Neurologic Critical Care

Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial*

David O. Okonkwo, MD, PhD[1]; Lori A. Shutter, MD[1]; Carol Moore, MA[2]; Nancy R. Temkin, PhD[3]; Ava M. Puccio, RN, PhD[1]; Christopher J. Madden, MD[4]; Norberto Andaluz, MD[5]; Randall M. Chesnut, MD[3]; M. Ross Bullock, MD, PhD[6]; Gerald A. Grant, MD, FACS[7]; John McGregor, MD[8]; Michael Weaver, PhD[9]; Jack Jallo, MD, PhD[10]; Peter D. LeRoux, MD, FACS[11]; Dick Moberg, MSE[12]; Jason Barber, MS[3]; Christos Lazaridis, MD[13]; Ramon R. Diaz-Arrastia, MD, PhD[14]

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[1]University of Pittsburgh School of Medicine, Pittsburgh, PA.
[2]Uniformed Services University of the Health Sciences, Bethesda, MD.
[3]University of Washington, Seattle, WA.
[4]UT Southwestern Medical Center, Dallas, TX.
[5]University of Cincinnati College of Medicine, Cincinnati, OH.
[6]University of Miami, Miller School of Medicine, Miami, FL.
[7]Stanford University, Stanford, CA.
[8]Ohio State University College of Medicine, Columbus, OH.
[9]Temple University, Philadelphia, PA.
[10]Thomas Jefferson University, Philadelphia, PA.
[11]Lankenau Medical Center, Wynnewood, PA.
[12]Moberg Research, Ambler, PA.
[13]Baylor St. Luke's Medical Center, Houston, TX.
[14]Department of Neurology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

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For information regarding this article, E-mail: okonkwodo@upmc.edu

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Objectives: A relationship between reduced brain tissue oxygenation and poor outcome following severe traumatic brain injury has been reported in observational studies. We designed a Phase II trial to assess whether a neurocritical care management protocol could improve brain tissue oxygenation levels in patients with severe traumatic brain injury and the feasibility of a Phase III efficacy study.

Design: Randomized prospective clinical trial.

Setting: Ten ICUs in the United States.

Patients: One hundred nineteen severe traumatic brain injury patients.

Interventions: Patients were randomized to treatment protocol based on intracranial pressure plus brain tissue oxygenation monitoring versus intracranial pressure monitoring alone. Brain

tissue oxygenation data were recorded in the intracranial pressure –only group in blinded fashion. Tiered interventions in each arm were specified and impact on intracranial pressure and brain tissue oxygenation measured. Monitors were removed if values were normal for 48 hours consecutively, or after 5 days. Outcome was measured at 6 months using the Glasgow Outcome Scale–Extended.

Measurements and Main Results: A management protocol based on brain tissue oxygenation and intracranial pressure monitoring reduced the proportion of time with brain tissue hypoxia after severe traumatic brain injury (0.45 in intracranial pressure–only group and 0.16 in intracranial pressure plus brain tissue oxygenation group; $p < 0.0001$). Intracranial pressure control was similar in both groups. Safety and feasibility of the tiered treatment protocol were confirmed. There were no procedure-related complications. Treatment of secondary injury after severe traumatic brain injury based on brain tissue oxygenation and intracranial pressure values was consistent with reduced mortality and increased proportions of patients with good recovery compared with intracranial pressure–only management; however, the study was not powered for clinical efficacy.

Conclusions: Management of severe traumatic brain injury informed by multimodal intracranial pressure and brain tissue oxygenation monitoring reduced brain tissue hypoxia with a trend toward lower mortality and more favorable outcomes than intracranial pressure–only treatment. A Phase III randomized trial to assess impact on neurologic outcome of intracranial pressure plus brain tissue oxygenation–directed treatment of severe traumatic brain injury is warranted. (*Crit Care Med* 2017; 45:1907–1914)

Key Words: brain oxygenation; hypoxia, intensive care unit monitoring; randomized clinical trial; traumatic brain injury

Traumatic brain injury (TBI) remains a significant public health burden, with severe TBI (Glasgow Coma Scale [GCS] score ≤ 8) contributing to 30% of all injury-related deaths in the United States and costing more than $76 billion in 2010 (1). The magnitude of this problem has led to multiple clinical trials attempting to improve survival and functional outcomes with few effective therapies identified.

Acute management of severe TBI focuses on addressing intracranial mass lesions and minimizing secondary brain injury, including increased intracranial pressure (ICP). Although ICP-guided therapy has not been validated in randomized trials, most clinicians believe that monitoring ICP and treating elevations may improve outcome after TBI (2), as reflected in the most current "Guidelines for the Management of Severe Brain Injury" (3). ICP elevations may be an insensitive and late indicator of secondary brain injury, and monitoring and treating other physiologic variables may enhance patient care (4). One physiologic variable of particular interest is brain tissue oxygenation ($PbtO_2$) because the brain depends on an uninterrupted supply of oxygen and glucose to maintain cellular metabolism and viability. Additionally, observational studies demonstrate that brain tissue hypoxia may occur even when ICP or cerebral perfusion pressure (CPP) is normal and result from diffusion rather than perfusion defects (5, 6). This raises the question whether medical interventions based on $PbtO_2$ may reduce secondary injury and improve outcomes.

The average normal $PbtO_2$ is 23 ± 7 mm Hg (7). Several observational studies have noted that reduced $PbtO_2$ is common after TBI; $PbtO_2$ values less than 20 mm Hg may occur in greater than 70% of monitored patients within the first few days after injury, including when ICP and CPP are normal (8–11). Reduced $PbtO_2$ has been associated with a poor outcome after TBI in several observational clinical studies (8, 10, 12–14). Several observational studies suggest that the addition of $PbtO_2$-directed care to conventional ICP/CPP-based management may be associated with improved outcome after severe TBI (15–18). However clinical equipoise remains because of the absence of randomized controlled trials. This prompted the Brain Oxygen Optimization in Severe TBI Phase II (BOOST-II) study. The primary hypothesis was that a management protocol informed by $PbtO_2$ and ICP values would reduce the total burden of brain hypoxia.

MATERIALS AND METHODS

Study Design

The BOOST-II study was a two-arm, single-blind, prospective randomized controlled multicenter Phase II trial assessing safety and efficacy of a management protocol optimizing $PbtO_2$ following severe TBI (ClinicalTrials.gov registration NCT 00974259). The study also obtained data required for design of a definitive phase III study, including evidence of physiologic efficacy, feasibility of implementing a complex management protocol at multiple centers, and confirming nonfutility of $PbtO_2$-directed interventions.

Participants

Patients with severe TBI who required ICP monitoring were screened at 10 Level 1 trauma centers with experience in $PbtO_2$ monitoring. Inclusion criteria and exclusion criteria are described in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/C763).

Patients admitted with an initial GCS greater than 8 who deteriorated neurologically (within 48 hr of injury) from a presumptive intracranial cause and met criteria for ICP monitoring could also be enrolled provided randomization and ICP monitor placement occurred within 12 hours of deterioration.

This study was performed under a site-specific Institutional Review Board–approved protocol, and a proxy informed consent was obtained before any research procedures. Continued participation consent was obtained at or before the 6-month follow-up if the patient regained cognitive capacity.

Randomization and Masking

Randomization (ICP-only or ICP + $PbtO_2$-guided management) was performed using a secure website (Data

Coordinating Center, University of Washington) after inclusion and exclusion criteria confirmation. To reduce likelihood of imbalance of important prognostic factors between groups, a stratified blocked randomization scheme was used consisting of clinical site and severity of TBI (GCS 3–5 or, if intubated, motor GCS 1–2 vs GCS 6–8 or, if intubated, motor GCS 3–5).

Study Procedures

Intracranial Monitoring Placement and Management. Patients had both intraparenchymal ICP and $PbtO_2$ monitors (Integra LifeSciences, Plainsboro, NJ) placed. $PbtO_2$ probes were inserted into brain parenchyma approximately 2 cm from the cortical surface to sample primarily subcortical white matter in the least trauma-affected frontal lobe. Probe position was confirmed by a CT scan and function by a brief oxygen challenge. Following randomization, the control group (ICP-only management) was medically managed with a standard-of-care stepwise intervention strategy triggered by an ICP greater than or equal to 20 mm Hg for greater than 5 minutes. The intervention group (ICP and $PbtO_2$ management) was medically managed with stepwise treatments to correct either an ICP increase or a reduction in $PbtO_2$ (≤ 20 mmHg, >5 minutes). Patients randomized to the control group also had $PbtO_2$ probes inserted; however, after device calibration by the study coordinator, a locked cover was placed over the $PbtO_2$ display, so values were accessible only to unblinded study coordinators. Digital data recorders (Moberg ICU Solutions, Ambler, PA) continuously recorded physiologic data for both groups.

The $PbtO_2$ treatment protocol was a set of physiologic interventions that addressed isolated intracranial hypertension, isolated brain hypoxia, or simultaneous occurrence of both. The treatment protocol was tiered in a hierarchical fashion, with less aggressive interventions attempted before more aggressive maneuvers. In the ICP-only group, interventions administered as part of medical care that could affect $PbtO_2$ such as transfusion, ventilator adjustments, or treatment of CPP were recorded in case report forms.

$PbtO_2$ monitors were kept in place a minimum of 48 hours if no abnormalities were found, until the patient awakened from coma, or for a maximum of 5 days. Removal was at the discretion of treating physicians (**Fig. 1*A*** for study schematic). At randomization, each control patient was assigned a prespecified duration of $PbtO_2$ monitoring known only by the study coordinators (range: 48 hr to 5 d). The unblinded study coordinator could direct the treatment team to continue monitoring up to 5 days if $PbtO_2$ was less than 20 mm Hg to balance monitoring duration between groups.

Patient Medical Management. Each enrolled patient, independent of randomization assignment, was medically managed according to the BOOST-II manual of operating procedures, adapted from the third edition Brain Trauma Foundation "Guidelines for the Management of Severe Traumatic Brain Injury" (19). This management included measures to maintain 1) euvolemia or slight hypervolemia and CPP of 50–70 mm Hg, using vasopressors if necessary, 2) $Paco_2$ 35–40 mm Hg and arterial oxygen saturation greater than or equal to 90%, 3) serum Na^+ greater than or equal to 135 mEq, serum glucose greater than 60 and less than 150 mg/dL, 4) normal PT coagulation values per local laboratory, 5) normothermia, and 6) timely evacuation of intracranial mass lesions.

Randomized control patients were medically managed for ICP greater than or equal to 20 mm Hg. The intervention group (patients randomized to both ICP and $PbtO_2$ monitoring) was managed with a treatment strategy to correct one or both variables, defined by four types of management (types A, B, C, and D; **Fig. 1*B***). For patients with $PbtO_2$ less than 20 mm Hg, a hierarchical treatment algorithm (**Web Appendix**, Supplemental Digital Content 1, http://links.lww.com/CCM/C763) was instituted. Treatment was directed to each individual episode.

Study protocol algorithms were developed through a combination of evidence-based data and best practices in neurocritical care to limit center-to-center variability. Treatments in tier 1 were started within 15 minutes of an episode start, and if ineffective after 60 minutes, an additional treatment option was started from the next tier. Initiation of at least one tier 1 treatment option was required before escalating care to tier 2. Tier 3 treatments were optional at the physician's discretion. To insure protocol compliance, in-service training was conducted at each site.

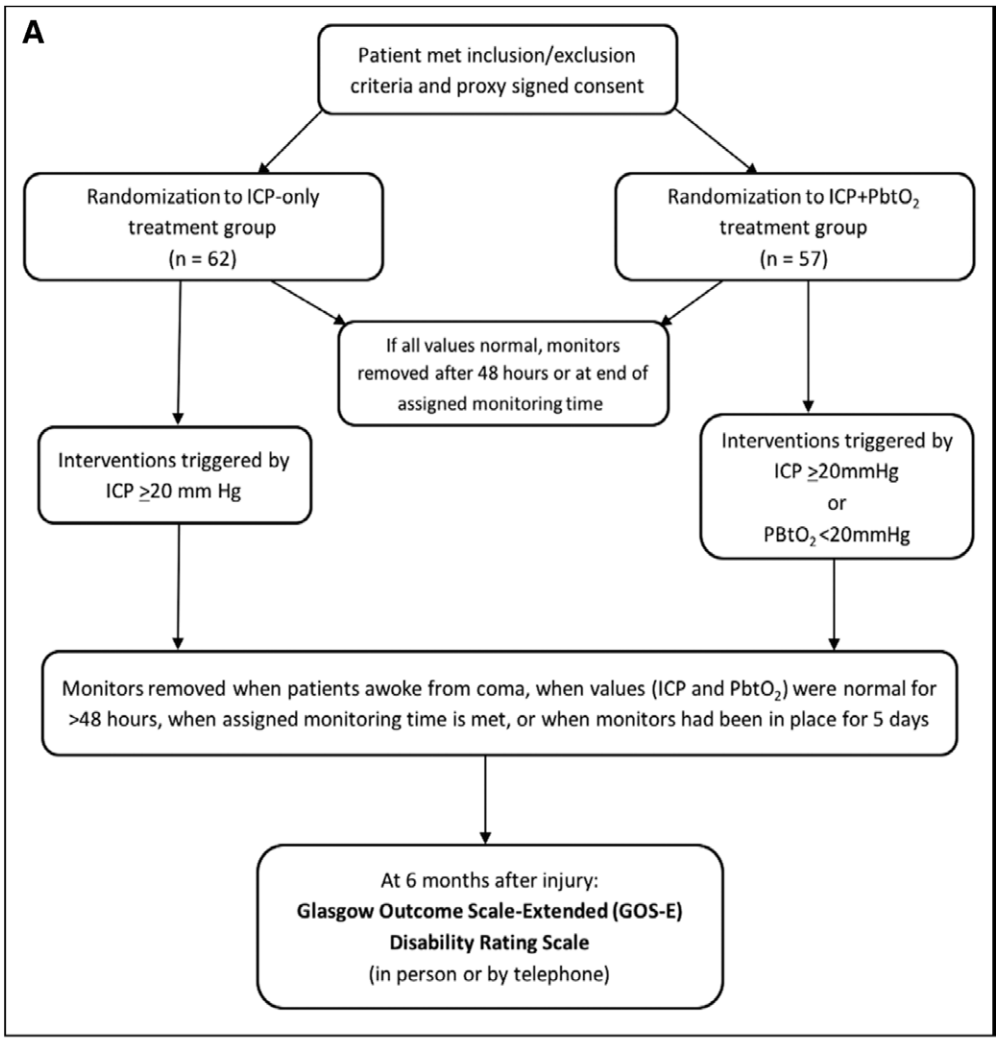
Outcomes

The primary outcome measure, physiologic efficacy of $PbtO_2$ treatment, was obtained from continuous $PbtO_2$ monitoring records. Patient safety was assessed through review of adverse events by site principal investigators, the Independent Medical Monitor and Data Safety Monitoring Committee (DSMC). For each occurrence of increased ICP and decreased $PbtO_2$, variables collected include the following: 1) time episode was recognized, 2) type and time of initial treatment, and 3) additional treatments required when less invasive interventions proved ineffective. The treating physician had discretion in following the tiered interventions if, in their opinion, it was indicated for patient safety.

A blinded, trained examiner assessed 6-month neurologic outcome in person or by telephone interview. The Glasgow Outcome Scale–Extended (GOS-E) score (primary outcome measure) (20) and Disability Rating Scale (DRS) were obtained (21).

Statistical Analysis

Patient demographics in each group were compared using Mann-Whitney *U* tests for ordinal or interval variables or Fisher exact tests for nominal categorical variables. $PbtO_2$ and ICP values were recorded multiple times per minute using a CNS multimodal neuromonitor (D.M.). Seven subjects were excluded from physiologic data analysis because of missing data or unknown monitor insertion times. Data were summarized into 1-minute averages for analysis and further summarized into 1) proportion of time $PbtO_2$ was less than 20 mm Hg or ICP was greater than 20 mm Hg, 2) average depth of brain tissue hypoxia (sum of the number of mm Hg $PbtO_2$ was < 20 mm Hg divided by number of minutes monitored times when $PbtO_2$ was > 20 mm Hg



B

	ICP < 20	ICP ≥ 20
$pBtO_2 \geq 20$	**Type A** No interventions directed at $pBtO_2$ or ICP needed	**Type B** Interventions directed at lowering ICP
$pBtO_2 < 20$	**Type C** Interventions directed at increasing $pBtO_2$	**Type D** Interventions directed at lowering ICP and increasing $pBtO_2$

Figure 1. A, Study schematic. **B**, Treatment scenarios. ICP = intracranial pressure, $PbtO_2$ = brain tissue oxygenation.

contribute 0 to the sum, but are included in the denominator), and 3) area over the curve (defined as sum of the amount by which $PbtO_2$ was < 20 mm Hg multiplied by the number of minutes it was at that value divided by 60 min) (**Fig. 2*A***). Physiologic outcomes were compared using *t* tests on the log of the variable, with zeros replaced by the power of 10 to make the distribution nearly normal (0.001 for proportion of time, 0.01 for average depth, and 10 for area over the curve). Six-month GOS-E and DRS scores were compared by Mann-Whitney *U* tests.

Role of the Funding Source

The National Institutes of Health (National Institute of Neurological Disorders and Stroke) funded the study; however played no role in study design, data collection, data analysis, data interpretation, composition of article, or decision to submit the article for publication.

RESULTS

Study Population

One hundred nineteen patients were enrolled, 62 randomized to the ICP-only treatment group and 57 to the ICP + $PbtO_2$ treatment group. Patient demographics and injury severity were similar in each treatment arm (**Table 1**).

Primary Outcome

Tiered management for episodes of $PbtO_2$ less than 20 mm Hg resulted in significantly less brain tissue hypoxia in the ICP + $PbtO_2$ group than in the ICP group. This result demonstrates that treatment of reduced $PbtO_2$ decreased total duration of hypoxia by 66% and average depth of hypoxia by 72%. The area over the curve (hr × mm Hg) was reduced by 77% (**Table 2** and **Fig. 2*B***). ICP was similar between groups (Fig. 2*B*, right panel).

Secondary Outcomes

Safety. The management protocol to optimize $PbtO_2$ and control ICP was safe. Number of serious adverse events (SAEs) was low and similar between groups (**Supplemental Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C763). There were no cases of hemorrhage or infection related to placement of monitoring catheters.

Feasibility. Time from injury to insertion of monitors was 9.05 (SD 5.22) hours. Time from insertion of monitors to onset of data analysis was 5 hours, to allow for equilibration and performing the FIO_2 challenge. Valid $PbtO_2$ data were obtained from an average of 80.3 (SD 42.6) hours, with unreliable data

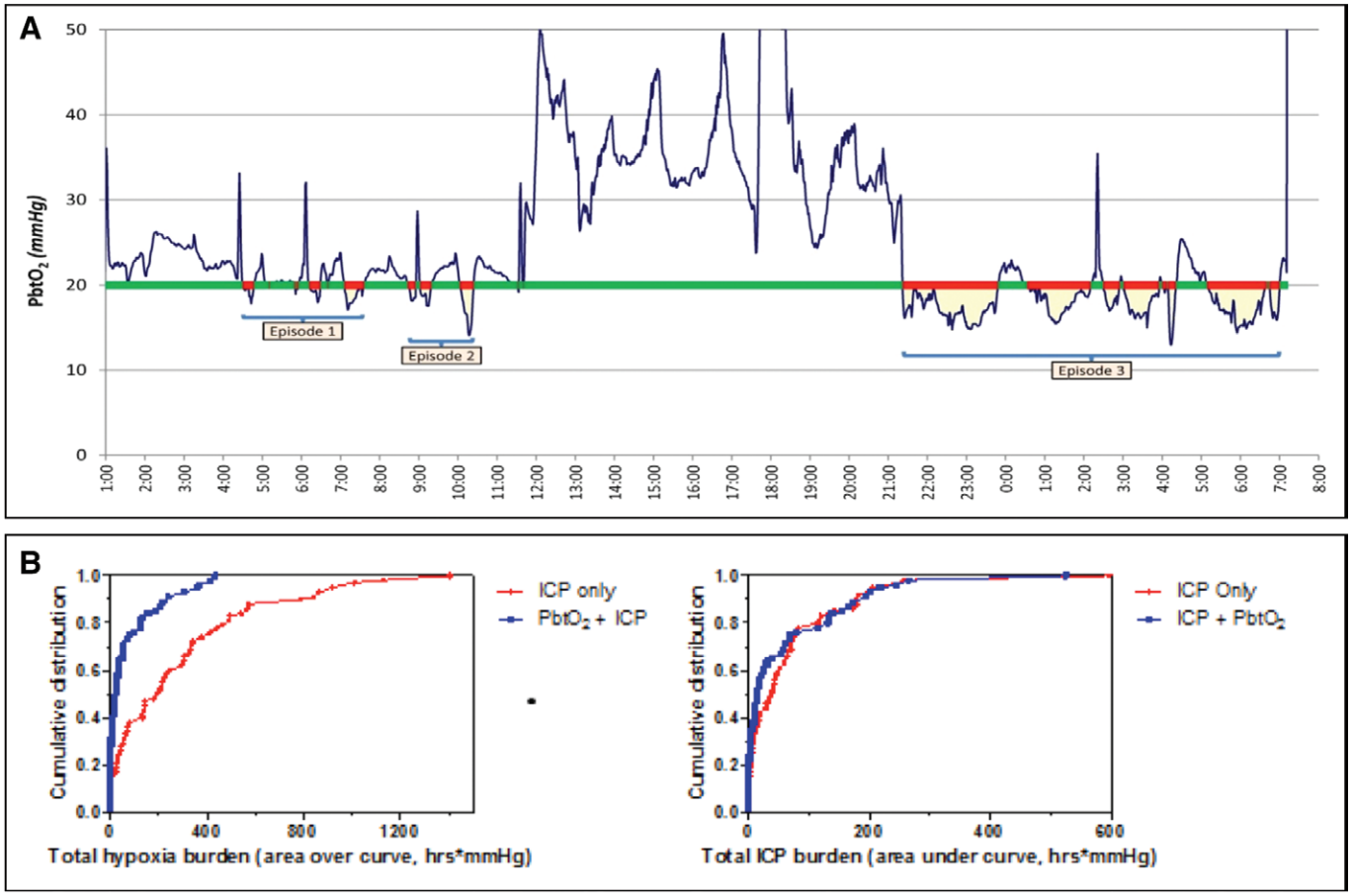


Figure 2. A, Sample trace of continuous brain tissue oxygenation ($PbtO_2$), illustrating how time of brain tissue hypoxia (*red bars*) and area over the curve (*yellow*) were assessed over time (*x*-axis). **B**, Left panel: Cumulative distribution of total hypoxia burden (area over the curve in hr × mm Hg) for each participant in Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II (BOOST-II). Mean hypoxia burden in 55 patients in $PbtO_2$ and intracranial pressure (ICP) treatment arm was 74.9 hour × mm Hg (95% CI, 43.9–105.9), whereas for the 58 patients in the ICP-only treatment arm, mean hypoxia burden was 285.8 hour × mm Hg (95% CI, 202.0–369.7), $p < 0.0001$. Right panel: Cumulative distribution of total intracranial hypertension burden (area under the curve in hr × mm Hg) for each participant in BOOST-II. Mean hypertension burden in 55 patients in $PbtO_2$ and ICP treatment arm was 61.1 hour × mm Hg (95% CI, 35.0–87.9), whereas for the 59 patients in the ICP-only treatment arm, mean hypertension burden was 67.9 hour × mm Hg (95% CI, 42.5–93.4), $p = 0.21$.

only 3% of monitoring time. Monitors were disconnected for an average of 4.1 hours while patients traveled for procedures, and an additional 2.5 hours data were considered invalid. There was no difference between treatment groups in total time of monitoring or the fraction of time with usable data.

The BOOST-II management protocol was complex (Web Appendix, Supplemental Digital Content 1, http://links.lww.com/CCM/C763). Our results show that the management protocol was feasible: treatment-related protocol deviations related to ICP management occurred with similar frequency between groups: ICP-only group, 13%; ICP + $PbtO_2$ group, 11% (**Supplemental Table 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C763). Nineteen percent of patients in the ICP + $PbtO_2$ group had untreated $PbtO_2$ less than 15 mm Hg for more than 30 minutes, and a similar percent had an episode where $PbtO_2$ of 15–19 mm Hg was untreated (both classified as protocol deviations). Five patients had both a deviation and a violation of the $PbtO_2$ treatment protocol.

There were substantial differences between the types of treatments instituted in each group. The ICP-only group received an aggregate of 933 interventions, whereas the ICP + $PbtO_2$ group received an aggregate of 867 interventions, 334 of those were during episodes of isolated low $PbtO_2$, whereas another 122 interventions were directed at both low $PbtO_2$ and high ICP. Additional details are provided in **Supplemental Table 4** (Supplemental Digital Content 1, http://links.lww.com/CCM/C763).

Outcomes. Six-month GOS-E scores were obtained in 106 patients (ICP-only group =53; ICP + $PbtO_2$ group = 53) and trended toward lower mortality and better outcomes in the ICP + $PbtO_2$ management group, though the difference did not reach statistical significance because of sample size (**Fig. 3*A***). Mortality in the ICP-only treatment group was 34% compared with 25% in ICP + $PbtO_2$ group. Furthermore, in the ICP + $PbtO_2$ group, 11% more patients had favorable outcomes (GOS-E 5–8) than the ICP-only group, and more than twice as many patients in the ICP + $PbtO_2$ group achieved the highest outcome category of GOS-E 8 (ICP + $PbtO_2$ group, 13%; ICP-only group, 6%). This outcome difference exceeded the protocol-specified nonfutility threshold needed to advance the intervention

TABLE 1. Demographics and Injury Characteristics of the Study Population

Characteristics	Overall	ICP Only	$PbtO_2$ + ICP	*p*
Subjects, *n*	119	62	57	
Age, mean (SD)	37.0 (17.3)	36.2 (17.5)	37.8 (17.2)	0.613
Male sex, *n* (%)	92 (79)	46 (74)	46 (84)	0.262
Race, *n* (%)				
White	100 (86)	53 (85)	47 (87)	0.359
Black	12 (10)	7 (11)	5 (9)	
Other	4 (4)	2 (4)	2 (4)	
Unknown	3	0	3	
Injury type				
Closed, *n* (%)	118 (99)	62 (100)	56 (98)	0.479
Penetrating, *n* (%)	0 (0)	0 (0)	0 (0)	
Blast, *n* (%)	0 (0)	0 (0)	0 (0)	
Crush, *n* (%)	1 (1)	0 (0)	1 (2)	
Glasgow Coma Scale motor, mean (SD)	3.7 (1.5)	3.7 (1.5)	3.6 (1.5)	0.858
CT scan results				
Contusions, *n* (%)		20 (38.4)	26 (56.5)	0.104
Midline shift, n (%)		28 (53.8)	26 (56.5)	0.841
Midline shift (mm), mean ± SD; median		3.38 ± 4.68; 2	2.98 ± 4.56; 1	0.918
Intraventricular hemorrhage, *n* (%)		17 (32.7)	15 (32.6)	1
Basal cisterns compressed or absent, *n* (%)		42 (80.7)	27 (58.7)	0.566
Craniectomy, *n* (%)		18 (35)	12 (24)	0.285

TABLE 2. Brain Tissue Oxygenation and Intracranial Pressure Parameters by Study Group

$PbtO_2$ Metric	ICP Only, (*n* = 58), Mean ± SD; Median	$PbtO_2$ + ICP, (*n* = 55), Mean ± SD; Median	*p*
Proportion of time below 20 mm Hg	0.44 (0.31); 0.45	0.15 (0.21); 0.07	0.0000147
Average depth (mm Hg)	3.6 (3.9); 2.3	1.0 (2.0); 0.2	0.0000005
Area (over) the curve (mm Hg × hr)[b]	255 (291); 187	58 (97); 14	0.0000002
Intracranial Pressure Metric	**ICP Only, (*n* = 57), Mean ± SD; Median**	**$PbtO_2$ + ICP, (*n* = 55), Mean ± SD; Median**	***p***
Proportion of time above 20 mm Hg	0.15 (0.19); 0.10	0.12 (0.19); 0.04	0.115
Average depth (mm Hg)	1.6 (6.9)[a]; 0.4	0.7 (1.3)[a]; 0.3	0.194
Average depth (mm Hg) (excluding the two extreme outliers)	0.7 (0.9); 0.4	0.6 (0.9); 0.2	0.195
Area under the curve (mm Hg × hr)[b]	103 (408)[a]; 36	50 (88)[a]; 17	0.113
Area under the curve (mm Hg × hr)[b] (excluding the two extreme outliers)	50 (56); 34	41 (59); 15	0.115

ICP = intracranial pressure, $PbtO_2$ = brain tissue oxygenation.

[a]One extreme outlier in each group is dominating the mean (SD) estimate.

[b]The "area under the curve (AUC)" analysis does not adjust for inconsistent monitoring durations; thus, a low AUC value could be due to normal brain tissue oxygenation values or a short duration of monitoring. (This pitfall is avoided with the "average depth" analysis, in which the AUC value is subsequently divided by the duration of monitoring. It also yields a more interpretable metric.)

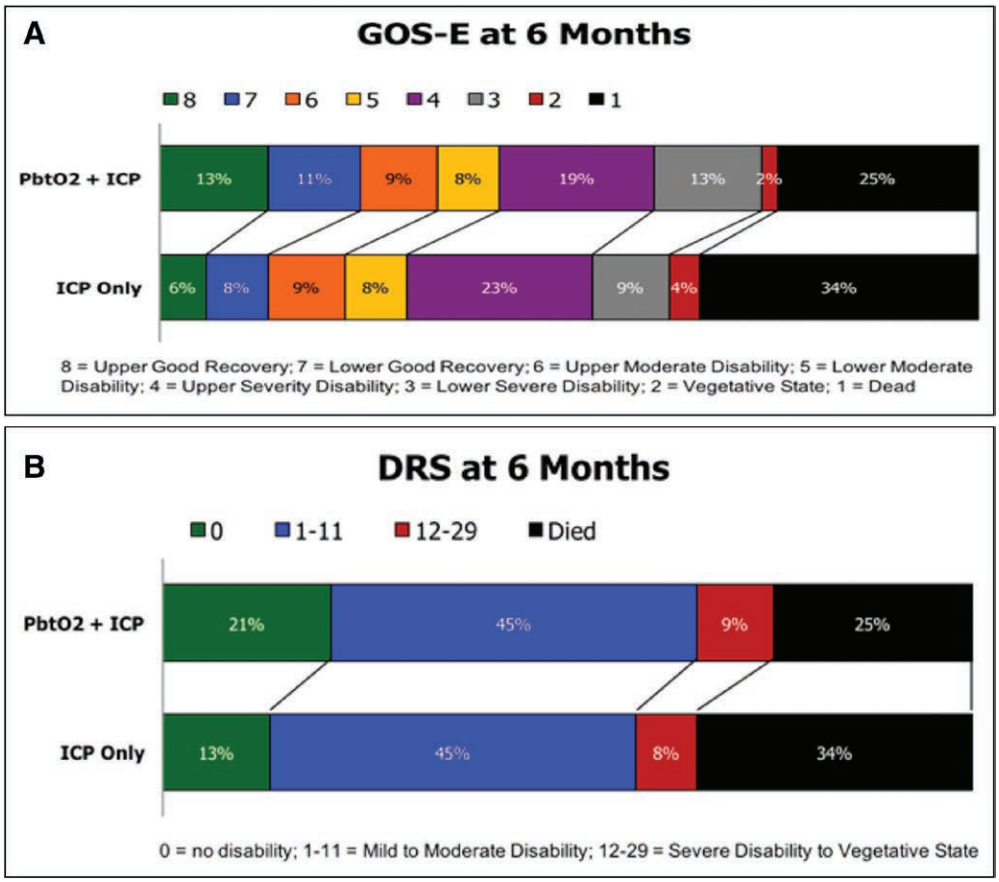


Figure 3. A, Glasgow Outcome Scale–Extended (GOS-E) at 6 months after injury in each study treatment group. **B**, Disability Rating Scale (DRS) at 6 months after injury in each study treatment group. ICP = intracranial pressure, $PbtO_2$ = brain tissue oxygenation.

strategy to a Phase III trial. DRS results demonstrated similar trends with better scores in the ICP + $PbtO_2$ arm (medians: 5, ICP + $PbtO_2$ group and 6, ICP-only group; $p = 0.217$) (**Fig. 3*B***).

The trial was stopped early by the DSMC after successful demonstration of the primary outcome in a smaller sample size than originally proposed.

DISCUSSION

In BOOST-II, management of severe TBI based on multimodal ICP and $PbtO_2$ monitoring compared with ICP monitoring alone reduced brain tissue hypoxia. The safety and feasibility of a $PbtO_2$-directed treatment protocol were confirmed; protocol violations were low (11–16%, and equal between groups), and adverse events were in the anticipated range for this patient population. The trend toward more favorable outcomes and lower mortality with ICP + $PbtO_2$-guided treatment exceeded the prespecified nonfutility threshold.

An important goal in TBI care is prevention, identification and treatment of secondary brain injury that can worsen patient outcome. ICP management has been at the center of this approach, but there is still no level I evidence to support this concept. Meta-analytic studies suggest that ICP-based care, particularly when Brain Trauma Foundation guidelines are followed, is associated with improved outcome (22–25). However, in recent years, there has been a conceptual shift in how ICP is managed to include inclusion of other clinical, radiologic and physiologic variables to better individualize therapy (4).

The management algorithm was not linear, offering multiple options within a given tier. This empowered two simultaneous goals: protocol-driven care to reduce variability with personalization of care based on clinical findings. The BOOST-II trial represents one of the first targeted TBI management trials, that is, precision medicine, a departure from the long-standing practice of treating all TBI as a uniform diagnosis. Overall, successful performance of the BOOST-II study indicates generalizability of multimodal, goal-directed therapy into broad clinical practice, should a Phase III trial be successful.

Physiologic Efficacy of $PbtO_2$-based Care

Management of severe TBI patients is premised on end-organ preservation and support to enable recovery. Brain tissue hypoxia following TBI is associated with worse outcomes clinically and with adverse pathophysiologic consequences in the experimental TBI literature (11–17). In the BOOST-II study, goal-directed therapy to maintain $PbtO_2$ greater than 20 mm Hg produced significant reductions in brain tissue hypoxia. Patients in the ICP + $PbtO_2$ group had, on average, 15% of ICP + $PbtO_2$ values consistent with brain hypoxia compared to 44% of patients in the ICP-only group. The results of BOOST-II support the hypothesis that $PbtO_2$-directed therapy can reduce secondary brain injury following TBI.

Although recently published studies suggest that a $PbtO_2$ threshold of less than 15 mm Hg is more highly correlated with brain ischemia (26), we believe that a treatment threshold of 20 mm Hg is appropriate because of the association with increased risk of unfavorable outcome in observational studies (27). We believe that treating $PbtO_2$ below 20 mm Hg is appropriate, because waiting until $PbtO_2$ falls below 15 mm Hg may not allow an adequate safety margin for therapy to reverse hypoxia.

Safety

Therapies to enhance $PbtO_2$ have potential risks, similar to ICP management, and respiratory complications are of

particular concern. Respiratory SAEs were observed in only 4% of patients and were similar between groups and consistent with those usually observed in severe TBI patients. Of the four respiratory SAEs observed in the ICP + $PbtO_2$ group, two were pneumonia and two were respiratory failure, and none were thought to be specifically associated with $PbtO_2$ therapy.

CONCLUSIONS

BOOST-II was designed to demonstrate feasibility and safety of a treatment protocol. The DSMC stopped the trial early after successful demonstration of the primary outcome in a smaller sample size than originally proposed. Six-month neurologic outcome indicated that $PbtO_2$-directed therapy is not futile. Indeed, patients in the ICP + $PbtO_2$ group showed a trend toward improved outcome with less mortality and more favorable outcomes. The planned BOOST-III study will assess impact on neurologic outcome of multimodal ICP + $PbtO_2$-directed management of severe TBI.

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