or functional outcomes. Discharge disposition was used as a surrogate for the latter, but this is a less sensitive measurement than GOS-E.

The results of this study suggest that $PbtO_2$ monitoring, when added to ICP monitoring, may reduce inpatient mortality in patients with sTBI. Although the retrospective nature of the study and the limited granularity of the database prevent commenting on causality, this is a promising association that warrants further study and underscores the importance of the ongoing BOOST3 trial. Given the longer ICU LOS and ventilation duration in the ICP + $PbtO_2$ group, future studies should address potential adverse effects of cerebral hypoxia treatment.

Conclusions

The combination of $PbtO_2$ and ICP monitoring is associated with lower mortality than ICP monitoring alone in patients with sTBI. $PbtO_2$ monitoring is also associated with longer duration of mechanical ventilation and ICU LOS, which could be a risk of treating $PbtO_2$ values. The safety and efficacy of $PbtO_2$ monitoring warrant further study.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Hoffman. Analysis and interpretation of data: Hoffman, Abi-Aad, Bunch, Beutler, Otite. Drafting the article: Abi-Aad, Bunch. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hoffman. Statistical analysis: Hoffman. Administrative/technical/material support: Beutler, Otite, Chin. Study supervision: Beutler, Chin.

Correspondence

Haydn Hoffman: State University of New York Upstate Medical University, Syracuse, NY. hoffmanh@upstate.edu.