Brain tissue oxygen and outcome after severe traumatic brain injury: A systematic review*

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Objective: **In this study, available medical literature were reviewed to determine whether brain hypoxia as measured by brain tissue oxygen (Bto_2) levels is associated with increased risk of poor outcome after traumatic brain injury (TBI). A secondary objective was to examine the safety profile of a direct BtO_2 probe.**

Data Source and Extraction: **Clinical studies published between 1993 and 2008 were identified from electronic databases, *Index Medicus*, bibliographies of pertinent articles, and expert consultation. The following inclusion criteria were applied for outcome analysis: 1) more than 10 patients described, 2) use of a direct Bto_2 monitor, 3) brain hypoxia defined as Bto_2 <10 mm Hg for >15 or 30 minutes, 4) 6-month outcome data, and 5) clear reporting of patient outcome associated with Bto_2. For the analysis, each selected article had to have adequate data to determine odds ratios (ORs) and confidence intervals (CIs). Thirteen studies met the initial inclusion criteria and three were included in the final outcome analysis. Safety data were abstracted from any report where it was mentioned.**

Data Synthesis: **The three studies included 150 evaluable patients with severe TBI (Glasgow Coma Scale ≤8). Brain hypoxia was identified in 71 (47%) of these patients. Among the patients with brain hypoxia, 52 (73%) had unfavorable outcome including 39 (55%) who died. In the absence of brain hypoxia, 34 (43%) patients had an unfavorable outcome, including 17 (22%) who died. Overall brain hypoxia (Bto_2 <10 mm Hg >15 minutes) was associated with worse outcome (OR 4.0; 95% CI 1.9–8.2) and increased mortality (OR 4.6; 95% CI 2.2–9.6). We reviewed published safety data; in 292 patients monitored with a Bto_2 probe, only two adverse events were reported.**

Conclusion: **Summary results indicate that brain hypoxia (<10 mm Hg) is associated with worse outcome after severe TBI and that Bto_2 probes are safe. These results imply that treating patients to increase Bto_2 may improve outcome after severe TBI. This question will require further study. (Crit Care Med 2009; 37:2057–2063)**

KEY WORDS: brain tissue oxygen; Licox; intracranial pressure; monitoring; traumatic brain injury

Traumatic brain injury (TBI) is a major cause of morbidity and mortality particularly among young people (1). Severe TBI, clinically defined as any head injury that results in a Glasgow Coma Scale (GCS) of 8 or less within the first 48 hours posttrauma, has a mortality rate between 20% and 40%. Another 20% of patients remain severely disabled (2). Much of this unfavorable outcome is due to secondary brain damage that occurs in the hours, days, and weeks after the primary insult (3). In fact, secondary cerebral ischemic injury has been observed in greater than 90% of patients who died of a head injury (4, 5). Secondary cerebral injury is associated with impaired cerebral metabolism, hypoxia, and ischemia, which result in a complex, potentially irreversible pathophysiologic cascade of events.

Current therapies to manage secondary brain injury, while effective in the laboratory, have disappointed in the clinical environment (6–14). This lack of efficacy results, in part, because we are only now beginning to elucidate methods to effectively monitor brain physiology after TBI. Neurologic monitoring can be classified broadly into four types: 1) pressure, e.g., intracranial pressure (ICP) from which cerebral perfusion pressure (CPP) is estimated; 2) blood flow, e.g., thermal diffusion or blood flow velocity e.g., transcranial Doppler; 3) electrophysiology, e.g., electroencephalogram; and 4) metabolic measures such as jugular venous oximetry, cerebral microdialysis, and direct brain tissue oxygen (Bto_2). It is believed that with effective neuromonitoring, secondary brain injury can be recognized early and better managed before irreversible injury occurs, thereby improving patient outcome. Current Guidelines for the Management of Severe Head Injury (15) as described by such organizations as the American Association of Neurologic Surgeons and Congress of Neurologic Surgeons Joint Section on Neurotrauma and Critical Care and the European Brain Injury Consortium emphasize the use of ICP monitors. The relationship between poor patient outcome, particularly mortality and increased ICP is well known (3, 15, 16, 17). In addition, ICP monitor use in some studies appears to be associated with better patient outcome although this has never been tested in a clinical trial (17). However, secondary brain injury is not always associated with pathologic changes in ICP or CPP (18–20) and adequate resuscitation (i.e., normal ICP and CPP) after TBI does not always prevent brain hypoxia (21). Recent positron emission tomography studies in humans after TBI (22) also suggest that mechanisms other than simple perfusion-limited ischemia e.g., intravascular microthrombosis (23), cytotoxic edema

***See also p. 2134.**

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(24), or mitochondrial dysfunction (25) may be responsible for brain hypoxia. These data suggest that newer metabolic monitors, e.g., microdialysis or direct Bto_2 may have an important role in TBI management.

Maintenance of adequate tissue oxygen is recognized as a primary objective in critical care medicine. Therefore, the ability to assess tissue oxygenation and detect tissue hypoxia is vital in neurocritical care, since ischemia and hypoxia significantly contribute to brain damage. Brain oxygen monitors were only included in the treatment guidelines for severe TBI in 2007 (26). Several review articles describing Bto_2 monitors that compare it with other techniques and its use in different diseases have appeared during the previous year but none have performed a statistical analysis on outcome data (27–31). The purpose of this study was to review the available medical literature to determine whether reduced Bto_2 is associated with poor outcome or mortality. A secondary objective was to determine whether direct Bto_2 monitor use is associated with complications after severe TBI. A direct Bto_2 measurement of 10 to 15 mm Hg has been proposed as the critical threshold for ischemic damage and poor patient outcome (32–36). In this study, we hypothesized that brain hypoxia (Bto_2 <10 mm Hg) is associated with poor outcome in patients with severe TBI. We chose this value since a variety of experimental and clinical studies including clinical comparisons with cerebral microdialysis and jugular bulb oxygen saturation indicate that a Bto_2 less than 10 mm Hg indicates critical brain ischemia (34, 36–40).

METHODS

Study Selection. We reviewed the published medical literature between January 1993 and September 2008. Published clinical studies were identified from electronic databases (MEDLINE [http://www.ncbi.nlm.nih.gov/sites/entrez], BIOSIS, and Dissertation Abstracts Online), *Index Medicus*, bibliographies of pertinent articles, and expert consultation using a combination of the following medical subject heading (MeSH) terms: Licox, revoxide, clark style probe, Fleckenstein, GMS (Gesellschaft fur Medizinische Sondentechnik [Kiel-Mielkendorf, Germany], the company that originally manufactured the Licox brain tissue oxygen monitoring system before being acquired by Integra Lifesciences in 2001), TBI, subarachnoid hemorrhage, brain O_2, brain oxygen probe, brain oxygen, brain oxygen clinical studies, $PBto_2$, PBo_2, $Ptio_2$, $pbro_2$, Bto_2, partial pressure of oxygen in brain tissue, and Po_2 of brain tissue. The search was restricted to the English language but was not restricted by type of publication. However, we eliminated experimental articles describing brain oxygen in animal models, reviews, purely technical articles and articles with small sample sizes ($n < 10$). Studies were selected using the following inclusion criteria: 1) publication reported on ≥10 patients; 2) diagnosis included severe head injury or TBI; 3) a direct brain oxygen monitor was used; 4) brain hypoxia was defined as Bto_2 <10 mm Hg; and 5) the publication included prospective patient outcome data associated with Bto_2 with well-defined end points (i.e., Glasgow Outcomes Scores at 6 months). For inclusion in the final analysis, each selected article had to have adequate data to determine odds ratios (ORs) and confidence intervals. To reduce selection bias, we assessed the quality of the articles based on checklists developed by the National Health Service Centre for Reviews and Dissemination (41) and by the U.S. Preventive Services Task Force (42). These checklists were modified for observational studies to address issues of particular importance in brain oxygen studies. A secondary objective was to review safety data. To do this, we abstracted data from any clinical report were Licox safety was mentioned specifically and used the reports that the Food Drug and Administration based its approval of the Licox monitor for clinical use in the United States (i.e., different reports were included in the primary and secondary objectives since the secondary objective included no statistical analysis).

Data Extraction. Two reviewers independently extracted data from the primary studies, and any disagreements were resolved through consensus. Extracted information included demographic data, GCS, brain oxygen, and outcome, as well as other interventions and physiologic goals for brain injury management.

Categorization of Patients. Patients were classified according to the partial pressure of oxygen in the brain, as measured by the Bto_2 probe. The following terms and abbreviations were used in the literature to describe regional partial pressure of oxygen in brain tissue: $P_{ti}o_2$, $Ptio_2$, $pbro_2$, partial pressure of oxygen in brain tissue, and Po_2 of brain tissue. In this article, the term Bto_2 has been used to refer to regional partial pressure of oxygen in brain tissue as measured by a direct brain oxygen probe. For the analysis, patients were categorized into two groups: those who had brain hypoxia (low Bto_2) and those who had acceptable levels of Bto_2. Brain hypoxic events were defined as low-partial pressure of Bto_2 <10 mm Hg as measured by a direct brain oxygen probe for greater than 15 or 30 minutes during the early posttrauma monitoring period. The duration of hypoxia, and the duration of critical care monitoring are described in Table 1. There is no consensus in the literature on ideal placement of a Bto_2 probe. However, if a Bto_2 monitor is placed in an undamaged area of the brain, the recorded values can be considered representative of the other undamaged areas of brain tissue. In the three studies included in the analysis, probes were placed through a modified three-channel intracranial bolt inserted in the right frontal lobe parenchyma in the absence of injury there (43), in the frontal lobe parenchyma contralateral to injury (44), or the nonlesioned frontal white matter (32).

Response Variables. We evaluated long-term patient outcome as the response variable in this analysis. The Glasgow Outcome Score (GOS) typically was used in the literature to categorize patient outcome. GOS values of 1 and 2 (dead, vegetative state) were always con-

Table 1. Study and patient characteristics for the studies selected for analysis

Study (First Author), Location	Number of Patients (Evaluable)	Gender/Age	Duration of Bto_2 Monitoring	Definition of Brain Hypoxia	No. Patients with Brain Hypoxia	Duration of Follow-Up
van den Brink et al 2000 (43), Rotterdam	101 (99)	83M/18F 34 ± 16 years	Average 86 hrs	Bto_2 <10 mm Hg >30 min	43	6 mo
Bardt et al 1998 (32), Berlin	35	28M/7F 33.2 ± 11.3 years	Average 119 hrs	Bto_2 <10 mm Hg >30 min	23	6 mo
Kiening et al 1997 (44), Berlin	23 (16)	19M/4F 26.3 years (15–66 years)	7 days	Bto_2 <10 mm Hg >15 min	5	6 mo

M, male; F, female.
Age is mean ± standard deviation.

sidered unfavorable. GOS values of 4 and 5 (moderately disabled, recovered) were always categorized as favorable. However, authors differed in how they categorized a GOS of 3 (severely disabled)—whether favorable or unfavorable. This analysis dichotomized outcomes for two different analyses: dead/alive (GOS 1 vs. GOS >1), and unfavorable/favorable (GOS 1–3 vs. GOS 4 or 5). Patient outcome was measured at 6 months.

Statistical Methods. The brain hypoxia group was compared with the nonhypoxic group based on OR. An OR <1.0 suggests a reduced risk of death or poor neurologic outcome for the brain hypoxia group compared with the nonhypoxic group. By contrast, an OR >1.0 suggests an increased risk. The homogeneity of the ORs was evaluated using the Breslow–Day test. In the absence of demonstrated heterogeneity, a common OR with 95% confidence limits was estimated using Mantel–Haenszel method.

RESULTS

Literature and Study Characteristics. Sixty potentially relevant publications that addressed outcome when using a brain oxygen monitor were retrieved. Of the 60 publications, 13 reports fulfilled the inclusion criteria for the primary objective (outcome analysis) and were selected for further evaluation. Three publications (32, 43, 44) had adequate data to perform statistical analyses and were ultimately chosen for inclusion in the final analysis (Table 1). These studies were observational studies. A qualitative assessment of the published data revealed that these three studies used similar research design, measures, and time periods, allowing for meaningful pooling of results. Statistical heterogeneity was not detected in the pooled results.

Outcome. A total of 159 (150 evaluable) patients with severe TBI were included in the analyses (32, 43, 44). All had an admission GCS ≤8 after TBI. Monitoring duration ranged from 24 hours to 7 days. Outcome was assessed using the GOS; the time to follow-up was 6 months for all three studies. Of the 150 evaluable patients 86 (57%) patients were in the cohort with an unfavorable outcome and 64 (43%) patients were in the cohort with a favorable outcome.

Outcome results and estimates of ORs are found in Tables 2 and 3. Among the patients with brain hypoxia, 52 (73%) had unfavorable outcome including 39 (55%) who died. In the absence of brain hypoxia, 34 (43%) patients had an unfavorable outcome, including 17 (22%) who died. The common OR of unfavorable outcome (death + disability) at 6 months was 4.00 (95% confidence interval 1.9–8.2) in patients with brain hypoxia. The OR of death at 6 months was 4.6 (95% confidence interval 2.2–9.6). This confirms that brain hypoxia (Bto_2 <10 mm Hg) is significantly associated with poor outcome after severe TBI.

Safety of the Licox System. A secondary objective of this analysis was to determine the safety profile of a direct Bto_2 monitor. In this analysis, we chose to examine the safety of the Licox System (Integra Neurosciences, Plainsboro, NJ) that measures only brain oxygen rather than all devices (i.e., Neurotrend) because the Neurotrend measures other parameters in addition to oxygen and, apart from a few regions of Europe, is no longer commercially available. We reviewed safety data in the literature (20, 33, 43, 45–51). In 292 patients monitored with the Licox probe, only two adverse events were reported (Table 4). Both these adverse events were iatrogenic hematomas reported by Dings et al (33, 46,

Table 2. The association between brain oxygen levels (i.e., brain hypoxia [<10 mm Hg]) and patient outcome at 6 months

Study (First Author), Location	Number of Patients (Evaluable)	Brain Hypoxia (n = 71)		No Brain Hypoxia (n = 79)		Odds Ratio (95% CI)
		Unfavorable Outcome (No. Patients)	Favorable Outcome (No. Patients)	Unfavorable Outcome (No. Patients)	Favorable Outcome (No. Patients)	
van den Brink et al 2000 (43), Rotterdam	101 (99)	29	14	24	32	4.0 (1.9–8.2)
Bardt et al 1998 (32), Berlin	35	18	5	3	9	
Kiening et al 1997 (44), Berlin	23 (16)	5	0	7	4	

CI, confidence interval; GOS, Glasgow Outcome Score.

This analysis dichotomized patient outcomes as unfavorable/favorable (GOS 1 to 3 [dead, vegetative state, severely disabled] versus GOS 4 or 5 [moderately disabled, good]). Patient outcome was measured at 6 months.

Table 3. The association between brain oxygen levels (i.e., brain hypoxia [<10 mm Hg]) and mortality at 6 months

Study (First Author), Location	Number of Patients (Evaluable)	Brain Hypoxia (n = 71)		No Brain Hypoxia (n = 79)		Odds Ratio (95% CI)
		Death (No. Patients)	Survivor (No. Patients)	Death (No. Patients)	Survivor (No. Patients)	
van den Brink et al 2000 (43), Rotterdam	101 (99)	24	19	14	42	4.6 (2.2–9.6)
Bardt et al 1998 (32), Berlin	35	13	10	1	11	
Kiening et al 1997 (44), Berlin	23 (16)	2	3	2	9	

CI, confidence interval; GOS, Glasgow Outcome Score.

This analysis dichotomized patient outcomes as dead/alive (GOS of 1 [dead] vs. GOS >1 [vegetative state, severely disabled, moderately disabled, good]). Patient outcome was measured at 6 months.

Table 4. Published safety results of the Licox System (Integra Neurosciences, Plainsboro, NJ) used to measure brain oxygen

Study (Reference)	Number of Patients	Safety Parameters	Adverse Effects
van den Brink et al 2000 (43)	101[a]	Hematoma; infection	None
Dings et al 1998 (33)	101	Hematoma; infection	Two iatrogenic hematomas
van den Brink et al 1998 (20)	82[a]	Hemorrhage; infection	None
van Santbrink et al 1996 (76)	22	Hematoma; infection	None
Meixensberger et al 1998 (39)	22	Bleeding; infection	None
Sarrafzadeh et al 1998 (50)	17	Hematoma; infection	None
Kiening et al 1996 (34)	15	Intracranial bleeding; infection	None
Bruzzone et al 1998 (45)	7	Intracranial bleeding; infection	None
Sarrafzadeh et al 1997 (50)	7	Infection; bleeding	None

[a]From Ref. (43), the 101 patients includes 82 from their previous publication, (20).

47) in a study of 101 patients. One was a small intracerebral hematoma most likely caused by placement of the probe too close to the patient's sagittal sinus and the second was a small epidural hematoma most likely caused by a perforation of the dura mater by a blunt, rather than a sharp object. Neither required treatment. No catheter-related complications or infections were reported. Thus, a review of the literature demonstrated that the Licox probe is a safe technique to monitor brain oxygen.

DISCUSSION

In our systematic literature review, the studies meeting inclusion criteria all showed an association between poor outcome and brain hypoxia after severe TBI. In particular, the largest studies confirmed the prognostic value of brain hypoxia and our safety review indicates that use of a direct Bto_2 monitor is safe. The common OR estimate for unfavorable outcome (death or disability at 6 months) was 4.00 when Bto_2 is less than 10 mm Hg. Thus the analysis indicates that brain hypoxia is associated with worse outcome after severe TBI. These results suggest that techniques to monitor Bto_2 and therapy to improve Bto_2 may improve outcome after severe TBI.

Methodologic Limitations. Our analysis depends on the quality of the included studies. Since a randomized trial evaluating brain oxygen monitors, or even ICP monitors for that matter, has never been performed, our analysis includes only observational studies. The studies, therefore, are subject to bias, including differences in how other risk factors for outcome e.g., pathology, pupil findings, computed tomography findings, other injuries and management differences among others (52) are controlled. However, the two major variables associated without outcome age and GCS were similar in the three studies reviewed. Second, by pooling data from different studies, there is still a chance to violate homogeneity assumption even though we failed to reject the homogeneity hypothesis in our analysis. Heterogeneity is a major threat to the interpretation and validity of a combined analysis and can be because of differences in methods, study populations, interventions, outcomes, or chance (53, 54). For example, differences in where monitors were placed, when the GCS was recorded, or how frequently physiologic data were recorded all may bias the results. Third, we found only three studies that met our inclusion criteria for final analysis and one of these studies contributed more than half the patients. In addition, monitors were inserted and patients were monitored for different time periods. These all may bias the results. However, our findings are biologically plausible and consistent with what is observed elsewhere in the literature, i.e., reduced brain oxygen is associated with poor outcome (26–31). In addition, for the data summarized in Tables 2 and 3, the three studies are consistent in that the results are all in the same direction and each have odds ratios greater than 1 for both death and unfavorable outcomes when there is brain hypoxia. Finally, our analysis evaluated only one brain oxygen value (Bto_2 <10 mm Hg). Despite these limitations, the results reported here support the hypothesis that Bto_2 is a predictor of patient outcomes and in particular that brain hypoxia is associated with poor outcome after severe TBI.

Direct Brain Oxygen Monitors. Brain oxygen may be assessed using imaging (e.g., positron emission tomography or magnetic resonance spectroscopy), jugular venous oximetry, near infrared spectroscopy (30) or with direct Bto_2 monitors. There are two direct Bto_2 monitor systems Licox (Integra Neuroscience) and Neurotrend (Diametrics Medical, St Paul, MN). We have focused on the Licox catheter because there is a larger scientific background (two-fold more publications) and it is more commonly used in clinical practice. Furthermore, while the Neurotrend monitor and the Licox monitor both measure Bto_2 they can be difficult to compare directly (55, 56). First the two catheters are fundamentally different. Licox is a Clark-type electrode that measures oxygen only. Neurotrend is a multiparameter sensor that uses optical fluorescence to measure oxygen, Pco_2 and pH. Second, both monitors initially were based on modified Clark-type electrodes. In 1998, Neurotrend changed design to a colorimetric method using optical fluorescence. This technology change makes it difficult to compare between old and more recent studies. Second Licox catheters are precalibrated and so available for immediate insertion. However, postinsertion stabilization (30 minutes to 2 hours) is necessary before data can be used. By contrast, the Neurotrend monitor requires bedside calibration to a defined oxygen concentration. Third, catheters are different lengths and the Neurotrend needs to be inserted at a greater depth than the Licox catheter (57). Finally, the Bto_2 threshold for critical cerebral ischemia is considered to be 10 mm Hg for Licox (39) whereas for Neurotrend it is 19 mm Hg (58).

Safety Considerations. Our literature review demonstrates that the use of a Licox Bto_2 monitor is safe: the complication rate was less than 1%. No catheter-related infections were reported and catheter-related hematomas were rare. Nonreporting of complications, however, does not mean their absence. This low-complication rate is similar to that reported in other reviews on brain oxygen monitors (30). There is a report of a subdural hematoma associated with a direct Bto_2 monitor but it appears that the insertion technique may have been different from what is commonly used and it is not clear if a Licox or Paratrend monitor

was used (57). There are some limitations to our safety analysis. Few investigators specifically addressed safety and not every patient included in the various articles received a CT scan after the brain oxygen monitor was placed. However, based on our own experience this literature review seems to be a very reasonable estimate of safety. We have placed greater than 500 LICOX monitors. All have had follow-up head CT scans. Two hematomas were found. Neither was symptomatic and both were related to user error during insertion rather than the device itself. We also did not observe any infections associated with the monitor including among patients monitored for 7 days or longer.

These safety results for the LICOX monitor (a parenchymal brain oxygen, temperature, and ICP monitor placed through a single bolt) compare very favorably with other parenchymal monitoring tools, i.e., ICP monitors where the complication rate also is reported to be about 1% including when placed by midlevel practitioners (59–63). Minor ICP monitor complications such as malfunction or dislodgment occur in less than 10% of patients' (61). ICP also may be monitored using a ventricular drain. However, the complication rate (5%–10%) is significantly greater when using a ventricular catheter rather than a parenchymal monitor (64–68). In addition, the risk of clinically significant infection is greater in those who receive a ventricular rather than a parenchymal monitor (64, 65, 68).

What Do Brain Oxygen Monitors Measure? What Bto_2 actually measures in humans is only now beginning to be elucidated. This is important from a therapeutic perspective since the debate is centered primarily on whether Bto_2 reflects cerebral blood flow (CBF) or oxygen extraction (69). Although Bto_2 is influenced by factors that regulate CBF, and in particular CO_2 and mean arterial pressure (70), a Bto_2 monitor is not simply an ischemia monitor (71, 72). Instead it likely is a marker of the balance between regional oxygen supply and cellular oxygen consumption. It also is influenced by changes in diffusion distance between capillaries and cells and the proportion of arterioles and venules where the probe is placed (22, 69). Several studies demonstrate that Bto_2 is influenced by a wide range of parameters including Fio_2, arterial partial pressure of oxygen (P_ao_2), mean arterial pressure, CPP, CBF, hemoglobin concentration, to name a few and may be inversely correlated with oxygen extraction fraction on positron emission tomography (73). Recently Rosenthal et al (74) challenged 14 severe TBI with an increase in Fio_2 to 1.0 (oxygen reactivity), a 10 mm Hg increase in mean arterial blood pressure (cerebral autoregulation), and a 10 mm Hg decrease in $Paco_2$ (CO_2 cerebral vascular reactivity). Although there were several study limitations their data suggest that Bto_2 reflects the product of cerebral blood flow and the arteriovenous difference in oxygen tension, that is, $Bto_2 = CBF \times$ arterio venous tension o_2. This finding is consistent with experimental studies, which indicate that Bto_2 does not simply reflect CBF (71), positron emission tomography studies in human TBI, which show that diffusion abnormalities can contribute to cerebral hypoxia (22), and microdialysis studies which indicate that increases in markers of anaerobic metabolism, can occur independently from CPP (75). In other words, a Bto_2 monitor can provide some insight into both ischemic and nonischemic derangements of brain physiology after TBI.

TBI Management and a Role for Brain Oxygen Monitors. Currently, TBI management aims to prevent or reduce secondary brain injury. It has become clear from both animal and human studies during the last two to three decades that neuronal survival after TBI depends largely on an adequate supply of oxygen and glucose. Many variables can influence this supply and, consequently, cerebral metabolism. For this reason, neurologic monitoring plays a crucial role in severe TBI management (10, 15, 26). Currently, intensive care unit management decisions are based largely on information provided by ICP monitors and, consequently, an estimate of CPP. The relationship between increased ICP and poor outcome, particularly mortality after TBI, is well described (3, 16). Although ICP monitoring has become routine in many neurointensive care units, the role of ICP monitoring has not been subject to a randomized clinical trial. Furthermore, ICP and CPP do not provide direct information about cerebral oxygenation and delayed neuronal injury or infarction can occur despite normal ICP or CPP (18, 19, 21, 22, 35).

In recent years, direct brain oxygen monitoring has become feasible and in October 2001 was approved by the Food Drug and Administration for clinical use in the United States. Studies have shown that normal brain oxygen is between 25 and 30 mm Hg (44, 50). Usually this occurs when ICP and CPP are normal. However, even in patients with TBI who are adequately resuscitated (i.e., ICP <20 mm Hg and CPP >60 mm Hg), severe brain hypoxia ($Bto_2 <10$ mm Hg) may still occur in nearly one third of patients (21). Experimental and clinical studies suggest that critical Bto_2 threshold for neuronal injury and for poor outcome is 10 mm Hg (32, 34, 35–40, 44, 57, 76). However, this critical threshold is not the only important variable that determines outcome. The frequency and duration of time below this threshold also are important. Furthermore, we have observed that whether a patient with brain hypoxia responds to directed management also may be a prognostic variable (77).

The results of our analysis support the hypothesis that Bto_2 may be a predictor of patient outcome and specifically that $Bto_2 <10$ mm Hg is associated with a greater risk of poor outcome. However, several questions remain: 1) what is the critical threshold, frequency, duration, and cumulative duration below that threshold for poor outcome, 2) what determines whether brain hypoxia occurs, 3) is Bto_2 monitoring cost effective, and 4) does clinical monitoring of Bto_2 influence treatment and therefore, the outcome of patients with TBI? Our own preliminary experience, in which we compared 28 severe TBI patients managed with brain oxygen-directed therapy to 25 matched historical controls managed with ICP/CPP-directed therapy suggests that Bto_2 monitoring maybe associated with improved patient outcome (78). These questions will require further study but, at the very least, our analysis suggests that direct Bto_2 monitoring is safe and provides reliable prognostic information after severe TBI.

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