

Brain tissue oxygen–directed management and outcome in patients with severe traumatic brain injury

Clinical article

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Object. The object of this study was to determine whether brain tissue oxygen (PbtO₂)–based therapy or intracranial pressure (ICP)/cerebral perfusion pressure (CPP)–based therapy is associated with improved patient outcome after severe traumatic brain injury (TBI).

Methods. Seventy patients with severe TBI (postresuscitation GCS score ≤ 8), admitted to a neurosurgical intensive care unit at a university-based Level I trauma center and tertiary care hospital and managed with an ICP and PbtO₂ monitor (mean age 40 ± 19 years [SD]) were compared with 53 historical controls who received only an ICP monitor (mean age 43 ± 18 years). Therapy for both patient groups was aimed to maintain ICP < 20 mm Hg and CPP > 60 mm Hg. Patients with PbtO₂ monitors also had therapy to maintain PbtO₂ > 20 mm Hg.

Results. Data were obtained from 12,148 hours of continuous ICP monitoring and 6,816 hours of continuous PbtO₂ monitoring. The mean daily ICP and CPP and the frequency of elevated ICP (> 20 mm Hg) or suboptimal CPP (< 60 mm Hg) episodes were similar in each group. The mortality rate was significantly lower in patients who received PbtO₂-directed care (25.7%) than in those who received conventional ICP and CPP-based therapy (45.3%, *p* < 0.05). Overall, 40% of patients receiving ICP/CPP-guided management and 64.3% of those receiving PbtO₂-guided management had a favorable short-term outcome (*p* = 0.01). Among patients who received PbtO₂-directed therapy, mortality was associated with lower mean daily PbtO₂ (*p* < 0.05), longer durations of compromised brain oxygen (PbtO₂ < 20 mm Hg, *p* = 0.013) and brain hypoxia (PbtO₂ < 15 mm Hg, *p* = 0.001), more episodes and a longer cumulative duration of compromised PbtO₂ (*p* < 0.001), and less successful treatment of compromised PbtO₂ (*p* = 0.03).

Conclusions. These results suggest that PbtO₂-based therapy, particularly when compromised PbtO₂ can be corrected, may be associated with reduced patient mortality and improved patient outcome after severe TBI. (DOI: 10.3171/2010.1.JNS09506)

KEY WORDS • brain oxygen • intracranial pressure • outcome • traumatic brain injury

EACH year more than 2 million people are treated for TBI in the US, and TBI remains a leading cause of death and disability among young people. Clinical and laboratory research demonstrate that not all neuron damage that contributes to this poor outcome occurs at the time of primary injury or impact. Instead TBI initiates a cascade of events that can lead to secondary brain injury or exacerbate the primary injury.^{16,28} The concept

of management of secondary neuron or brain injury is the focus of modern TBI management. However, current therapies to prevent secondary injury (for example, efforts to improve cerebral perfusion, hypothermia, or neuroprotection^{6,11,14,26,37,41,43,52}), while effective in the laboratory, have disappointed in the clinical environment. New therapies are therefore needed.

Neuromonitoring is essential to identify secondary cerebral insults, and it is believed that when recognized early, secondary insults can be better managed and patient outcome can be improved. The Current Guidelines for the Management of Severe Head Injury^{7,8} as described by the American Association of Neurological Surgeons and Congress of Neurological Surgeons Joint Section on Neurotrauma and Critical Care and the European Brain Injury Consortium emphasize the use of ICP monitors

Abbreviations used in this paper: CPP = cerebral perfusion pressure; FiO₂ = fraction of inspired oxygen; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; HUP = Hospital of the University of Pennsylvania; ICP = intracranial pressure; ICU = intensive care unit; ISS = Injury Severity Score; LOS = length of stay; PbtO₂ = partial pressure of brain tissue O₂; SaO₂ = arterial O₂ saturation; TBI = traumatic brain injury.

(and so calculation of CPP), although their value has not been tested in a clinical trial. However, accumulating data from clinical studies that use other intracranial monitors such as microdialysis, PET, or MR imaging show that secondary brain injury is not always associated with pathological changes in ICP or CPP and that mechanisms other than simple perfusion-limited abnormalities may be responsible for cellular injury after TBI.^{5,24,27,33,49,59} These data suggest that newer monitors (for example, microdialysis or direct brain oxygen [PbtO₂] monitors) may have a role in the care of patients with TBI.

The brain is highly dependent on a continuous supply of oxygen and glucose (aerobic metabolism) to maintain cellular integrity.^{3,45} This metabolism is altered after severe TBI and brain hypoxia is common in patients with this condition.^{16,19,51} Observational clinical studies demonstrate a significant association between poor patient outcome and the number, duration, and intensity of brain hypoxic episodes (PbtO₂ < 15 mm Hg) after severe TBI.^{4,13,23,55–58} In addition, converging experimental and clinical evidence suggest that therapy to augment or correct PbtO₂ may improve TBI outcome.^{17,40,46,47,53} In a small preliminary clinical study that included 53 patients we observed that PbtO₂-directed therapy was associated with a lower mortality rate than was seen in patients identified from a historical cohort who received only ICP and CPP-directed treatment.⁵⁰ In the current study we examined how PbtO₂-directed therapy influenced patient outcome in a larger cohort (123 patients) that included new patients not examined in our original study. We hypothesized the following: 1) PbtO₂-directed therapy combined with ICP/ CPP-based therapy was associated with a reduced mortality rate and better short-term outcome than ICP/ CPP-based therapy alone; and 2) successful treatment of compromised PbtO₂ would improve outcome.

Methods

Patient Population

Patients with severe TBI admitted to the Hospital of the University of Pennsylvania (HUP), a Level I trauma center, within 8 hours of TBI were eligible for this study. Patients were identified retrospectively from a prospective observational database with institutional review board approval. Study inclusion criteria were patient age $\geq$ 16 years, a postresuscitation admission GCS score $\leq$ 8, an ISS $\geq$ 16, and a head CT scan to exclude other causes for their condition. Patients who at admission were 1) brain dead, 2) had bilateral fixed and dilated pupils, 3) had a penetrating TBI, or 4) had a previous CNS disease or TBI were excluded from analysis. In addition, patients whose postresuscitation systolic blood pressure was < 90 mm Hg or SaO₂ < 90% were not included in this study. Two groups of patients, each from a defined time period before or after we introduced formal PbtO₂ monitoring and management protocols to our institution (October 2001) and between January 2000 and September 2004, were identified. Patients treated in the 3 months before or after the introduction of PbtO₂ monitoring at our institution were not considered for analysis. The control group

(Group I), a historical cohort population who received only an ICP monitor for ICP/ CPP-directed therapy was identified retrospectively from the HUP Prospective TBI database. The study population (Group II) consisted of patients who received an ICP and PbtO₂ monitor and PbtO₂-directed care and are included in our Brain Oxygen Monitoring Outcome database.

Monitoring

Patients were cared for in the Neurosurgical and Trauma Intensive Care Unit. Heart rate, blood pressure as measured via an arterial catheter, and SaO₂ were recorded in all patients. Each Group I patient was monitored using a Camino ICP monitor (Integra NeuroSciences), whereas Group II patients received ICP, PbtO₂, and brain tissue temperature monitors (LICOX, Integra NeuroSciences). Intracranial monitors were inserted at the bedside through a bur hole into the frontal lobe and secured with a triple-lumen bolt. The monitors were placed into white matter that appeared normal on admission head CT and on the side of maximum pathology. When there was no asymmetry in pathology on head CT, the monitors 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. Follow-up noncontrast head CT scans were performed in all patients within 24 hours of admission to confirm correct placement of the various monitors (for example, not in a contusion or infarct). Probe function and stability were confirmed by an appropriate PbtO₂ increase following an O₂ challenge (FiO₂ 1.0 for 5 minutes). Each patient was monitored for at least 72 hours unless care was withdrawn or the patient died during that period. Intracranial monitors were removed only when ICP was normal (< 20 mm Hg) for 24 hours without treatment except sedation for ventilation. All physiological variables were continuously recorded using a bedside critical care monitor system (Component Monitoring System M1046–9090C, Hewlett Packard).

Management

Each patient was resuscitated and managed according to a standard policy adapted to local practice from published recommendations for severe TBI and ICU care.^{2,7,8,42} This included the following: 1) early identification and evacuation of traumatic hematomas; 2) intubation and ventilation with FiO₂ and minute ventilation adjusted to maintain SaO₂ > 93% and to avoid PaO₂ < 60 mm Hg; 3) PaCO₂ was set at approximately 35–45 mm Hg unless ICP was elevated when PaCO₂ was maintained between 30 and 40 mm Hg; 4) sedation using propofol during the first 24 hours, followed by sedation and analgesia using lorazepam, morphine, or fentanyl; 5) normothermia ($\sim$ 35–37°C); 6) euvolemia using a baseline crystalloid infusion (0.9% normal saline, 20 mEq/L KCl; 80–100 ml/hour); and 7) anticonvulsant therapy (phenytoin) for 1 week or longer if seizures occurred.

The treatment goal for Group I patients (those treated with conventional ICP/ CPP-guided therapy) was to keep

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ICP < 20 mm Hg and CPP > 60 mm Hg. A standard staircase approach was used to treat intracranial hypertension (ICP > 20 mm Hg for more than 2 minutes). Initial management consisted of elevation of the head of the bed, sedation (lorazepam), analgesia (fentanyl), intermittent CSF drainage using an external ventricular drain if inserted, and moderate hyperventilation. If ICP remained > 20 mm Hg for > 10 minutes despite the initial management, osmotherapy using mannitol boluses (0.5–1 g/kg) was started, provided that serum osmolality was < 320 mOsm/L and serum Na⁺ < 155 mmol/L. Phenylephrine (10–100 mcg/minute) was administered when CPP was ≤ 60 mm Hg for > 15 minutes and after adequate fluid resuscitation. If the patient's ICP remained elevated despite mannitol, a ventriculostomy (if one had not been placed at admission) was inserted to drain CSF. Thereafter, optimized hyperventilation (PaCO₂ ~ 30 mm Hg), additional propofol, or a decompressive hemicraniectomy were used as second-tier therapies if ICP and CPP remained compromised. Pentobarbital-induced burst suppression was used if decompressive craniectomy failed to control ICP. Induced hypothermia for ICP control and hypertonic saline were not used in either treatment group since they were formally introduced into our treatment protocols in October 2006 and May 2006, respectively.

Group II patients (the PbtO₂-guided therapy group) received the same ICP and CPP treatment as Group I patients. In addition, Group II patients, received “cause-directed” therapy to maintain PbtO₂ ≥ 20 mm Hg.^{39,60} In our previous study we used a PbtO₂ threshold of 25 mm Hg.⁵⁰ Initial intervention included an O₂ challenge (100% FiO₂) or increased CPP to improve PbtO₂. Pulmonary-associated or ventilation-associated PbtO₂ reductions were assessed for and corrected. Then ICP, metabolic delivery (for example, volume status or mean arterial blood pressure) or demand (for example, pain, fever, seizures) abnormalities were corrected. If these measures failed, a blood transfusion was administered to achieve a hemoglobin ≥ 10 mg/dL.⁴⁸ A decompressive craniectomy was performed when there was a progressive PbtO₂ decline, or when the PbtO₂ was < 20 mm Hg for > 15 minutes despite maximal medical management for elevated ICP.

Data Collection

For each patient, the number of days and hours monitored, daily maximum ICP, daily mean ICP, number and duration of episodes of increased ICP (≥ 20 mm Hg), daily minimum CPP, daily mean CPP, and number and duration of episodes of CPP < 60 mm Hg during the entire monitoring period were recorded. For each Group II patient, the daily minimum and maximum PbtO₂, daily mean PbtO₂, number and duration of episodes of compromised PbtO₂ (< 20 mm Hg), and number and duration of episodes of cerebral hypoxia (PbtO₂ < 15 mm Hg) were also recorded. The relevant variables and patient characteristics were then compared between the groups to determine if there were any significant differences.

Outcome

Patient mortality rates were calculated on the basis

of deaths during the first 3 months following TBI. Patient disposition was recorded and divided into 2 groups: 1) discharged home or to rehabilitation; or 2) patient died or was discharged to a nursing home or required ongoing hospital care for their head injury. Short-term patient outcome at 3 months (± 2 weeks) post-TBI was assessed using the GOS by telephone follow-up or medical record review. Outcome was recorded as favorable if the patient had a good outcome or only moderate disability and unfavorable if the patient died, was in a vegetative state, or had severe disability.

Statistical Analysis

Statistical analyses were performed using commercially available software, SAS version 9.0 (SAS Institute, Inc.) and Instat Version 2.03 (GraphPad Software). Data are expressed as the mean ± SD or as the median where the data are not normally distributed. Patient and physiological variables and outcome were compared using the Kruskal-Wallis nonparametric ANOVA test, Student t-test, chi-square approximate test, or the Mann-Whitney Fisher exact test, selected for their appropriateness to the measurement level and distributional properties of the data. Random effects models were used to adjust for clustering of repeated daily measurements in patients receiving PbtO₂-guided management when comparing the 2 groups. Statistical significance was defined as a 2-sided *p* < 0.05.

Results

Patient Characteristics

Fifty-three patients, 42 male and 11 female (mean age 43 ± 18 years), who received ICP/CPP-directed TBI care formed the historical control group, Group I. Group II (patients receiving PbtO₂-directed care) consisted of 70 patients, 57 male and 13 female (mean age 40.1 ± 19 years). Age, sex, admission GCS and ISS, and the pathology observed on initial head CT were similar in the 2 groups (Table 1). Apart from a slightly higher incidence of assault among Group II patients (11 vs 2%, *p* = 0.04), the mechanisms of injury were similar in both groups. A similar number of patients underwent craniotomy for a mass lesion at admission (10 in Group I and 18 in Group II, *p* = 0.5). Variables such as temperature, hematocrit, pulmonary function, and serum glucose level that may influence PbtO₂ or outcome are listed in Table 2. The mean PaO₂/FiO₂ ratio was greater in Group II patients, since transient hyperoxia (FiO₂ 1.0) or an increase in FiO₂ (for example, from 50 to 60%) was used to treat compromised PbtO₂. Device malfunction, drift, or complications were rare (< 1%) in both treatment groups. Second-tier therapies such as barbiturates were used infrequently (1 case in each group). However decompressive craniectomy was more frequently performed in patients who received PbtO₂-guided management (performed in 9 cases) than in those who received ICP/CPP-guided therapy (performed in 1 case, *p* = 0.04).

Intracranial and Cerebral Perfusion Pressure

Data were obtained from a total of 12,148.8 hours

TABLE 1: Clinical characteristics in 123 patients who received ICP/CPP-based therapy (Group I) or PbtO₂-based therapy (Group II) after severe TBI*

Characteristic	Group I (53 patients)	Group II (70 patients)	p Value
mean age in yrs	43 ± 18	40 ± 19	0.4
sex			
M	42 (79)	57 (81)	0.8
F	11 (21)	13 (19)	0.8
admission GCS			
3	41 (77)	47 (67)	0.2
4–6	6 (11)	16 (23)	0.09
7–8	6 (11)	7 (10)	0.9
mean admission ISS	35 ± 14.1	35 ± 12.0	1.0
mechanism of injury			0.07
MVC	20 (38)	29 (41)	0.7
fall	13 (25)	21 (30)	0.6
ped vs car	5 (9)	6 (9)	0.9
assault	1 (2)	8 (11)	0.04
work-related	6 (11)	2 (4)	0.2
uncertain	8 (15)	4 (6)	0.1
pathology†			0.597
EDH	4 (7.5)	3 (4.3)	0.5
SDH	18 (34)	28 (40)	0.5
CHI	9 (17)	11 (16)	0.9
DAI	10 (19)	16 (23)	0.7
SAH	6 (11)	10 (14)	0.6
contusion	5 (9)	2 (3)	0.1
depressed fracture	1 (2)	0 (0)	0.2

* Values represent numbers of patients (%), except as otherwise indicated. Means are shown ± SDs. Abbreviations: CHI = closed head injury; DAI = diffuse axonal injury; EDH = epidural hematoma; MVC = motor vehicle collision; ped vs car = pedestrian struck by vehicle; SAH = traumatic subarachnoid hemorrhage; SDH = subdural hematoma.

† Pathology was classified according to the admission head CT scan and clinical evaluation.

of continuous ICP monitoring in the ICU from the 123 patients included in this study. There was a trend toward a longer period of monitoring among Group II patients (mean 4.7 ± 3.8 days in Group II vs 3.5 ± 2.9 days in Group I, $p = 0.056$). The mean values for daily mean ICP and daily mean calculated CPP, mean number of daily episodes of elevated ICP (ICP > 20 mm Hg), or reduced CPP (CPP < 60 mm Hg) were similar in Groups I and II (Table 2).

Brain Tissue O₂ Monitoring

The Group II patients received both an ICP and a PbtO₂ monitor (LICOX). Data were analyzed from a total of 6,816 hours of continuous PbtO₂ monitoring. The mean value for daily mean PbtO₂ among all Group II patients was 36.5 ± 17 mm Hg. A total of 604 episodes of compromised PbtO₂ (PbtO₂ < 20 mm Hg) and 140 episodes of

brain hypoxia (PbtO₂ < 15 mm Hg) were detected during this period of monitoring.

Outcome

Twenty-four (45.3%) of the patients who received ICP/CPP-directed care died within 3 months of TBI. By contrast 18 (25.7%) of the patients who received PbtO₂-directed care died within 3 months. The mortality rate was significantly lower in patients who received PbtO₂-directed care than in those who received conventional ICP and CPP-based therapy ($p < 0.05$; Fig. 1 left). The overall mean hospital LOS (including survivors and nonsurvivors) was similar in the 2 groups (Group I: 19 ± 21.8 days; Group II: 23 ± 18.67 days; $p = 0.29$; Table 3). Of surviving Group I patients, 59% were discharged to a rehabilitation center, 13% to home, 21% to a skilled nursing facility, and 7% to another hospital. By contrast 6% of surviving Group II patients were discharged to a skilled nursing facility and the remaining patients were discharged home (8%) or to a rehabilitation center (86%; $p < 0.01$). Overall, 21 (39.6%) of the patients treated with ICP/CPP-guided management and 45 (64.3%) of those receiving PbtO₂-guided management had a favorable outcome (GOS good or moderate disability) at 3 months (± 2 weeks) after TBI ($p = 0.01$, Fig. 1 right).

Treatment of Compromised Brain O₂

The PbtO₂-based therapy was targeted and occurred in a physiology-based parallel process rather than as a linear therapy (therapy based on ICP alone). We identified 27 therapies that were used to treat compromised PbtO₂ in our institution during the study period (Table 4). The success of the individual treatments varied between 33 and 88%, although the efficacy of each separate therapeutic intervention cannot be reliably assessed because multiple interventions often were used simultaneously or in sequence. The therapy most commonly used, often transiently and with other therapies, to treat compromised PbtO₂ was an FiO₂ increase. To examine what FiO₂ dose is needed to reverse compromised PbtO₂, we examined data from 618 ventilator days from the 70 Group II patients. The PbtO₂ threshold for treatment (< 20 mm Hg) occurred during 384 (62%) of 618 ventilator days. The mean FiO₂ to restore PbtO₂ was 68.3% (95% CI 66.1–75.5%). When PbtO₂ was > 20 mm Hg, the mean FiO₂ was 43.9% (95% CI 41.9–45.8%).

Mortality Rate Associated with PbtO₂-Guided Management

In the Group II patients, the mean daily PbtO₂ was significantly less in the 18 patients who died within 3 months of TBI (31.55 ± 20.64 mm Hg) than in those who survived (37.43 ± 16.54 mm Hg, $p < 0.05$). Patients who died also had a longer mean total duration of compromised brain O₂ (446.3 ± 495.0 vs 217.1 ± 347.0 minutes, $p = 0.013$), a tendency toward more daily episodes of brain hypoxia (PbtO₂ < 15 mm Hg, $p = 0.06$), and a longer cumulative duration of brain hypoxia (209.1 ± 418.4 vs 30.0 ± 112.8 minutes, $p = 0.001$) than did survivors. Therapy to increase PbtO₂ during a discrete episode of compro-

TABLE 2: Comparison of monitored physiological variables*

Variable	Group I (53 patients)	Group II (70 patients)	p Value
ICP monitor, mean no. days per patient	3.5 ± 2.9	4.7 ± 3.8	0.056
mean daily ICP (mm Hg)	17.85 ± 11.74	18.2 ± 11.21	0.87
mean no. of episodes ICP >20 mm Hg per day	1.59 ± 2.1	2.08 ± 2.6	0.25
mean daily CPP (mm Hg)	72.48 ± 14.31	73.88 ± 13.46	0.58
mean no. of episodes of CPP <60 mm Hg per day	1.30 ± 1.7	1.41 ± 1.9	0.68
mean max body temp	100.71 ± 1.59	101.48 ± 1.57	0.001
mean min PaO ₂ /FiO ₂ ratio	2.25 ± 0.9	2.74 ± 1.28	0.0005
mean max hematocrit	30.21 ± 5.15	30.83 ± 4.74	0.18
mean min hematocrit	27.17 ± 5.91	27.4 ± 5.12	0.85
mean max glucose	141.48 ± 43.2	149.34 ± 55.7	0.12

* Values are shown ± SDs.

mised PbtO₂ was more frequently successful in survivors (81.4%) than in nonsurvivors (56%, $p = 0.033$).

Discussion

In this study involving 123 patients with severe TBI we examined how a PbtO₂-based management strategy influenced patient mortality and short-term outcome at a Level I trauma center. We compared 70 patients who received PbtO₂-directed care and ICP/ CPP-based therapy to 53 historical controls who received only ICP/ CPP-based therapy. Our results extend our preliminary observations⁵⁰ and suggest that PbtO₂-based therapy may be associated with reduced patient mortality and better short-term outcome. In addition, among those patients who received PbtO₂-based therapy, survival was associated with successful treatment of episodes of compromised PbtO₂. These results should be regarded as hypothesis-generating and suggest that randomized trials are needed to examine whether PbtO₂-directed care benefits patients with TBI.

Methodological Limitations

Our study has several potential limitations. First, the data were examined retrospectively and this may bias our results. Second, the study included only patients treated at a single institution, so it may lack external validity. Third, the sample size, 123 patients, although larger than our earlier study of 53 patients,⁵⁰ is still relatively small; however, the magnitude of the effect is reasonably large and the effect is both biologically plausible and consistent with TBI pathophysiology. Fourth, we do not have any information on adherence to the treatment protocols, and so it is conceivable that the results simply represent outcome differences over time that have been observed on a national basis—rather than a specific therapy. However, the same team of physicians and nurses in the same ICU provided care to both patient groups using the same basic management strategy according to formal treatment paradigms. Therapy to correct compromised PbtO₂ appears to be the only management parameter that was different between the 2 groups. Fifth, outcome was assessed approxi-

mately 3 months after TBI and within a range of 2 weeks before and after this date. Patient improvement can continue to occur after 3 months, and so it is conceivable that we may have underestimated outcome in some patients. This likely will affect both groups equally and is unlikely to have a significant effect on mortality rates. Nevertheless, it is conceivable that the difference in the treatment effect may be less than indicated by our data. Sixth, the mortality rate among the patients who received ICP/ CPP-based therapy is higher than expected from outcome data published in some clinical trials of severe TBI. Selected patients usually are treated in clinical trials and this may bias the results. Our patients also did not have isolated head injuries since all had an ISS greater than 16. In addition, there is no established expected outcome for TBI and there is heterogeneity of TBI and patient demographics at each institution where the patients are treated.¹⁰ It also is possible that outcome in the ICP/ CPP group might have been better if induced hypothermia, hypertonic saline, or decompressive hemicraniectomy had been used more frequently. However, the exact role of these therapies in severe TBI is still being elucidated.

Finally, the study population was compared with historical controls. There are well-known limitations to this kind of analysis. From a statistical point of view, since patients in each group were treated according to a standard

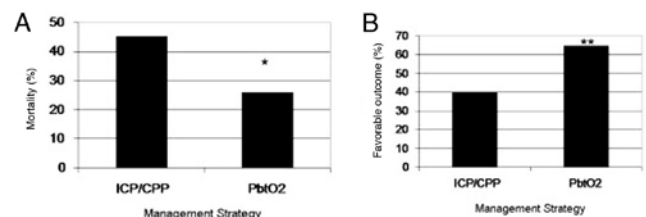


Fig. 1. Left: Histogram illustrating the mortality rates (%) in patients undergoing traditional ICP/ CPP management and PbtO₂ management. * $p < 0.05$. **Right:** Histogram illustrating short-term outcome (%) for patients undergoing traditional ICP/ CPP management or PbtO₂ management. A favorable outcome denotes a GOS of good or moderate disability. An unfavorable outcome denotes death, vegetative state, or severe disability. ** $p = 0.01$.

TABLE 3: Mean hospital LOS and ICU LOS*

LOS (days)	Group I (53 patients)	Group II (70 patients)	p Value
hospital			
all patients	19 ± 21.8	23 ± 18.67	0.29
survivors	29.9 ± 24	28 ± 18.3	0.71
nonsurvivors	5.7 ± 6	7 ± 7.4	0.49
ICU			
all patients	8 ± 7.64	12 ± 11.67	0.03
survivors	11.5 ± 7.8	15 ± 12.4	0.2
nonsurvivors	5.1 ± 6.1	6 ± 5.6	0.59

* Values are shown ± SDs.

protocol and were similar with respect to age, sex, and admission GCS and ISS, as well as having comparable pathology on admission CT and meeting clearly delineated inclusion criteria, the study has some characteristics of a 2-sample design but with 2 important exceptions: it was not randomized and the groups were not contemporaneous. More patients in the PbtO₂ group underwent a decompressive craniectomy. Since we are comparing 2 management strategies based on different physiological information rather than a single therapy (for example, a drug), it is perhaps not surprising that there is this management difference. What we do not know is whether this particular difference is associated with the use of a PbtO₂ monitor or represents another trend. In contrast to a difference in management and more importantly, the groups are matched when age, GCS, ISS, pathology on admission CT, and other variables are compared (Tables 1 and 2). These variables are among the most powerful independent prognostic variables after TBI³⁵—that is,

the outcome effect is likely to be associated with what we are examining, a management strategy or process of care, rather than patient characteristics. In our opinion, the results therefore suggest but do not prove that PbtO₂-directed TBI care may have a beneficial effect. Ideally, a randomized clinical trial will be needed to demonstrate the benefit of PbtO₂-directed TBI care. The data from this study provide some information needed to plan for such a trial.^{1,37}

Current Conventional TBI Management

Clinical and laboratory research demonstrate that not all neuron damage occurs at the time of injury, but damage also occurs through secondary neuronal injury that evolves during the hours and days after TBI.^{16,28} Current TBI therapy is therefore centered on management of secondary brain injury, and, in particular, current TBI management emphasizes ICP reduction, in part to maintain CPP and prevent cerebral ischemia. This ischemia increases the risk of poor TBI outcome.^{7,42} The association between increased ICP or reduced CPP and poor outcome is well described.^{29,34,36} However, increased ICP is responsible for fewer than half the episodes of cerebral ischemia, and cerebral infarction can occur despite normal ICP and CPP.^{18,24,49,58} Furthermore, recent PET studies in human patients after TBI suggest that mechanisms other than simple perfusion-related ischemia may be associated with cellular hypoxia in the brain.³³ In addition, cerebral microdialysis studies in TBI suggest that an elevated lactate/pyruvate ratio (that is, anaerobic metabolism) is independent of CPP.⁵⁹ We also have observed that a third of patients with severe TBI who are adequately resuscitated according to published Advanced Trauma Life Support² and TBI guidelines^{7,42}—that is, CPP > 60 mm Hg—still have evidence of severe brain hypoxia (PbtO₂ ≤ 10 mm

TABLE 4: Therapies used to treat compromised brain O₂*

Frequently Used Therapy	Less Frequently Used Therapy
adjust ventilator parameters to increase PaO ₂	ventriculostomy
increase FiO ₂ (example: 50 to 60%)	continuous or intermittent CSF drainage
increase PEEP	
transient normobaric hyperoxia 100% FiO ₂	blood transfusion
augment CPP	neuromuscular paralysis
colloid bolus	pancuronium, vecuronium
phenylephrine, dopamine	
pharmacological analgesia & sedation	adjust ventilator rate
propofol, midazolam, lorazepam, fentanyl, morphine	increase to lower PaCO ₂ (ICP)
	decrease to increase EtCO ₂ , PaCO ₂
head position or avoid turning, certain positions	pulmonary toilette and suction
ICP control	
sedation, mannitol, IV lidocaine	thiopental (barbiturate burst suppression)
ensure temp <38°C	labetalol
decompressive craniectomy (or other cranial op)	

* The PbtO₂-directed therapy was targeted and occurred in a physiology-based parallel process with ICP management. Therapies were titrated to effect and were often used in various combinations rather than singly. Abbreviations: EtCO₂ = end tidal CO₂; IV = intravenous; PEEP = positive end-expiratory pressure.

Hg) in the early hours after TBI.⁵¹ These results may explain, in part, why therapies to improve CPP have not improved patient outcomes.^{12,43} Other therapies, including hypothermia, neuroprotection, steroids, and barbiturates, while effective in the laboratory, have not been successful in patients.^{6,11,14,26,37,41,42,52} Together these data suggest that while an ICP monitor and ICP/CPP management are important in TBI, measures of other parameters or other management strategies also may be necessary.

Biological Plausibility of PbtO₂-Directed TBI Care

The adult brain weighs about 2% of body weight yet consumes about 20% of the O₂ consumed by the entire body. More than 90% of this oxygen is used by the mitochondria during aerobic metabolism. The pathophysiological processes after TBI are complex; however, following severe TBI, a huge metabolic load is placed on brain tissue during a time when there is impaired O₂ delivery, compromised aerobic metabolism, and reduced cerebral blood flow.^{5,16,21,22,30,56} This results in cellular hypoxia. Consistent with the pathophysiological processes, histopathological examination of brain tissue, in some studies, demonstrates that 80–90% of patients who die of TBI have evidence of ischemic or hypoxic brain injury. Together these data suggest it is reasonable to assume that use of a PbtO₂ monitor and efforts to increase brain O₂ delivery may improve TBI outcome.

Several lines of converging experimental and clinical evidence suggest that PbtO₂-directed care is a potential TBI therapy. First, brain hypoxia (PbtO₂ < 15 mm Hg) is a well-described marker of poor outcome in many clinical TBI studies.^{13,54–58} Second, reduced PbtO₂ is associated with independent neurochemical markers of brain ischemia;²⁰ by contrast, an increase in PbtO₂ is associated with improved brain metabolism in clinical TBI studies.⁵³ Third, strategies to augment PbtO₂ are associated with reduced secondary brain damage in experimental TBI models⁴⁰ and reduced infarct volumes in animal stroke models.^{17,47} Finally, Singhal et al.⁴⁶ recently demonstrated in a small, randomized clinical trial that high-flow O₂ therapy (to improve PbtO₂) was associated with a transient improvement in clinical deficits and MR imaging abnormalities in patients with acute cerebral ischemia. These various data are consistent with the 2 important observations in this paper: 1) PbtO₂-directed care is associated with better outcome; and 2) successful correction of compromised PbtO₂ is associated with better survival after severe TBI.

Clinical Outcome and PbtO₂-Directed TBI Care

There is limited research into how different techniques to monitor patients' conditions, including use of ICP and PbtO₂ monitors, affect outcome after severe TBI. For example, while ICP monitors and ICP management have been used since the 1960s and represent a TBI "standard," their benefit to patient outcome has not been directly assessed in a clinical trial.⁷ Therapy to optimize CPP, which is estimated from an ICP monitor, does not appear to benefit patients,^{12,43} and consequently there is debate about what constitutes optimal CPP after

TBI.^{15,25,38} Also, CPP guidelines have changed over the years; current guidelines suggest that CPP < 50 mm Hg or aggressive attempts to keep CPP > 70 mm Hg should be avoided.⁸ During the time period in which our study was performed we used a CPP of 60 mm Hg to guide therapy. It is our contention that PbtO₂-guided management may help prevent cellular hypoxia and also may help establish what ICP or CPP is appropriate in an individual patient. This is important because there is marked heterogeneity in TBI pathology and pathophysiology, and therapies to treat ICP and CPP all are associated with potential deleterious effects.

The value of direct PbtO₂ monitoring and care based on this technique has undergone little direct study with respect to patient outcome. In a small series of 53 patients with TBI we observed that PbtO₂-based care was associated with a lower mortality rate than conventional ICP/CPP therapy.⁵⁰ The sample size was small, and thus, the conclusions were preliminary. In the current series, which includes 123 new patients, we observed that PbtO₂-based care is associated with better outcome. Furthermore, survival is more likely when compromised PbtO₂ can be treated successfully. Exactly what constitutes the most effective method to correct compromised PbtO₂ remains unclear because we used many different strategies in a "cause-directed manner," often in combination or in sequence. Certainly, our outcome measures (mortality, discharge disposition, and short-term GOS score) are crude. Nevertheless, they represent reasonable markers of outcome. Future studies will need to examine neuropsychological and long-term functional outcome in survivors.

There is one other published study that examined PbtO₂-based therapy in TBI (although others have been published since this manuscript was submitted).³² In this study using historical controls, Meixensberger et al.³² studied 93 patients. There was a tendency, but no statistical difference, for patients who received PbtO₂-based rather than ICP/CPP-based treatment to have a better outcome. There are several important differences in the management used by Meixensberger et al. and us. First, these authors attempted to maintain CPP > 70 mm Hg. Clinical evidence now suggests that adherence to this CPP may be deleterious in some patients.^{12,15,38,42} In addition, a direct relationship between CPP and PbtO₂ is not observed in every patient, in large part because autoregulation frequently is disturbed.^{19,44} Instead, we aimed to maintain CPP > 60 mm Hg, and in some patients tolerated a CPP between 50 and 60 mm Hg provided their PbtO₂ was normal (25–40 mm Hg). Second, Meixensberger et al. treated decreased PbtO₂ only by increasing CPP. By contrast, we used a "cause-specific" management protocol.⁶⁰ We have identified 27 different therapies used to correct compromised PbtO₂ in our ICU and found that each, if used in a cause-directed fashion, is successful in up to 80% of patients. These differences related to CPP may be important since therapies to increase CPP can adversely affect lung function,^{12,43} which in turn can compromise cellular oxygenation in the brain.¹⁹ Finally, patients treated by Meixensberger et al. received PbtO₂ therapy when their PbtO₂ was ≤ 10 mm Hg. At that threshold the brain is already severely hypoxic. By contrast, we initiated therapy when

PbtO₂ was < 20 mm Hg. There are several reasons why we chose this threshold. Neuronal mitochondria, where the vast majority of brain oxygen is used, require a low intracellular PO₂ that corresponds to a minimum PbtO₂ threshold of about 20 mm Hg to maintain aerobic metabolism.⁴⁵ Brain hypoxia (PbtO₂ < 15 mm Hg) is associated with poor outcome; this association depends also on the duration of hypoxia. We have found that compromised PbtO₂ can take several minutes to respond to a therapy. We therefore start therapy to correct compromised PbtO₂ rather than wait for brain hypoxia to develop before starting therapy. Consistent with this approach, van den Brink et al.,⁵⁶ in a series of 101 patients with TBI, confirmed that neurological outcome depends not only on the depth but also the duration of brain hypoxia. This concept is consistent with the well-known threshold for cerebral blood flow beyond which neuronal injury progresses from reversible to irreversible.

While this study was not intended to answer how a PbtO₂ monitor altered care beyond data provided by an ICP monitor alone, we have learned several important concepts. First, there is a well-described association between secondary cerebral insults and poor outcome after TBI. Monitoring is essential to identify secondary cerebral insults, and it is believed that when recognized early, they can be better treated, thus improving patient outcome. There are many methods with which to monitor brain physiology, but until 2007, an ICP monitor was the only recommended monitor. Certainly ICP monitors are useful, but several recent studies suggest that brain hypoxia or ischemia is common even when ICP is normal.^{5,24,27,33,49,51,59} We believe a PbtO₂ monitor provides additional information about the health of the brain. Second, each and every treatment for elevated ICP and reduced CPP has associated adverse effects. When using a PbtO₂ monitor there is a tendency for us to tolerate slightly higher ICPs and so avoid some ICP management side effects. In addition, the effects of a particular treatment, good or bad, can be recognized even if there is no alteration in ICP; and trends in PbtO₂, rather than ICP thresholds alone, can be used to guide aggressive strategies (for example, decompressive craniectomy). Third, in a few select patients, a PbtO₂ monitor has helped to identify extracerebral complications, particularly cardiopulmonary complications, before other monitors do. Finally, there is marked heterogeneity in patients, including their premorbid condition and extracerebral physiology as well as the structural brain injury after TBI. The additional information provided by a PbtO₂ monitor allows care to be better targeted and individualized and so allows us to begin to move away from the “one size fits all” approach to severe TBI that still is prevalent. This is analogous to obtaining a culture and sensitivity analysis in a patient with a fever rather than simply giving antibiotics on an empirical basis.

Conclusions

Several studies suggest that a direct PbtO₂ monitor may be an ideal complement to ICP monitors in TBI management.^{9,19,31,39,50,51,54–58} Our results, derived from retrospective analysis of data that was collected prospectively,

suggest that therapy targeted at maintaining adequate O₂ tension is associated with better outcome after severe TBI than conventional ICP/CPP-based therapy. This management strategy represents a paradigm shift in TBI care that will need to be confirmed in prospective studies.

Disclosure

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