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ORIGINAL ARTICLE

Medical Management of Compromised Brain Oxygen in Patients with Severe Traumatic Brain Injury

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Abstract
Background Brain tissue oxygen ($PbtO_2$) monitoring is used in severe traumatic brain injury (TBI) patients. How brain reduced $PbtO_2$ should be treated and its response to treatment is not clearly defined. We examined which medical therapies restore normal $PbtO_2$ in TBI patients.
Methods Forty-nine (mean age 40 ± 19 years) patients with severe TBI (Glasgow Coma Scale [GCS] ≤ 8) admitted to a University-affiliated, Level I trauma center who had at least one episode of compromised brain oxygen ($PbtO_2$ <25 mmHg for >10 min), were retrospectively identified from a prospective observational cohort study. Intracranial pressure (ICP), cerebral perfusion pressure (CPP), and $PbtO_2$ were monitored continuously. Episodes of compromised $PbtO_2$ and brain hypoxia ($PbtO_2$ <15 mmHg for >10 min) and the medical interventions that improved $PbtO_2$ were identified.
Results Five hundred and sixty-four episodes of compromised PbtO2 were identified from 260 days of PbtO2 monitoring. Medical management used in a "cause-directed" manner successfully reversed 72% of the episodes of compromised $PbtO_2$, defined as restoration of a "normal" $PbtO_2$ (i.e. ≥25 mmHg). Ventilator manipulation, CPP augmentation, and sedation were the most frequent interventions. Increasing FiO_2 restored $PbtO_2$ 80% of the time. CPP augmentation and sedation were effective in 73 and 66% of episodes of compromised brain oxygen, respectively. ICP reduction using mannitol was effective in 73% of treated episodes, though was used only when $PbtO_2$ was compromised in the setting of elevated ICP. Successful medical treatment of brain hypoxia was associated with decreased mortality. Survivors ($n = 38$) had a 71% rate of response to treatment and non-survivors ($n = 11$) had a 44% rate of response ($P = 0.01$).
Conclusion Reduced $PbtO_2$ may occur in TBI patients despite efforts to maintain CPP. Medical interventions other than those to treat ICP and CPP can improve $PbtO_2$. This may increase the number of therapies for severe TBI in the ICU.

Keywords Brain tissue oxygen pressure · Brain hypoxia · Intracranial pressure · Cerebral perfusion pressure · Outcome · Traumatic brain injury · Head injury · Monitoring

Abbreviations

$PbtO_2$	Brain tissue oxygen
GCS	Glasgow Coma Scale
ICP	Intracranial pressure
CPP	Cerebral perfusion pressure
TBI	Traumatic brain injury

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Introduction

Traumatic brain injury (TBI) affects 2 million people per year and is a leading cause of death and disability among young people in the United States. Clinical and laboratory studies demonstrate that poor outcome is associated with ongoing (secondary) injury that evolves over time after the initial (primary) injury. Intensive care management of TBI patients therefore involves monitoring to identify secondary injury. Intracranial pressure (ICP) is the physiological parameter most frequently monitored. Other physiological parameters may be monitored continuously at the bedside, including partial pressure of brain tissue oxygen ($PbtO_2$), cerebral metabolites (via microdialysis catheters), and regional cerebral blood flow among others. [1–5].

The most recent Guidelines for Severe Traumatic Brain Injury include the use of $PbtO_2$ monitors but do not provide guidance about how $PbtO_2$ should be managed although a threshold for treatment is suggested [6, 7]. Reduced $PbtO_2$ is common after severe TBI [8] and may occur despite a normal ICP and CPP [9]. Furthermore, there is an association between brain hypoxia and both poor outcome and mortality after severe TBI [10]. We therefore sought to identify the medical therapies used to treat reduced $PbtO_2$ and to assess their efficacy.

Methods

Patient Population

Subjects were identified retrospectively from a prospective observational database (Brain Oxygen Monitoring Outcome study) of patients with severe TBI treated in the NeuroIntensive Care Unit at Hospital of the University of Pennsylvania (HUP), an academic Level 1 Trauma Center. We selected patients treated between November 2001 and September 2004, a time period when we still were evaluating different treatments for compromised $PbtO_2$. All patients treated during the study period were evaluated for inclusion in the study. During that period, we initiated treatment when $PbtO_2$ was <25 mmHg, whereas our current treatment threshold is $PbtO_2$ <20 mmHg. Inclusion criteria were as follows: admission within 3 h of injury; an admission Glasgow Coma Score (GCS) ≤ 8; and an admission injury severity score (ISS [11]) ≥ 16. Patients with cranial gunshot wounds or other penetrating cranial injuries were excluded from analysis. While survival data were previously published for this cohort, the relationship between medical interventions to treat brain oxygen, the response rate, and survival has not been examined [7]. The Institutional Review Board approved this study.

Intracranial and Physiological Monitoring

Patients were cared for in the NeuroIntensive Care Unit and were monitored continuously using ICP, $PbtO_2$, and brain tissue temperature using commercially available devices (LICOX CMP Triple Lumen Monitoring System, Integra NeuroSciences, Plainsboro, NJ). Probes were inserted at the bedside through a burr-hole into the frontal lobe and secured with a triple lumen bolt. The ICP and $PbtO_2$ monitors were placed into white matter that appeared normal on admission head CT and on the side of maximal pathology or swelling. To allow for probe equilibration, data from the first 3 h were discarded. All patients were monitored for at least 72 h unless care was withdrawn first. The monitors were removed when ICP had been normal for 24 h without specific treatment (except sedation for ventilator care) or when the patient was able to consistently follow commands.

Each patient had an indwelling arterial (usually radial artery) catheter and mean arterial pressure (MAP) was recorded continuously in all patients. Cerebral perfusion pressure (CPP) was calculated from measured parameters (CPP = MAP − ICP). Heart rate and arterial oxygen saturation (SpO_2) were recorded in all patients.

General Management

All patients were resuscitated according to Advanced Trauma Life Support (ATLS) guidelines and were managed according to a local algorithm based on the Brain Trauma Foundation Guidelines for Severe TBI and published recommendations for severe TBI and ICU care [2–5, 12–16]. This included: (1) early identification and evacuation of traumatic hematomas, (2) intubation and ventilation with low-volume pressure-limited ventilation to maintain PaO_2 between 80 and 100 mmHg, and SaO_2 $>93\%$, and $PaCO_2$ between 35 and 40 mmHg, (3) sedation using propofol during the first 24 h followed by sedation (lorazepam) and analgesia using morphine or fentanyl, (4) bedrest with head elevation initially of $\geq 30°$, (5) normothermia ~ 35–$37°C$, (6) euvolemia, (7) anticonvulsant prophylaxis with phenytoin for 1 week (longer if seizures occurred), and (8) packed red blood cell transfusion if Hgb was <10.

ICP and CPP Management

Therapies were instituted to maintain ICP <20 mmHg and CPP >60 mmHg, according to our local protocol (Fig. 1). Elevated ICP >20 mmHg for >2 min was initially treated with adjustment of head position, sedation, and analgesia. If ICP remained >20 mmHg for more than 10 min despite these initial measures osmotherapy was administered using

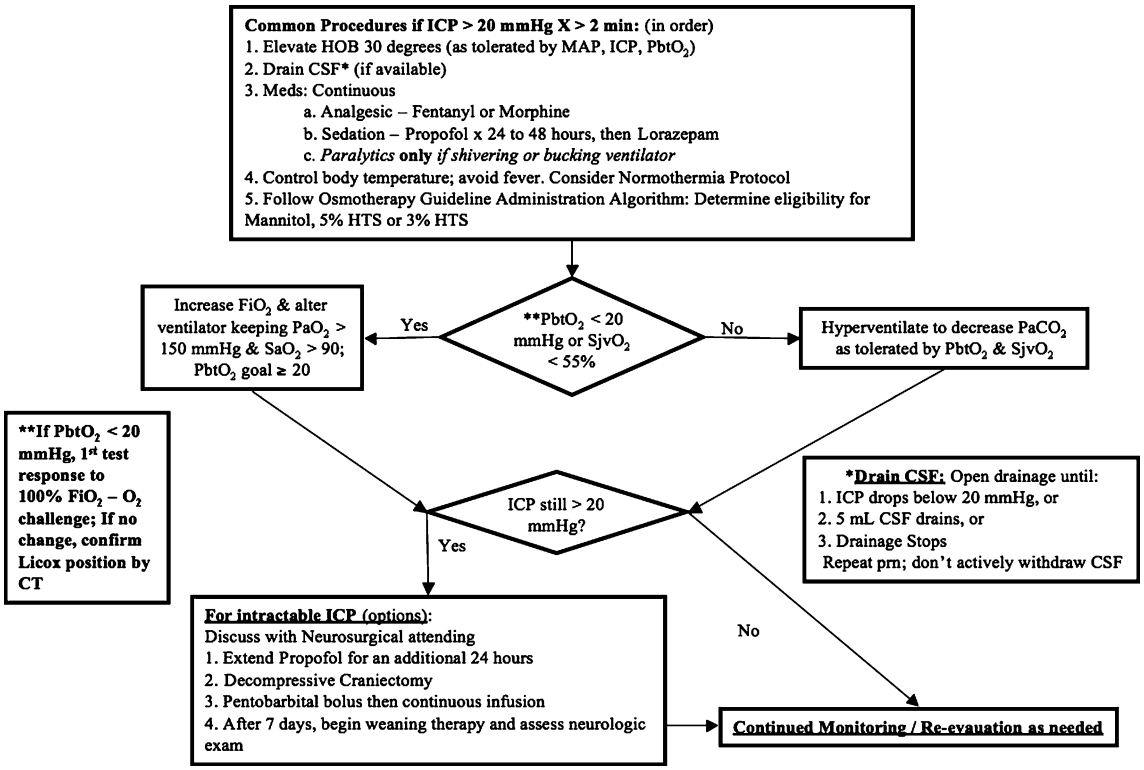

Fig. 1 ICP management algorithm

repeated boluses of mannitol (0.5–1 g/kg, 25% solution). After adequate fluid resuscitation phenylephrine (10–300 mcg/min) was administered when CPP $\leq$60 mmHg for greater than 15 min. Thereafter optimized hyperventilation $PaCO_2$ $\sim$30 mmHg, ventriculostomy placement, additional propofol or a decompressive hemicraniectomy (DCH) were used as second-tier therapies for refractory intracranial hypertension ($>$20 mmHg for $>$15 min continuously despite therapy). Induced hypothermia and hypertonic saline were not used to manage ICP in the patients included in this study.

$PbtO_2$ Management

Patients received cause-directed therapy to maintain $PbtO_2$ $\geq$25 mmHg [17]. When $PbtO_2$ was $<$25 mmHg and there was intracranial hypertension (ICP $>$20 mmHg), measures were taken to reduce ICP as described above. An oxygen challenge (100% FiO_2 for 2 min) was used as a temporary measure to restore $PbtO_2$ and to verify probe function. If ICP $<$20 mmHg or ICP reduction did not increase $PbtO_2$, then CPP was increased (usually with phenylephrine). If the cause of low $PbtO_2$ was thought to be due to lung dysfunction (based on assessment of arterial blood gas, chest X-ray, and ventilator requirements) then pulmonary function was optimized (e.g., by increased FiO_2 and/or positive end-expiratory pressure, tracheal suction or pulmonary toilette). 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 $<$10 mg/dl, then a blood transfusion was administered.

Data Collection, Analysis, and Definitions

Clinical and radiological variables of this study included age, admission (post-resuscitation) Glasgow Coma Scale (GCS), mode of injury, brain oxygen ($PbtO_2$), intracranial pressure, brain temperature, core body temperature, blood pressure, heart rate, inspired fraction of oxygen (FiO_2), serum, hemoglobin level, serum sodium, serum glucose. All physiologic and intracranial variables were continuously recorded using a bedside critical care monitor system (Component Monitoring System M1046-9090C, Hewlett Packard, Andover, MA) and were recorded in the ICU flow-sheet usually every 15 min and at least every 30 min. Marshall and Rotterdam CT classifications were determined by consensus of two neurosurgeons (LM and LEB) who evaluated the images independently and who were blinded to patient clinical information at the time of their assessment.

Increased ICP was defined as ICP $>$20 mmHg for $>$2 min. Refractory intracranial hypertension was defined as ICP $>$20 mmHg for $>$15 min in a 1-h period despite therapy. Compromised brain oxygen was defined as $PbtO_2$

<25 mmHg for >10 min. Brain hypoxia was defined as $PbtO_2$ <15 mmHg for >10 min. A successful response to $PbtO_2$ therapy was defined as a return of $PbtO_2$ to normal value (>25 mmHg) sustained over >10 min. In-hospital mortality was collected from hospital discharge data.

Statistical Analysis

Statistics were performed in GraphPad Prism 4.0 (GraphPad Inc., La Jolla, CA). Data are expressed as the mean ± standard deviation of the mean (SD) or as the median where the data is not normally distributed. A P value <0.05 was considered statistically significant. Mann–Whitney U tests were used to compare two groups of observations with non-parametric distributions. When the data were normally distributed a Student's T test was used to compare groups. The Kruskal–Wallis test was used to look for correlation between categorical variables (such as the Marshall Score) and outcome.

Results

Patient Population

Forty-nine patients including 40 were male and 9 were females (mean age 42 ± 19 years) who had episodes of compromised $PbtO_2$ ($PbtO_2$ <25 mmHg for >5 min) that required treatment were identified. Thirty-four (69%) of these patients had a GCS of 3 on admission. Forty-one (84%) patients had a Marshall Score on their admission CT scan of 3 or more. Patient characteristics at presentation are presented in Table 1.

Table 1 Patient characteristics

Mean age	41 ± 19.2
Male (%)	82
Average monitor (days)	5.2 ± 3.5
Admission GCS	
3	34 (69%)
4	1 (2%)
5	0 (0%)
6	8 (16%)
7	5 (10%)
8	1 (2%)
Marshall score	
1	0 (0%)
2	8 (16%)
3	21 (43%)
4	4 (8%)
5	16 (33%)
6	0 (0%)
Rotterdam score	
1	1 (2%)
2	2 (4%)
3	13 (27%)
4	25 (51%)
5	7 (14%)
6	6 (12%)
Mode of injury	
Assault	10%
Fall	29%
Motor vehicle collision	35%
Pedestrian struck	8%
Other/unknown	18%

Physiologic Variables

Data were analyzed from a total of 260 days of continuous $PbtO_2$ monitoring (mean 5.2 ± 3.5 days). The daily mean $PbtO_2$ among all patients was 33.8 ± 11.8 mmHg. A total of 564 episodes of compromised $PbtO_2$ ($PbtO_2$ <25 mmHg) and 127 episodes of brain hypoxia ($PbtO_2$ <15 mmHg) were detected during this period of monitoring.

Medical Management of Compromised $PbtO_2$

Of the 564 episodes of compromised $PbtO_2$ ($PbtO_2$ <25 mmHg), 379 episodes in 49 patients were treated with goal-directed therapy. Forty-three (88%) of these patients had more than one episode of compromised $PbtO_2$. Thirty-eight patients (78%) had at least 1 episode of brain hypoxia ($PbtO_2$ <15 mmHg for >10 min), 28 patients (57%) had 2 or more episodes. Medical management corrected 72% of the episodes of compromised $PbtO_2$.

Ventilator manipulation, CPP augmentation, and sedation were the most frequent interventions. Increasing FiO_2 was implemented as a treatment 186 times and restored normal $PbtO_2$ 77% of the time. Cerebral perfusion pressure augmentation was achieved by ICP reduction ($n = 24$) or increasing MAP ($n = 69$) in 93 episodes of reduced $PbtO_2$ and was effective 62% of the time. When ICP was increased, treating it restored $PbtO_2$ in 54% of episodes. Mannitol, the most commonly used agent, was successful 9 (75%) of 12 times it was used. When ICP was not considered a cause of reduced $PbtO_2$, vasopressors were used 55 times to elevate CPP to ≥ 60 mmHg and restored $PbtO_2$ 75% of the time. Phenylephrine was the most frequently administered vasopressor and was effective 35 of the 46 times (76%) it was administered. Norepinephrine was effective 5 of the 7 times (71%) it was administered. Dopamine was effective the one time it was used whereas epinephrine did not improve $PbtO_2$ following its single administration. Titrating patient sedation was used to

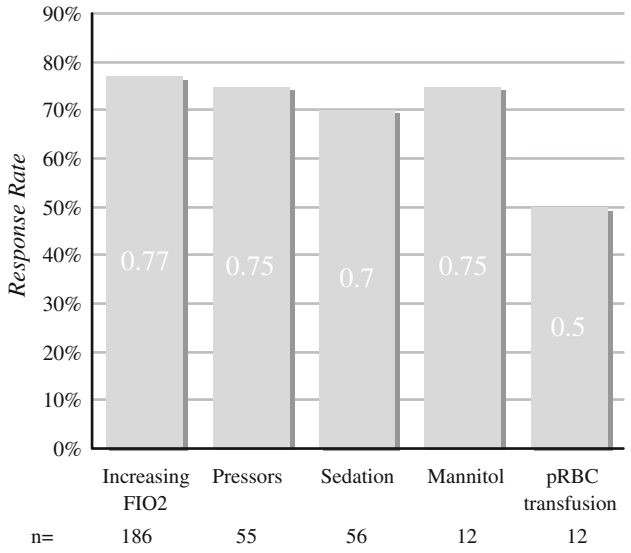

Fig. 2 Medical interventions for compromised $PbtO_2$ (use/response rate)

improve patient $PbtO_2$ 56 times and was effective in 70% of treatments. Additional interventions including intravenous fluid bolus ($n = 2$), head repositioning ($n = 6$), airway suctioning ($n = 8$), and blood transfusions ($n = 12$) were effective in 50, 83, 88 and 50% of treated episodes of compromised brain oxygen, respectively. See Fig. 2.

Treatment Response Rates

Our data suggest similar response rates among various treatments and the variability in overall response to therapy among the patients. This may in part be associated with the "cause-directed" approach we used to correct reduced $PbtO_2$. We compared the response rate observed for each intervention to the overall response rate for the patients who received that treatment. The intervention-specific to overall response rate ratios were calculated and are presented in Fig. 3. The interventions with a better than expected response rate (a ratio >1) were increasing FiO_2, pressors (both neosynephrine and norepinephrine), airway suctioning, and benzodiazepines (midazolam and/or lorazepam). On the other hand, propofol, fentanyl, mannitol, and blood transfusion had ratios less than 1; these interventions were less effective than the average intervention for the patients in whom they were used.

$PbtO_2$ Treatment Response and Mortality

Eighteen patients (37%) died and 31 (63%) were alive at hospital discharge. The overall response rate (defined as total responses/total interventions) to medical treatment of compromised brain $PbtO_2$ was associated with outcome. Survivors ($n = 38$) had a 71% response rate to therapy for abnormal $PbtO_2$, whereas non-survivors ($n = 11$) had only a 44% response rate ($P = 0.01$). Mean daily $PbtO_2$ (31.55 ± 20.64 mmHg) was significantly less in the 11 patients who died than in those who survived (37.43 ± 16.54 mmHg; $P < 0.05$). Non-survivors had more daily episodes (1 ± 0.8 vs. 0.5 ± 0.6, $P = 0.03$) and longer cumulative duration (273 ± 178 vs. 132 ± 159, $P = 0.002$) of brain hypoxia ($PbtO_2$ <15 mmHg). Non-survivors also had a longer cumulative duration of brain hypoxia (461.8 ± 584.7 vs. 264 ± 494.8 min; $P = 0.03$) than survivors (Table 2). Survivors had more interventions for compromised $PbtO_2$ than non-survivors (8.5 vs. 4.9, $P = 0.15$), however, this trend was non-significant and reflected the longer number of monitored days (5.7 vs. 3.4, $P = 0.06$) for survivors compared to non-survivors. The number of interventions per monitor day for survivors (1.48) was similar to that for non-survivors (1.45).

Older age and worse GCS are associated with worse outcome in patients with TBI. We asked if these two variables affected treatment response. Age less than 40 was associated with a significant increased response rate to

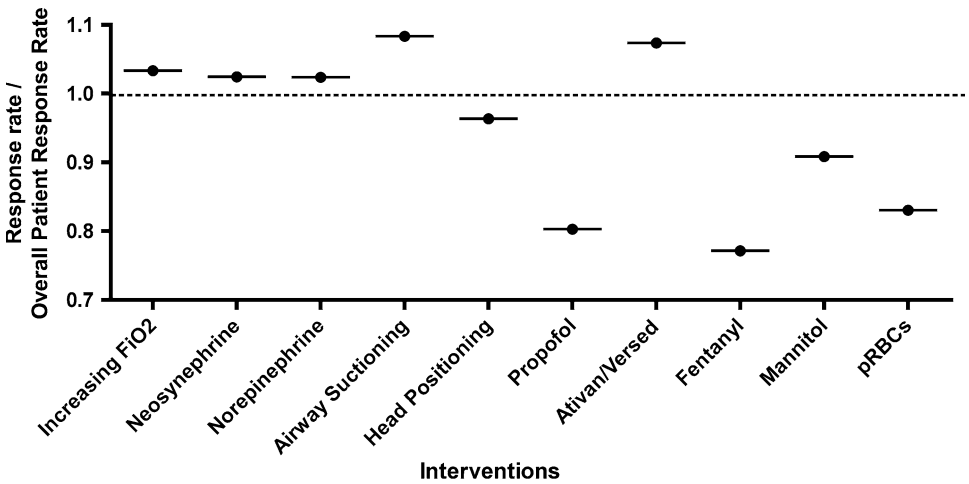

Fig. 3 Marginal patient-specific effectiveness of interventions

Table 2 Comparison of $PbtO_2$ in survivors versus non-survivors

	Overall ($n = 49$)	Survivors ($n = 38$)	Non-survivors ($n = 11$)	P value
Mean daily $PbtO_2$	33.8 ± 11.8	35.2 ± 11.8	28.8 ± 11.1	0.07
Mean daily episodes of $PbtO_2$ <25 mmHg	2.0 ± 1.2	2.0 ± 1.3	2.0 ± 0.9	0.66
Mean daily episodes of $PbtO_2$ <15 mmHg	0.6 ± 0.6	0.5 ± 0.6	1.0 ± 0.8	0.03
Mean no. interventions	7.7 ± 6.3	8.5 ± 6.6	4.9 ± 2.9	0.15
Mean response rate	0.65 ± 0.34	0.72 ± 0.33	0.44 ± 0.28	0.01
Mean daily minutes of $PbtO_2$ <25 mmHg	295 ± 287	232 ± 234	513 ± 357	0.003
Mean daily minutes of $PbtO_2$ <15 mmHg	102 ± 210	69.9 ± 140	213 ± 351	0.009
Mean length of episodes $PbtO_2$ <25 mmHg	163 ± 171	132 ± 159	273 ± 178	0.002
Mean length of episodes $PbtO_2$ <15 mmHg	106 ± 182	76.3 ± 137	210 ± 273	0.01

Table 3 Differences in response rate to $PbtO_2$-directed interventions and outcome by age and GCS

mean ± SEM	Age ≤ 40 ($n = 23$)	Age > 40 ($n = 26$)	P value[a]	GCS = 3 ($n = 34$)	GCS 4–8 ($n = 15$)	P value
Response rate	0.76 ± 0.064	0.56 ± 0.067	0.04	0.67 ± 0.054	0.63 ± 0.10	0.72
Survival	0.87 ± 0.072	0.69 ± 0.092	0.14	0.76 ± 0.073	0.80 ± 0.11	0.79

[a] Student's t test

$PbtO_2$-directed therapy (76 ± 6.4% vs. 56 ± 6.7%, $P = 0.04$) and showed a trend toward improved outcome (survival rate at discharge 87 ± 7.2% vs. 69 ± 9.2%, $P = 0.14$). We did not find a relationship between GCS and response to therapy or mortality (Table 3). There was a trend for the Marshall CT score to be associated with outcome: 8 of 8 (100%) of patients with a Marshall score of 2 survived, whereas 7 of 15 (47%) patients with Marshall score of 5 survived (Kruskal–Wallis test, $P = 0.07$). The Marshall score was not associated with response rate to therapy (data not shown, Kruskal–Wallis test, $P = 0.21$).

Discussion

In this study, we examined 49 patients who received medical management for reduced $PbtO_2$. Our findings can be summarized as follows: (1) the commonest therapies to correct reduced $PbtO_2$ were manipulation of pulmonary function, CPP augmentation, and sedation; (2) three quarters of episodes of compromised $PbtO_2$ responded to medical management; (3) younger age was associated with a better response to therapy; and (4) responders had a lower mortality. These data suggest that $PbtO_2$-based care when combined with ICP and CPP management may reduce mortality in some patients with severe TBI and provide useful information to design $PbtO_2$ treatment strategies in severe TBI.

Study Limitations

Our study has several potential limitations. First, the study was performed on patients treated at a single institution so it may lack external validity. Second, the data were examined retrospectively and this may bias our results. Third, while management of compromised $PbtO_2$ was protocol-driven, we do not have data on protocol compliance. Fourth, there are several reported thresholds for brain hypoxia or when to initiate therapy for brain hypoxia. In this study, we initiated therapy when $PbtO_2$ was <25 mmHg and defined brain hypoxia as <15 mmHg. Fifth, therapies were often administered in parallel or in rapid sequence. Therefore, the efficacy of each separate therapeutic intervention may be confounded by combination treatments and less frequently used interventions may have lower response rates simply because they are second-tier therapies used in patients who have not responded to more commonly used interventions. In addition, it is conceivable that an intervention could have occurred for reasons other than to correct $PbtO_2$ deficits or the effect of therapies applied as part of general care, e.g., positioning, rather than when a specific abnormality occurred may have been underestimated. Instead our data provide an expectation of what may happen when compromised $PbtO_2$ is treated. Sixth, we do not have reliable data to exclude any deleterious effects of $PbtO_2$-based interventions. While we think this is unlikely, it may be important since many of the therapies we used (e.g. increased FiO_2, CPP augmentation, blood transfusion) are known to have adverse effects. This question is to be addressed in a Phase II trial of $PbtO_2$-based care currently underway at our and other institutions. Seventh, our primary patient outcome measure was in-hospital mortality since it was included in the prospective database. While this is useful and accepted in ICU studies, it may not adequately describe TBI outcome where

more long-term functional measures are important. Finally, since our sample size is small and the study was not designed to determine whether $PbtO_2$-based therapy may improve severe TBI outcome, as suggested by some but not all studies our results only suggest but do not prove the value of $PbtO_2$-based care [7, 18–23]. Large clinical trials are needed to verify this issue. The data in this study provide useful information to help plan for such a trial.

Management of Reduced $PbtO_2$

The use of $PbtO_2$ monitors recently was incorporated into the Guidelines for Severe Traumatic Brain Injury [22]. However, $PbtO_2$ monitors should not to be used alone but instead used with other monitors in particular an ICP monitor and standard ICU monitors. Our data show that compromised $PbtO_2$ or brain hypoxia may not always be associated with ICP or CPP abnormalities. Medical interventions to improve ICP and CPP, however, often but not always can help improve abnormal $PbtO_2$. Indeed, one-quarter of interventions with mannitol to reduce ICP and with phenylephrine to increase CPP did not correct brain hypoxia. We found that the most commonly used therapies to increase $PbtO_2$ were increased FiO_2, CPP augmentation usually with vasopressor administration, and sedation. However, overall only three-quarters of the episodes of compromised $PbtO_2$ responded to medical therapies.

The response of abnormal $PbtO_2$ to the most commonly used interventions was similar with a response rate of about 70%. This may reflect how we used the various therapies, i.e. in a cause directed manner. When we examined relative response rates of various interventions (Fig. 3), the most commonly used interventions (FiO_2 supplementation, CPP augmentation with vasopressors, and reduction of brain metabolic demand with benzodiazepines) appeared to have better relative response rates when compared to other interventions in the same patients. For example, blood transfusion was successful in 50% of the instances it was used to correct abnormal $PbtO_2$. However, the relative efficacy of various treatments must be interpreted with caution since those that appear to be less effective often were used as later tier therapies, i.e., they appear less effective since the abnormal $PbtO_2$ was "refractory" to other interventions. Patient-specific factors also may be important: in our series younger age was associated with a better response rate to $PbtO_2$-directed therapies.

There are few other studies that have addressed an overall strategy how best to manage compromised $PbtO_2$ or brain hypoxia. We have observed that decompressive craniectomy can improve $PbtO_2$ and reduce the therapeutic intensity level in severe TBI patients with medically refractory intracranial hypertension [24, 25]. In the present study, we chose only to examine medical therapies for reduced $PbtO_2$. Previous studies that have addressed this question have tended to focus on one particular therapeutic intervention. For example, Kiening et al. in 21 patients observed that a CPP increase CPP from 32 ± 2 to 67 ± 4 mmHg improved $PbtO_2$ by 62%. However, a CPP increase >68 mmHg did not lead to further improvement in $PbtO_2$ [26]. Other reports have detailed the effects of individual therapies on $PbtO_2$ in TBI or subarachnoid hemorrhage such as transfusion [27–30], body position [31], barbiturates [32], hypertension [33], hyperventilation [34], CPP changes [35–37], or hypertonic saline [38, 39] among others.

The Potential Importance of Correcting Reduced $PbtO_2$

How the information provided by various monitors used in severe TBI patients is interpreted and how abnormalities are treated has the potential to provide a therapeutic benefit. It is conceivable that the information provided by a $PbtO_2$ monitor may be used to establish the optimal ICP or CPP in individual patients (i.e., target patient and pathology specific factors) and to individualize therapy. Further work will be necessary to examine whether other factors such as cerebral autoregulation (pressure or metabolic) or $PbtO_2$ reactivity can further target therapy. Our data, however, imply that among patients who receive standard ICP and CPP management and who develop reduced $PbtO_2$ those who respond to $PbtO_2$ therapy have a reduced mortality. In addition, a longer cumulative duration of brain hypoxia was associated with increased mortality. Whether the effect of $PbtO_2$-directed therapy is an independent factor associated with mortality remains uncertain. However, this finding is consistent with other observational data that suggests that reduced $PbtO_2$ is associated with mortality and worse outcome [10, 40–42].

Conclusions

Our data provide information about the efficacy of various medical therapies for reduced $PbtO_2$ and suggest that successful treatment of compromised $PbtO_2$ may be associated with reduced mortality. Our data also show that there are medical interventions other than those to improve ICP and CPP that can correct compromised $PbtO_2$. Our data, however, do not prove a benefit to correction of $PbtO_2$—this important question requires a rigorous clinical trial. These data may be used to aid the design of such a trial.

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