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ORIGINAL PAPER

Brain tissue oxygen tension monitoring in pediatric severe traumatic brain injury

Part 1: Relationship with outcome

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Abstract
Introduction Intracranial pressure (ICP) monitoring and cerebral perfusion pressure (CPP) management are the current standards to guide care of severe traumatic brain injury (TBI). However, brain hypoxia and secondary brain injury can occur despite optimal ICP and CPP. In this study, we used brain tissue oxygen tension ($PbtO_2$) monitoring to examine the association between multiple patient factors, including $PbtO_2$, and outcome in pediatric severe TBI.
Materials and methods In this prospective observational study, 52 children (less than 15 years) with severe TBI were managed with continuous $PbtO_2$ and ICP monitoring. The relationships between outcome [Glasgow Outcome Score (GOS) and Pediatric Cerebral Performance Category Scale] and clinical, radiologic, treatment, and physiological variables, including $PbtO_2$, were examined using multiple logistic regression analysis.
Results Outcome was favorable in 40 patients (77%) and unfavorable (mortality, 9.6%; $n=5$) in 12 (23%). In univariate analysis, the following variables had a significant association with unfavorable outcome: initial GCS, computed tomography classification, ICP_{peak}, $mICP_{24}$, mICP, CPP_{low}, $CPP^{<40}$, pupil reactivity, $PbtO_{2_{low}}$, $PbtO_2<5$ mmHg, $PbtO_2<10$ mmHg, $mPbtO_{2_{24}}$, and time–severity product. $PbtO_2$ parameters had the strongest independent association with poor outcome in multiple regression analysis. In particular, when $PbtO_2$ was <5 mmHg for >1 h, the adjusted OR for poor outcome was 27.4 (95% confidence interval, 1.9–391). No variables apart from $PbtO_2$ were independently associated with mortality when controlled for $PbtO_2$.
Conclusion Reduced $PbtO_2$ is shown to be an independent factor associated with poor outcome in pediatric severe TBI in the largest study to date. It appears to have a stronger association with outcome than conventionally evaluated measures.

Keywords Brain tissue oxygen tension · Outcome · Hypoxia · Children · Traumatic · Brain injury

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Introduction

The goal of neurosurgical and critical care management of children with severe traumatic brain injury (TBI) is to avoid or ameliorate secondary injury to maximize the chance of a favorable outcome. Evidence from postmortem [9] and clinical studies [3, 4, 24] suggests that secondary brain hypoxia–ischemia contributes significantly to poor outcome. However, adherence to physiological targets for intracranial pressure (ICP) control, cerebral perfusion pressure (CPP) management, and respiratory function may

not avoid brain hypoxia in all patients [5, 33]. This suggests that direct monitors of brain oxygenation that can be used continuously in the intensive care unit (ICU) may help guide patient care. However, continuous measures of brain oxygen have been infrequently used in pediatric neurocritical care. By contrast, brain tissue oxygen tension ($PbtO_2$) monitors are used increasingly in adult TBI patients to obtain additional information to guide therapy. Furthermore, several studies in adult TBI demonstrate a relationship between low $PbtO_2$ and poor outcome [17, 19, 32, 38, 40, 42, 43]. However, few studies have examined the association between $PbtO_2$ and outcome in pediatric TBI [5, 21, 34], and these studies have included relatively few patients. In this study, we examined the relationship between $PbtO_2$ and outcome in a larger (n=52) group of children with severe TBI. This allowed us to control for other clinical, physiological, and treatment factors that may influence outcome to examine whether $PbtO_2$ is an independent factor associated with outcome.

Materials and methods

Ethics approval for the study was obtained from the Institutional Review Boards of the Red Cross Children's Hospital and the University of Cape Town.

Patient selection

Data from a consecutive series of pediatric patients who underwent $PbtO_2$ and ICP monitoring for severe TBI at Red Cross Children's Hospital between June 2006 and May 2008 were prospectively collected. All patients were less than 15 years old. Children with TBI were considered for intracranial monitoring if their postresuscitation Glasgow Coma Score (GCS) was ≤8 or deteriorated to this level after admission, unless extubation was planned early for an improving patient or brain death was imminent [GCS 2T/15, fixed and dilated pupils, and 'black brain' on computed tomography (CT) head scan]. Patients were resuscitated, underwent endotracheal intubation, and were mechanically ventilated in the pediatric ICU.

Patient management

The details of patient management have been previously described [5]. In general, patient care was based on the current recommendations for the management of severe TBI in children [1]. ICP was measured through a ventriculostomy or intraparenchymal monitor [Codman ICP Express (Codman, Raynham, MA, USA) and Camino (Integra Neurosciences, Plainsboro, NJ, USA)]. ICP was treated according to the guidelines for ICP management in children [2], which recommends a treatment threshold of 20 mmHg and a stepwise approach to treat ICP>20 mmHg. We aimed to keep CPP>50 mmHg in children >2 years old and >45 mmHg in children <2 years old. When an ICP monitor was placed, we also monitored and treated $PbtO_2$. $PbtO_2$ catheters (Licox®, Integra Neurosciences) were inserted into normal-appearing right frontal white matter if there were no localized lesions or in the hemisphere with the greater swelling or containing focal lesions. Data from patients were collected for analysis after a 2-h run-in period to avoid potential artifacts from a stabilizing catheter. Compromised (low) $PbtO_2$ was defined as <20 mmHg and was treated using a hierarchical treatment algorithm that started with a search for a possible cause for low $PbtO_2$. In the absence of a specific cause, the following measures were used depending on ICP, mean arterial pressure (MAP), arterial partial pressure of oxygen (P_aO_2), hemoglobin (Hb), arterial partial pressure of carbon dioxide (P_aCO_2), transcranial Doppler flow velocities, and status of autoregulation (when known): (1) elevated or borderline ICP was treated more aggressively when present, (2) the patient's blood pressure (BP) was elevated to test $PbtO_2$ at a higher CPP with volume infusion and/or inotropic support unless loss of autoregulation caused an ICP increase with elevated BP, (3) higher P_aCO_2 was tolerated to induce cerebral vasodilation if ICP was not elevated, (4) blood was transfused to increase Hb to ≥10 g/dl, and (5) the inspired fraction of oxygen (F_iO_2) was increased as an emergency temporary measure or if $PbtO_2$ remained low despite optimization of the above parameters.

Data collection

Data collected included age, gender, mechanism of injury, initial clinical assessment (see below), length of time after injury, and injury to other systems. The following markers of potential prehospital clinical insults were recorded: initial hypoxia, initial MAP, initial systolic blood pressure less than 90 mmHg (SBP<90), and initial Hb. Physiological monitoring data collected in the ICU included arterial blood gas (ABG) parameters, continuous pulse oximetry (S_aO_2), MAP, ICP, CPP, and $PbtO_2$. Continuous data were recorded as hourly variables from nursing records.

Initial assessment At admission and following resuscitation, patients were assessed using (1) postresuscitation GCS or the Pediatric Coma Scale [28] for preverbal children, (2) the motor component of the GCS, (3) the Pediatric Trauma Score [35], and (4) the Pediatric Index of Mortality score [31]. The type of TBI was classified according to the Marshall Classification based on the admission head CT scan findings [18], and patients were defined as having polytrauma or isolated TBI. Postresuscitation pupillary reactions

were classified as bilaterally reactive (1), unilaterally nonreactive (2), or bilaterally nonreactive (3). The influence of medications was excluded.

Physiological variables

Intracranial monitoring was started as soon as possible after admission to the ICU and, in general, was continued until both ICP and $PbtO_2$ were controlled for >48 h or until the patient died. Terminal data were excluded from analysis (defined as data collected after the diagnosis of brainstem death was made or when $PbtO_2$ was 0 mmHg for >1 h).

$PbtO_2$ The following $PbtO_2$ values were calculated for each patient: lowest $PbtO_2$ recorded during the monitored period ($PbtO_{2_{low}}$), mean $PbtO_2$ during the first 24 h of monitoring ($mPbtO_{2_{24}}$), and the number of episodes of $PbtO_2$< 10 mmHg ($PbtO_2$<10) or $PbtO_2$<5 mmHg ($PbtO_2$<5) experienced. Since brain injury is determined by both the depth and duration of brain hypoxia, we defined a measure of low $PbtO_2$ that reflects both. Therefore, for each episode that $PbtO_2$ was <10 mmHg ($PbtO_2=X$ mmHg) in each patient, we calculated the value $10-X$ mmHg. A $PbtO_2$ of 10 mmHg is considered a critical tissue hypoxia threshold [26, 38]; therefore, 10-X represents the depth of hypoxia. Thereafter we averaged all of these ($10-X$) values from each patient. This average was then multiplied by the number of episodes that $PbtO_2$ was less than 10 mmHg in that patient. This was termed the time–severity product to reflect the overall brain hypoxia burden.

Intracranial pressure The following ICP values were recorded for each patient: mean ICP for the duration of monitoring (mICP), mean ICP for the first 24 h of monitoring ($mICP_{24}$), the number of episodes of ICP>20 mmHg ($ICP_{>20}$), the mean of all episodes of $ICP_{>20}$ ($mICP_{>20}$), and the highest ICP (ICP_{peak}) experienced.

Cerebral perfusion pressure Potential CPP insults were calculated for each patient as initial CPP ($CPP_{initial}$), the lowest CPP experienced (CPP_{low}), and the number of episodes that CPP was <40 mmHg ($CPP_{<40}$) and <50 mmHg ($CPP_{<50}$).

Systemic oxygenation Potential **s**ystemic hypoxic episodes were defined as P_aO_2<8 kPa (60 mmHg) obtained on ABG analysis, or S_aO_2<90% on peripheral oximetry or ABG. The lowest P_aO_2 ($P_aO_{2_{low}}$) observed also was recorded.

Hemoglobin Concentration of Hb (g/dl) was recorded as initial Hb ($Hb_{initial}$), lowest Hb (Hb_{low}) and mean Hb for the duration of the ICU stay (mHb).

Treatment The duration of monitoring was recorded in each patient. Treatment factors recorded included red blood cell transfusion (RBCT), hypertonic saline given (HTS; recorded as the number of times given), decompressive hemicraniectomy, the use of thiopentone, and use of inotropes to elevate BP.

Clinical outcome

The place (e.g., ICU or general ward) and time of deaths were recorded. Clinical outcome of survivors was determined from follow-up clinical visits, at least 6 months after injury, which included assessments by neurosurgeons, occupational therapists, speech therapists, pediatric developmental specialists, and school progress reports where appropriate. Outcome was assessed using the Glasgow Outcome Score (GOS) and the Pediatric Cerebral Performance Category Scale (PCPCS). The GOS [13] was dichotomized to unfavorable (1, death; 2, vegetative; and 3, severe disability) and favorable (4, mild disability; 5, minor; or no disability) outcome. The PCPCS [6, 7] was similarly dichotomized to favorable (1, normal; 2, mild disability; and 3, moderate disability) and unfavorable (4, severe disability; 5, coma or vegetative state; and 6, death) outcome.

Statistical analysis

All data were analyzed with *R* statistical computing (http://wwww.r-project.org) and Stata software (version 7.0, College Station, TX, USA). Relationships between clinical and physiological variables and outcome were examined with the Wilcoxon's rank sum test for continuous variables and Pearson's X^2 test for categorical variables. Variables with significant relationships in univariate analysis were entered into a stepwise multivariate logistic regression model. Limited covariates were used in individual models to ensure model stability. Separate models were constructed for individual $PbtO_2$ parameters. Values were examined as continuous and dichotomized variables. Regression models were constructed separately for GOS (dichotomized into favorable and unfavorable outcome) and mortality. Results are reported as odds ratios (OR) and 95% confidence intervals (CI) for death and unfavorable outcome (severe disability and death). Significance was set at $p=0.05$. Descriptive statistics are reported as mean±SD or median and interquartile range (IQR) depending on distribution characteristics.

Results

Clinical characteristics Fifty-two pediatric patients with severe TBI (GCS <8) received monitoring for ICP, CPP,

and $PbtO_2$ between June 2006 and May 2008. There were 39 boys (75%) and 13 girls. The age distribution was as follows: <2 years (n=5, 9.6%), 2–3 years (n=9, 17.3%), 4–7 years (n=20, 38.5%), 8–11 years (n=16, 30.8%), and 12–14 years (n=2, 3.8%). Other baseline demographic and clinical variables on admission are summarized in Table 1. Mechanisms of injury were as follows: motor vehicle accident related in 40 (76.9%), crush injury in three (5.8%), gunshot wound in four (7.7%), blunt assault in two (3.8%), fall from a height in one (1.9%), stab to the head in one (1.9%), and inflicted injury (shaken baby syndrome) in one (1.9%). Penetrating injury accounted for 9.6% of cases (n=5).

Early insults Thirteen patients (25%) had an initial SBP<90 mmHg, and 14 (26.9%) had initial systemic hypoxia (S_aO_2<90% or P_aO_2<8 kPa) before or on admission to the hospital.

Treatment factors

Inotropes were used for BP support in 31 patients (60%). Thirty-four patients (65%) received RBCT. Forty patients (77%) received HTS to treat serum sodium<140 mmol/L or to treat elevated ICP. Ten patients received thiopentone (19.2%) and seven patients (13.5%) received decompressive craniectomy for elevated ICP refractory to conventional treatment.

Physiological factors

Median (IQR) length of time from injury to the start of $PbtO_2$ monitoring was 9 h (7–16 h), and the median (IQR) duration of invasive monitoring was 5 days (3–7 days). Values for mICP, $mICP_{24}$ and ICP_{peak} (median, IQR) were 14 mmHg (12–16 mmHg), 14 mmHg (11–18 mmHg), and 31 mmHg (22–44 mmHg), respectively. The median lowest (IQR) CPP was 43 mmHg (33–50 mmHg). Mean $PbtO_2$ (excluding terminal data) was 34±13 mmHg. Episodes of $PbtO_2$<10 mmHg and of $PbtO_2$<5 mmHg occurred in 27 (52%) and 12 patients (23%), respectively. Lowest $PbtO_2$ and $mPbtO_{2_{24}}$ (median, IQR) were 10 mmHg (6–17 mmHg) and 28 mmHg (22–35 mmHg), respectively.

Outcome

Overall mortality for the whole group was 9.6% (n=5). Of the patients who died, three died while in ICU (all within 24 h after head injury), and two died after discharge to the ward (both polytrauma patients who had respiratory related deaths). All deaths occurred in hospital and within 30 days of injury (median, 2 days after injury; range, 1–26). Survivors were followed up for at least 6 months (median, 10 months; range,

Table 1 Admission clinical and radiographic characteristics

Category	Value
Age	6.5±3.4 years (9 months to 14 years)
Initial GCS	5±1 (3–8)
GCS 3	5
GCS 4	9
GCS 5	12
GCS 6	10
GCS 7	11
GCS 8	5
Motor component of GCS (median, range)	3 (1–5)
Pupil reaction on admission	
Bilaterally reactive	41 (78.8%)
Unilaterally nonreactive	5 (9.6%)
Bilaterally nonreactive	6 (11.5%)
PTS (median, range)	3.5 (−1–5)
PIM 2	0.16±0.2
CT classification (initial)	
I	3 (5.8%)
II	31 (59.6%)
III	13 (25%)
IV	3 (5.8%)
Evacuated mass lesion	2 (3.8%)
Non-evacuated mass lesion	0

Values are expressed as mean± SD (or median and range where specified) or as numbers and proportions. *PTS* Pediatric Trauma Score, *PIM2* Pediatric Index of Mortality, *CT classification* admission head CT scans were classified according to the Marshall criteria (see "Materials and methods")

6–26 months). Dichotomized outcome results were the same when using GOS and PCPCS; therefore, further analysis was performed using the GOS. Outcome was unfavorable in 12 patients, including the five who died (23%) and favorable in 40 (77%). There were no vegetative survivors.

Factors associated with unfavorable outcome (severe disability or death)

The relationships between outcome (as the dependent variable) and clinical, physiological, and treatment factors examined using univariate analysis are summarized in Table 2. Variables that had significant relationships with unfavorable outcome in univariate analysis included initial GCS (p=0.001), CT classification (p=0.03), ICP_{peak} (p=0.02), $mICP_{24}$ (p=0.02), mICP (p=0.03), CPP_{low} (p=0.03), $CPP_{<40}$ (p=0.03), pupil reactivity (p=0.004), $PbtO2_{low}$ (p<0.0001), $PbtO2_{<5}$ (p<0.0001), $PbtO2_{<10}$ (p<0.0001), $mPbtO2_{24}$ (p=0.02), and the time–severity product (p<0.0001).

Episodes of $PbtO_2$<10 mmHg occurred in 40% (n=16) of patients who had a favorable outcome and in 92% (n=

Table 2 Comparison of variables between two groups expressed as median [interquartile range] or number (percentage)

Variable	Favorable (n=40)	Unfavorable (n=12)	Coefficient	p value
Patient age (years)	6 [5–7]	5.8 [3.3–8.1]	−0.06	0.6914
Gender (male)	30 (75%)	9 (75%)	0.00	1.0000
Initial GCS	6 [5–7]	4 [3–5]	−0.46	0.0006[a]
Motor GCS	3 [3–4]	3 [2–4]	−0.23	0.0941
Polytrauma (freq)	15 (37.5%)	5 (41.6%)	0.04	0.7995
PTS	3.5 [2–4]	3.5 [3–4]	0.10	0.4653
PIM2	0.07 [0.1–0.1]	0.13 [0.1–0.6]	0.20	0.1474
ICP > 20	5 [1–22]	22.5 [13.2–28]	0.21	0.1367
mICP>20 (mmHg)	24 [22–26.8]	25.5 [24–32]	0.22	0.1217
ICP_{peak} (mmHg)	29 [22–40]	47 [32–55]	0.33	0.0168
$mICP_{24}$ (mmHg)	14 [11–16]	20 [13–29]	0.32	0.0198
$mICP_{total}$ (mmHg)	13 [11–15]	17 [12–20]	0.30	0.0320
CPP_{low} (mmHg)	44 [35–51]	29 [20–45]	−0.31	0.0236[a]
CPP<40 (episodes)	0 [0–1]	3 [0–10]	0.30	0.0304[a]
CPP<50 (episodes)	3 [0–8.8]	8 [2–18.5]	0.21	0.1366
Pupil reactivity	1 [1–1]	2 [1–3]	0.40	0.0032[a]
Initial hypoxia	10 (25%)	4 (33%)	0.08	0.5770
Initial MAP (mmHg)	78 [69–89]	71 [67–93]	−0.03	0.8556
Initial SBP<90	11 (28%)	2 (17%)	−0.11	0.4570
Initial Hb (g/dl)	10 [9–11]	10.5 [9.6–11]	0.02	0.8636
P_aO_2<8 (episodes)	0 [0–0]	0 [0–1]	0.24	0.0901
$P_aO_{2_{low}}$ (kPa)	10.6 [8.5–13]	9 [7.9–12.2]	−0.07	0.6146
$mPaO_2$ (kPa)	19.5 [17.5–22.9]	23.2 [18.8–25.9]	0.22	0.1162
Hb_{low} (g/dl)	8.8 [8–9.4]	8.8 [7.8–9.1]	−0.1	0.4852
mHb (g/dl)	9.8 [9.4–10.9]	10.4 [9.8–10.7]	0.14	0.3167
SaO2<90 (episodes)	0 [0–1]	1 [0–2]	0.25	0.0787
$PbtO_{2_{lowest}}$ (mmHg)	13.6 [7.3–17.8]	3.6 [0.2–8.8]	−0.49	0.0002[a]
$PbtO_2$<5 (episodes)	0 [0–0]	1 [0–8.5]	0.59	<0.0001[a]
$PbtO_2$<10 (episodes)	0 [0–1]	4 [1.8–13.8]	0.55	<0.0001[a]
$mPbtO_{2_{24}}$ (mmHg)	31.1 [26.6–35]	20.8[11.4–27.8]	−0.32	0.0197[a]
Time–severity prod	0 [0–2.8]	20.5 [2.6–75.1]	0.52	0.0001[a]
Duration (h)	109 [63–153]	138 [93–184]	0.10	0.4789
HTS (number given)	4 [0–9]	3 [2–8]	0.04	0.7542
RBCT	24 (60%)	10 (83%)	0.21	0.1416
Inotropes	22 (55%)	9 (75%)	0.17	0.2235
Thiopentone	7 (17.5%)	3 (25%)	0.08	0.5721
DCH	4 (10%)	4 (33%)	0.27	0.0507

Comparison of clinical and physiological variables between patients who had favorable (n=40) and unfavorable (n=12) outcomes

Coefficient Spearman's correlation coefficients for the association between the variable and outcome with the corresponding p values (similar results were found with Wilcoxon's rank sum test and Pearson's X^2); *time–severity prod* product of depth and duration of hypoxia (see text); *duration* length of invasive monitoring, *RBCT* red blood cell transfusion, *HTS* hypertonic saline (number of times used), *thiopentone* use of thiopentone for ICP control; *DCH* decompressive craniectomy used; *inotropes* use of inotropes to increase blood pressure

[a] Significant results

11) of patients who had an unfavorable outcome. $PbtO_2$< 5 mmHg occurred in 10% (n=4) and 67% (n=8) of patients with a favorable or unfavorable outcome, respectively. $mPbtO_{2_{24}}$ was 30.4±8.9 mmHg in patients with favorable outcome and 21.9±16.4 mmHg in patients with unfavorable outcome. $PbtO_2$ decreased to 0 mmHg in all patients who developed brain death while being monitored (n=3).

Multivariate analysis

Unfavorable outcome (GOS) Variables that were significant in univariate analysis were then examined in multivariate analysis. Age was forced into the model because of its clinical importance. All $PbtO_2$ parameters had significant relationships with outcome in multivariate analysis when analyzed as continuous or binary (Table 3) variables. In particular, when $PbtO_2$ was <5 mmHg for >1 h, the adjusted OR for unfavorable outcome (severe disability or death) was 27.4. Similarly, when $PbtO_2$ was <10 mmHg for >2 h, outcome often was poor (adjusted OR=10.8). $mPbtO_{2_{24}}$ had a marginal relationship with outcome when analyzed as a continuous variable (p=0.048) but not when analyzed as a binary variable (dichotomized at 16 mmHg, p=0.062). Significant associations with outcome also were found for initial GCS, CT classification, ICP_{peak}, CPP_{low}, and P_aO_2<8 kPa when tested in multivariate models with some, but not consistently with all of the $PbtO_2$ parameters. Table 3 summarizes the adjusted ORs for the multivariate results of $PbtO_2$ parameters examined as dichotomized variables with outcome as the dependent variable.

Mortality Variables that were significant in univariate analysis were entered into multivariate analysis. All $PbtO_2$ parameters were independently associated with mortality. No other variables were independently associated with mortality when tested in models with $PbtO_2$ parameters. Table 4 displays the multivariate results for dichotomized $PbtO_2$ parameters tested with mortality as the dependent variable.

Discussion

In this study of 52 children (<15 years old) with severe TBI, we examined the relationships between outcome and clinical, physiological, and treatment factors, with an emphasis on $PbtO_2$. The main findings were the following: (1) $PbtO_2$ is an independent factor associated with mortality and unfavorable outcome in children with severe TBI, and (2) $PbtO_2$ was reduced to lower values and for a longer duration of time in patients with poor outcome. Factors such as initial GCS, CT classification, peak ICP, and lowest CPP were significant in some but not all of the multivariate models for dichotomized outcome, and none of these were independently associated with mortality. These findings suggest that $PbtO_2$ data may help guide severe pediatric TBI management.

$PbtO_2$ thresholds and outcome

Several lines of experimental and clinical evidence suggest that a $PbtO_2$ of 20 mmHg is a reasonable treatment threshold and that a $PbtO_2$<10 mmHg is associated with poor outcome in adult TBI [11, 16, 17, 22, 37, 38, 40, 41]. Consistent with this, results of a preliminary series from our institution suggested that an increased depth and duration of $PbtO_2$<20 mmHg was associated with poor outcome [5] and that this relationship was strongest when $PbtO_2$ is <10 mmHg. However, there were too few observations of $PbtO_2$<5 mmHg for meaningful analysis. In the present series, a $PbtO_2$ of 20 mmHg was used a treatment threshold, and the current findings confirm and extend our previous observations and show a high likelihood of poor outcome when $PbtO_2$ is <10 mmHg for >2 h or when $PbtO_2$

Table 3 $PbtO_2$ parameters with adjusted Odds ratios for unfavorable outcome from multivariate logistic regression models

Parameter	p value	OR	95% CI	R^2
$PbtO_{2_{low}}$ <5 mmHg	0.004[a]	24.6	2.8–214.6	0.561
$PbtO_2$<5 for >1 hour	0.015[a]	27.4	1.9–391	0.54
$PbtO_2$<10 for >2 h	0.021[a]	10.8	1.4–82.4	0.563
$mPbtO_{2_{24}}$ <16 mmHg	0.062	8.9	0.9–87.5	0.521
Time–severity product >20	0.002[a]	47.6	4.2–543.6	0.564

p values, adjusted Odd's ratios (OR), confidence intervals, and Nagelkerke's R^2 for each multivariate model (other variables not shown). OR is reported as the odds of unfavorable outcome (severe disability or death)

[a] Significant results

Table 4 $PbtO_2$ parameters with adjusted ORs for mortality from multivariate logistic regression models

Parameter	p value	OR	Confidence interval	R^2
$PbtO_{2_{low}}$ <5 mmHg	0.016[a]	26.9	1.9–387.4	0.464
$PbtO_2$<5 for >1 h	0.005[a]	26.8	2.7–265.0	0.33
$PbtO_2$<10 for >2 h	0.017[a]	20.4	1.7–244.7	0.442
$mPbtO_{2_{24}}$ <16 mmHg	0.012[a]	25.8	2.1–323.9	0.439
Time–severity product >20	0.002[a]	43.3	3.8–491.3	0.453

p values, adjusted Odds ratios (OR), confidence intervals, and R^2 for each multivariate model (other variables not shown). ORs are reported as the odds of mortality

[a] Significant results

was <5 mmHg for >1 h. These thresholds are consistent with human and animal studies that suggest that $PbtO_2$ generally is <10 mmHg at critical thresholds of ischemia [12, 26]. Therefore, $PbtO_2$ values between 15 and 20 mmHg may act as an early warning sign for impending oligemia or cell damage. However, in addition to perfusion-limited brain tissue hypoxia, diffusion limitation also may be significant. Tissue oxygen tension decreases nonlinearly in the extracellular space with increasing distance from the vessel [27]. In TBI, this distance may be increased due to diffusion barriers, such as cytotoxic cell swelling, perivascular edema, collapsed capillaries, and arteriovenous shunting in the microvasculature [20]. Therefore, $PbtO_2$ may be a marker of both mechanisms of limited transport of oxygen to the cells.

To answer the question whether brain oxygen is an independent variable associated with outcome, we constructed separate models for individual $PbtO_2$ parameters using stepwise multivariate logistic regression. Two points are important when interpreting the findings of this multivariate analysis. First, the model only examined variables that demonstrated a direct association with outcome; nonsignificant factors that may have been associated with outcome were not included. However, we did force age into the model because of its clinical importance. In addition, the other variables found to be associated with outcome in initial analysis [i.e., initial GCS, CT classification (Marshall grade), increased ICP, reduced CPP and pupil reactivity] are all common covariates associated with outcome in many clinical TBI studies. Second, the estimates of several odds ratios were imprecise with wide confidence intervals. Bearing these caveats in mind, our data show that $PbtO_2$ is an independent factor associated with mortality and unfavorable outcome in children with severe TBI.

$PbtO_2$ treatment and outcome

$PbtO_2$ monitoring affords the clinician an opportunity to continuously monitor changes in brain oxygen in the ICU. The relationship between low $PbtO_2$ and poor outcome and the high incidence of brain hypoxia despite conventional treatment [5, 33] suggests that $PbtO_2$-directed treatment may benefit some TBI patients including pediatric patients. Although there is no class 1 evidence currently available, several lines of evidence support the concept of $PbtO_2$-directed TBI care. An increase in $PbtO_2$ is associated with improved brain metabolism in clinical TBI [36], greater mitochondrial ATP production [44], and attenuated secondary brain damage in experimental TBI models [23]. Augmented oxygen delivery reduces infarct volumes in animal stroke models [8, 30], and high flow oxygen therapy is associated with a transient improvement of clinical deficits and MRI abnormalities in patients with acute cerebral ischemia [29]. Historical case–control studies in adult TBI also suggest that $PbtO_2$-directed treatment may be associated with improved outcome [19, 32].The site of the $PbtO_2$ monitor is an important consideration because the area of brain tissue monitored is small [15, 16]. Therefore, it is our institutional practice to monitor in normal-appearing right frontal white matter if there is no focal injury. In these circumstances, the monitor is thought to reflect global oxygenation [14, 15, 25, 26, 39]. When there is focal pathology, we attempt to place a peri-lesional monitor, since pericontusional tissue has different physiological responses compared with normal white matter and is at higher risk of ischemia [10, 14].

Methodological limitations

There are several potential limitations to this study. First, the sample size is small; however, it is relatively homogeneous because it includes only children with severe TBI who were less than 15 years old. Second, the age range (9 months to 14 years old) represents wide differences in physiological thresholds. Ideally, a larger number of patients in each age category should be examined separately, as there may be age-related differences in threshold tolerance. However, few institutions treat large enough numbers of children with severe TBI for this to be accomplished easily in single-center studies. In this study, we included age in all multivariate models to control for its effect on the relationship between physiological variables and outcome. Third, outcome evaluation in children is difficult, and pediatric neuropsychological testing was not performed in this study. However, the GOS and PCPCS used in this study can be dichotomized easily to enable examination for associations with death and severe disability. These outcome assessments are used commonly in pediatric TBI, which allows for comparison with other studies. Fourth, this was not a pure observational study in that interventions were directed at low $PbtO_2$, low CPP, and high ICP. Untreated values for each of these may have different associations with outcome parameters. Fifth, even though $PbtO_2$ is associated with outcome, we did not examine the effect of interventions for low $PbtO_2$; therefore, we cannot comment on which methods may be effective, what their adverse effects are, and what impact these may have on outcome. Finally, our $PbtO_2$ data does not contain enough detail to allow us to conclude what is the lower limit of $PbtO_2$ and what duration of brain hypoxia can be tolerated. Despite these limitations, we believe that our results show an independent association between low $PbtO_2$ and poor outcome in pediatric TBI and a more consistent relationship with mortality and poor outcome than the traditional methods of monitoring used commonly

in the pediatric ICU for patients with severe TBI (ICP and CPP). These findings suggest that future studies to examine the impact of interventions for low $PbtO_2$ in children are warranted.

Conclusion

In this study of 52 children with severe TBI, the largest to date, we found that episodes of low $PbtO_2$ have an independent association with poor outcome and mortality after pediatric severe TBI. In addition, $PbtO_2$ appears to have a stronger relationship with outcome than ICP and CPP. These findings suggest that we may need to augment current monitoring strategies and reconsider treatment strategies recommended for the management of severe TBI in children.

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