

A prospective, randomized Phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury

Clinical article

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Object. Preclinical and clinical investigations indicate that the positive effect of hyperbaric oxygen (HBO₂) for severe traumatic brain injury (TBI) occurs after rather than during treatment. The brain appears better able to use baseline O₂ levels following HBO₂ treatments. In this study, the authors evaluate the combination of HBO₂ and normobaric hyperoxia (NBH) as a single treatment.

Methods. Forty-two patients who sustained severe TBI (mean Glasgow Coma Scale [GCS] score 5.7) were prospectively randomized within 24 hours of injury to either: 1) combined HBO₂/NBH (60 minutes of HBO₂ at 1.5 atmospheres absolute [ATA] followed by NBH, 3 hours of 100% fraction of inspired oxygen [FiO₂] at 1.0 ATA) or 2) control, standard care. Treatments occurred once every 24 hours for 3 consecutive days. Intracranial pressure, surrogate markers for cerebral metabolism, and O₂ toxicity were monitored. Clinical outcome was assessed at 6 months using the sliding dichotomized Glasgow Outcome Scale (GOS) score. Mixed-effects linear modeling was used to statistically test differences between the treatment and control groups. Functional outcome and mortality rates were compared using chi-square tests.

Results. There were no significant differences in demographic characteristics between the 2 groups. In comparison with values in the control group, brain tissue partial pressure of O₂ (PO₂) levels were significantly increased during and following combined HBO₂/NBH treatments in both the noninjured and pericontusional brain ($p < 0.0001$). Microdialysate lactate/pyruvate ratios were significantly decreased in the noninjured brain in the combined HBO₂/NBH group as compared with controls ($p < 0.0078$). The combined HBO₂/NBH group's intracranial pressure values were significantly lower than those of the control group during treatment, and the improvement continued until the next treatment session ($p < 0.0006$). The combined HBO₂/NBH group's levels of microdialysate glycerol were significantly lower than those of the control group in both noninjured and pericontusional brain ($p < 0.001$). The combined HBO₂/NBH group's level of CSF F₂-isoprostane was decreased at 6 hours after treatment as compared with that of controls, but the difference did not quite reach statistical significance ($p = 0.0692$). There was an absolute 26% reduction in mortality for the combined HBO₂/NBH group ($p = 0.048$) and an absolute 36% improvement in favorable outcome using the sliding dichotomized GOS ($p = 0.024$) as compared with the control group.

Conclusions. In this Phase II clinical trial, in comparison with standard care (control treatment) combined HBO₂/NBH treatments significantly improved markers of oxidative metabolism in relatively uninjured brain as well as pericontusional tissue, reduced intracranial hypertension, and demonstrated improvement in markers of cerebral toxicity. There was significant reduction in mortality and improved favorable outcome as measured by GOS. The combination of HBO₂ and NBH therapy appears to have potential therapeutic efficacy as compared with the 2 treatments in isolation. Clinical trial registration no.: NCT00170352 (ClinicalTrials.gov). (<http://thejns.org/doi/abs/10.3171/2013.2.JNS121468>)

KEY WORDS • hyperbaric oxygen • normobaric hyperoxia • traumatic brain injury • cerebral metabolism • intracranial pressure • oxygen toxicity • clinical outcome

Abbreviations used in this paper: ATA = atmospheres absolute; ATP = adenosine triphosphate; BAL = bronchial alveolar lavage; FiO₂ = fraction of inspired oxygen; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; HBO₂ = hyperbaric oxygen; ICP = intracranial pressure; L/P = lactate/pyruvate; MMP = matrix metalloproteinase; NBH = normobaric hyperoxia; PaCO₂ = partial pressure of arterial carbon dioxide; PaO₂ = partial pressure of arterial O₂; PEEP = positive end-expiratory pressure; PO₂ = partial pressure of O₂; TBI = traumatic brain injury; TIL = therapeutic intensity level.

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THE enormous negative social and economic impact of TBI throughout the world cannot be overemphasized. The major issue is premature death and disability both in civilian and military populations. Conservative estimates of the prevalence of long-term disability due to TBI in the United States are well over 3 million people. The economic toll of TBI exceeds \$60 billion per year.¹⁸

Our previous investigations of HBO₂ in the treatment of severe TBI strongly suggest that the beneficial effect

demonstrated does not occur during the treatment but in the hours following the treatment.^{44,45} The data suggest that HBO₂ enables the brain to use increased FiO₂ in the posttreatment period. Experimental investigations also support the concept of using HBO₂ followed by continued increased O₂ at normobaric pressures as a single treatment.^{9,65} These studies have documented significant improvement in mitochondrial function, ATP production, reduced hippocampus cell loss, and functional recovery following a combined HBO₂/NBH treatment as compared with NBH alone or control animals. The case for evaluating the combination of HBO₂ and NBH as a single treatment appeared compelling. The 2 treatments in tandem are potentially synergistic.

The goal of this study was to evaluate cerebral metabolism, ICP, potential O₂ toxicity, and clinical outcome during a prospective, randomized Phase II clinical trial comparing a combined treatment of HBO₂/NBH to standard care in patients with severe TBI. This study was a subsequent supplement to a larger prospective, randomized clinical trial.⁴⁵ This report differs from that previously published study in that O₂ delivery and cerebral metabolism were studied in the pericontusional areas of some patients and clinical outcome was assessed at 6 months using the GOS; moreover, in the present study, HBO₂ and NBH were evaluated in combination rather than separately.

Methods

This study was registered with the ClinicalTrials.gov database (<http://clinicaltrials.gov>), and its registration number is NCT00170352.

Forty-two patients treated for severe TBI at the Hennepin County Medical Center, a Level 1 trauma center, were entered into a prospective randomized Phase II clinical trial to evaluate the mechanisms of action of hyperoxia on cerebral metabolism, ICP, O₂ toxicity, and clinical outcome. This study was a subsequent supplement to a larger prospective, randomized clinical trial.⁴⁵ The protocol for this study was approved by the Human Subjects Research Committee at our institution. All patients had sustained severe TBI as defined by a GCS score of 8 or less after resuscitation. This score was determined when no effects from paralytic agents, sedation, alcohol, and/or street drugs were present. Patients were entered into the study within 24 hours of their injury. Patients also were entered into the study if they were admitted to the hospital with a mild or moderate TBI and deteriorated to a GCS score of 8 or less within 48 hours after their injury (2 patients in the combined HBO₂/NBH group and 3 in the control group).^{29,43} All CT scan scores were II or greater, in conformance with the classification system of the Traumatic Coma Data Bank.²⁸ After eligibility and the GCS score were established, informed consent was obtained from the patients' legally authorized representative. Randomization occurred immediately after consent for study enrollment was obtained. Inclusion/exclusion criteria are listed in Table 1. All patients received intensive neurosurgical care closely paralleling that of the Brain Trauma Foundation "Guidelines for the Management of Severe TBI, Third Edition."⁷ This protocol included stabilization

TABLE 1: Study inclusion and exclusion criteria

Inclusion Criteria
all closed-head trauma victims w/ GCS score of 3–8 after resuscitation, w/o effects from paralytics, sedation, alcohol &/or street drugs
HBO ₂ treatment to begin w/in 24 hrs after injury
admission to hospital w/ a mild or moderate brain injury & deterioration w/in 48 hrs
CT scan score \geq 2 in accordance w/ classification system of Traumatic Coma Data Bank
Exclusion Criteria
bilateral fixed midposition pupils
severe pulmonary injury requiring FiO ₂ > 50% &/or PEEP > 10 cm H ₂ O to maintain adequate oxygenation
history of severe pulmonary disease (e.g., asthma or chronic obstruction pulmonary disease)
fixed coagulopathy
pregnancy
severe mental retardation or prior severe brain injury or stroke
high-velocity penetrating injury to head

with early intubation while the patient was in the emergency department, surgical evacuation of significant hematomas, continuous monitoring of ICP, and treatment of ICP greater than 15 mm Hg. All patients received prophylactic phenytoin sodium. The protocol adhered to the principles set forth in the US Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects and the World Medical Association Declaration of Helsinki.

This randomized Phase II clinical trial was designed as a 2-treatment comparison: combined HBO₂/NBH treatment compared with standard care. Twenty patients received the combined HBO₂/NBH treatment, which consisted of 100% FiO₂ delivered for 60 minutes at 1.5 ATA followed by 3 hours at 1.0 ATA. Standard care was the control treatment, which 22 patients received. The first O₂ treatment was administered as soon as the entry criteria were met and the patient's condition was clinically stable. Subsequent treatments were given every 24 hours. Patients received 3 consecutive treatments unless they became brain dead or were consistently able to follow commands. The first 2 patients randomized to the combined HBO₂/NBH arm were placed in a Class A, 4-lock multiplace chamber (Vacudyne, Inc.), and the next 18 in a 34-inch-diameter Bara-Med XD monoplace chamber (Environmental Tectonics Corp.). Compression to 1.5 ATA occurred at a rate of 1.0 lb/in²/min and lasted 17 minutes. The patients were kept at depth for 60 minutes and underwent decompression at the same rate.

Important baseline parameters were maintained between the pretreatment and posttreatment periods. Patients in the combined HBO₂/NBH treatment group were first transported to the hyperbaric chamber area, which can essentially function as an ICU. Once they were there, their baseline PaCO₂, PaO₂, ICP, and cerebral perfusion pressure were meticulously reestablished. The FiO₂ necessary to achieve a PaO₂ in the range of 90–130 mm Hg was established. The PaCO₂ was kept relatively constant,

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at approximately 35–40 mm Hg. The Licox catheter brain tissue PO₂ microprobe was calibrated in the HBO₂ chamber (Integra Neurosciences). The respiratory settings were kept constant for 1 hour to establish a baseline. Subsequently, the HBO₂ was administered. The patient was then transported back to the regular ICU where again equilibrium was established. Bilateral myringotomies were performed in all patients in the combined HBO₂/NBH treatment group.

Monitored Variables

Variables were measured before initiation of therapy and for 24 hours after therapy. There were no significant differences in baseline values between the 2 groups prior to hyperoxia treatments except for bronchial alveolar lavage (BAL) fluid IL-8 levels (see Table 2). Continuously monitored outcome variables included brain tissue PO₂, ICP, and microdialysate lactate, glucose, pyruvate, and glycerol levels. The brain tissue PO₂ measurements were downloaded into a Dell personal computer. Mean values over each 30-minute interval were calculated, except during HBO₂, when mean values were calculated over each 15-minute interval. Microdialysate samples were collected every hour. The recovery rate of the microdialysate was reduced during compression, so samples could not be obtained during the HBO₂ sessions, but they were taken during the NBH portion of the hyperoxia treatments.²¹ Intracranial pressure measurements were recorded hourly. Measurements of O₂ toxicity, including ventricular CSF F2-isoprostanes and BAL IL-8 and IL-6, were taken before treatment and 6 hours after treatment. All monitored variables were recorded in a database (Access 2003, Microsoft Corporation) and synchronized. However, for each variable measured, some patients had missing data and so were not included in that particular statistical analysis. Differences in the numbers of patients are reflected in the figures. In all cases, the missing number of patients was approximately equivalent in the combined HBO₂/NBH treatment and control groups. The missing data for brain tissue PO₂ and microdialysate levels were attributable to probe malfunction or placement directly into injured tissue such as contusion or hemorrhage. One patient in the combined HBO₂/NBH group did not have ICP measurements as the ventriculostomy could not be placed because of a bilateral decompressive craniectomy.

The results of the trial allowed a direct comparison of the combined treatment of HBO₂ and NBH with standard care in terms of the treatment efficacy on the surrogate outcome variables as well as the patients' functional outcome and mortality.

Continuous Metabolic Monitoring

A Licox catheter brain tissue PO₂ microprobe was used to measure brain tissue PO₂ and temperature (Integra LifeSciences). A CMA-70 microdialysis catheter was used to obtain all microdialysate samples (CMA Microdialysis). This catheter was inserted through the triple lumen bolt, along with the O₂ and temperature probes, into the frontal cortex of the brain to the desired depth of 14–24 mm. No data were collected in the first 3 hours to avoid insertion artifacts. Artificial CSF solution was infused through the probes at the rate of 0.3 µl/min. Dialysates were collected in outflow vials and frozen at –80° C. Lactate, glucose, pyruvate, and glycerol levels from the collected dialysate were measured using an off-line analyzer (CMA 600 Microdialysis Analyzer). The microdialysate L/P ratios were calculated as a marker for ischemia and the cellular redox state. Brain tissue PO₂ probes and microdialysis catheters were placed in either the right or left frontal lobe, whichever was least damaged. This location represented our “standard or non-injured area” of brain tissue not overtly traumatized. In 9 patients, a second brain tissue PO₂ probe and a second microdialysis catheter were placed in a pericontusional area or “traumatic penumbra” tissue. The pericontusional area was defined as the hypodense area around the core of the contusion or hematoma on CT scan.¹⁶ The position of the brain tissue PO₂ probes and the microdialysis catheters were checked by a CT scan as soon as possible after insertion.

Intracranial Pressure

Global ICP measurements were obtained with a tunneled intraventricular catheter. Any ICP greater than 15 mm Hg was treated. This treatment sequentially included mild hyperventilation, CSF drainage, administration of osmotic agents, sedation/administration of paralytic agents, and finally, decompressive craniectomy. Therapeutic intensity level (TIL) scores were recorded with ICP measurements.³⁰

TABLE 2: Baseline mean values for combined HBO₂/NBH and control groups for measured values prior to treatment*

Parameter	HBO ₂ /NBH	Control	p Value
mean brain tissue PO ₂ (mm Hg)	31.7 ± 3.6	28.9 ± 2.7	0.5398
microdialysate lactate (mmol)	2.12 ± .25	2.68 ± 0.2	0.5877
microdialysate L/P ratio	27.5 ± 2.4	26.9 ± 3.8	0.9490
microdialysate glycerol (mmol)	72.5 ± 18.6	78.7 ± 18.6	0.8149
ICP (mm Hg)	11.3 ± 1.4	11.3 ± 0.9	0.2672
ventricular CSF F2-isoprostane (pg/ml)	57.1 ± 11.4	49.2 ± 3.9	0.3538
BAL IL-6 (ng/ml)	7.37 ± 3.4	4.37 ± 1.3	0.2047
BAL IL-8 (ng/ml)	188.4 ± 49.2	41.2 ± 8.5	0.0258

* Means are given ± SEMs.

Oxygen Toxicity Markers

Bronchial alveolar lavage fluid samples were obtained through the endotracheal tube using sterile technique and routine respiratory care. A suction catheter (Medline Industries) was wedged into a distal lung segment, and 30 ml of sterile saline (0.9% NaCl, 37°C) was instilled and aspirated with suction into a sterile specimen collector (Allegiance Healthcare). All samples were chilled at 4°C immediately and processed within 15 minutes of collection. Samples were strained through a 60-mesh steel screen to remove mucus and then were centrifuged to remove cells, aliquoted, and frozen at -80°C until assayed for IL-8 and IL-6. The BAL IL-8 and IL-6 concentrations were determined by a commercial enzyme-linked immunosorbent assay kit per the manufacturer's direction (BD Biosciences Pharmingen).

Cerebrospinal fluid samples taken from the buretrol of the ventriculostomy were chilled at 4°C immediately and processed within 15 minutes of collection. Samples were centrifuged to remove cells, aliquoted, and frozen at -80°C. The CSF F2-isoprostane content was measured using a commercial enzyme immunoassay kit (Cayman Chemical).

Outcome

The baseline severity-adjusted dichotomized GOS score was used as the primary outcome measure for assessing recovery. At 6 months, a blinded assessment using the structured GOS interview was completed with either the patient or, if the patient was unable to participate, the patient's closest family member or legal guardian. The patient was then assigned to one of 5 categories: 1) good recovery (independent, but minor physical or mental deficits may be present); 2) moderately disabled (independent but disabled); 3) severely disabled (dependent on others); 4) vegetative; or 5) dead.⁶² Patients with enrollment GCS scores of 3, 4, or 5 were considered to have a favorable outcome if they achieved a GOS score of 1 (good recovery), 2 (moderate disability), or 3 (severe disability). Patients with enrollment GCS scores of 6, 7, or 8 were considered to have a favorable outcome if they achieved a good recovery or moderate disability. The dichotomized GOS score was also evaluated so that all patients had to achieve a good recovery or have only moderate disability to be considered to have a favorable outcome.

Statistical Analysis

Demographic characteristics as well as functional outcome and mortality rates across groups were compared using chi-square tests. This study was not powered as an outcome study as the primary focus was on cerebral metabolism, ICP, and oxygen toxicity.

The outcome analyses focused on the posttreatment effects because the primary study hypothesis was that the effects of hyperoxia on cerebral metabolism and ICP occur primarily after, not during, treatment. However, to examine the efficacy of HBO₂ during the NBH treatment, test values obtained 1 hour after the HBO₂ treatment were analyzed as well. A ratio of in- to pretreatment as well as a ratio of post- to pretreatment values was used to study

differences among treatment groups for all tests except those for ICP, for which the difference between pre- and posttreatment values was used because of 0 values. All posttreatment values were obtained after the NBH portion of the combined HBO₂/NBH treatment.

A mixed-effects linear model with fixed effects of treatment (group), time, day, and the treatment-time interaction (with only the significant variables kept in the final model), random patient effect, and autoregressive covariance matrix was used for testing the treatment effect. Due to the skewness of the in-treatment/pretreatment as well as the posttreatment/pretreatment ratios, natural log transformation was made to all in-treatment/pretreatment and posttreatment/pretreatment ratios. When an overall significant group or time*group interaction effect was found in the models using in-treatment/pretreatment and/or posttreatment/pretreatment ratios, post hoc orthogonal contrasts were used to determine the between-groups difference at each time point.

The graphs are simply a representation of the raw data, and the conclusions are based on the mixed-effects linear statistical model, which takes into account the longitudinal nature of the data. The treatment effect did not differ between treatment periods, so the data are shown in a binary fashion. In addition, there were no significant time*group interactions, so only the global pre- to post-treatment ratio means are shown.

Statistical significance was set at $p < 0.05$ in all analyses, and SAS version 9.1 (SAS Institute) was used to perform all analyses.

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics, including age, sex, mass lesion evacuations, decompressive craniectomies, Marshall CT scan scores, entry-to-study GCS scores, and episodes of intracranial hypertension were compared between the treatment and control groups (Table 3). There were no statistically significant differences ($p > 0.05$). All but 3 surgeries took place prior to randomization; the 3 exceptions involved 1 patient in the combined HBO₂/NBH group and 2 patients in the control group, all of whom underwent decompressive craniectomy after the treatment period had begun. Lung injuries such as pulmonary contusions (4 in the combined HBO₂/NBH group and 2 in the control group) and pneumo- or hemothoraces (3 in the combined HBO₂/NBH group and 3 in the control group) were compared and found to be similar ($p = 0.1045$). There also were no differences in chest radiograph findings between the 2 groups throughout the treatment period ($p = 0.7512$). There were no significant between-groups differences in the number or type of polytrauma cases ($p > 0.05$, Table 4). There were no statistically significant differences between the number or type of brain lesions (findings of blood, contusion, or bone fracture on CT) that the combined HBO₂/NBH treatment group and the control group sustained ($p > 0.05$, Table 5).

Cerebral Metabolic Measurements

In the combined HBO₂/NBH group, patients' brain

TABLE 3: Summary of demographic and clinical characteristics in 42 patients with severe TBI*

Variable	Treatment Group		
	HBO ₂ /NBH	Control	Total
no. of pts	20	22	42
M/F ratio	5:1	4:1	11:3
average age (yrs)	33	36	35
average study-entry GCS score	5.6	6.0	5.7
% w/ mass lesion evacuation	30	27	29
% w/ decompressive craniectomy	50	24	36
% w/ episode of intracranial hypertension	35	45	40
Marshall CT scan score (% of pts)			
II	10	27	19
III	50	32	40
V	30	27	28
VI	10	14	12

* There is no statistically significant difference in any comparison ($p > 0.05$). Abbreviation: pts = patients.

tissue PO₂ in both the noninjured and pericontusional brain rose during the treatment sessions to approximately 600% of the control group value ($p < 0.0001$). The mean baseline brain tissue PO₂ level in both groups was approximately 30 ± 4 mm Hg in the noninjured brain. During the HBO₂ portion of the combined HBO₂/NBH treatment, the mean brain tissue PO₂ level in noninjured brain rose to 221 ± 20 mm Hg. In comparison with the control group, the combined HBO₂/NBH treatment group's mean brain tissue PO₂ levels remained higher by approximately 30% throughout the posttreatment period, but the improvement was only statistically significant for the first 2.5 hours following treatment ($p < 0.0001$). In the pericontusional brain, the mean brain tissue PO₂ levels remained significantly higher in the combined HBO₂/NBH treatment group than the control group by approximately 20% throughout the posttreatment period ($p < 0.0001$). Figure 1 shows brain tissue PO₂ in relatively noninjured brain with in-treatment and posttreatment/pre-treatment ratio means.

TABLE 4: Summary of additional injuries in TBI patients with polytrauma*

Variable	Treatment Group		
	HBO ₂ /NBH (n = 20)	Control (n = 22)	Total (n = 42)
polytrauma (all cases)	65%	64%	64%
pelvic fracture	20%	18%	19%
spinal fracture	30%	23%	26%
abdominal injury	25%	18%	21%
extremity fracture	10%	23%	17%
facial fracture	0%	9%	5%
other†	15%	18%	17%

* Patients may have more than one injury. There is no statistically significant between-groups difference for any comparison ($p > 0.05$).

† Rib fracture, shoulder dislocation, diaphragmatic injury.

In the HBO₂/NBH group, the microdialysate levels of lactate in the pericontusional brain significantly decreased below the control group levels by approximately 14% during the treatment ($p = 0.0003$) and for 12 hours posttreatment ($p = 0.0193$). There was no significant change in the noninjured brain. Figure 2 shows microdialysate lactate in pericontusional brain with in-treatment and posttreatment/pre-treatment ratio means.

The L/P ratio of microdialysate in the noninjured brain was significantly decreased both during treatment ($p = 0.0157$) and for the entire posttreatment period by approximately 5% for the combined HBO₂/NBH groups in comparison with the control group ($p = 0.0078$). The combined HBO₂/NBH group's dialysate L/P ratio tended to stay below that of the control group throughout the posttreatment period in the pericontusional brain, but this difference did not reach statistical significance. Figure 3 shows microdialysate L/P ratios with posttreatment/pre-treatment ratio means.

TABLE 5: Summary of brain lesions*

Variable	Treatment Group		
	HBO ₂ /NBH (n = 20)	Control (n = 22)	Total (n = 42)
total w/ brain lesions	95%	86%	90%
contusion	55%	41%	48%
subdural hematoma	30%	41%	36%
epidural hematoma	15%	9%	12%
subarachnoid hemorrhage	35%	32%	33%
intracerebral hemorrhage	30%	18%	24%
diffuse axonal injury	30%	27%	29%
intraventricular hemorrhage	15%	9%	12%
skull fracture	15%	14%	14%

* Values represent percentages of patients with the specified lesion. Some patients had more than one lesion. There was no statistically significant between-groups difference for any comparison ($p > 0.05$).

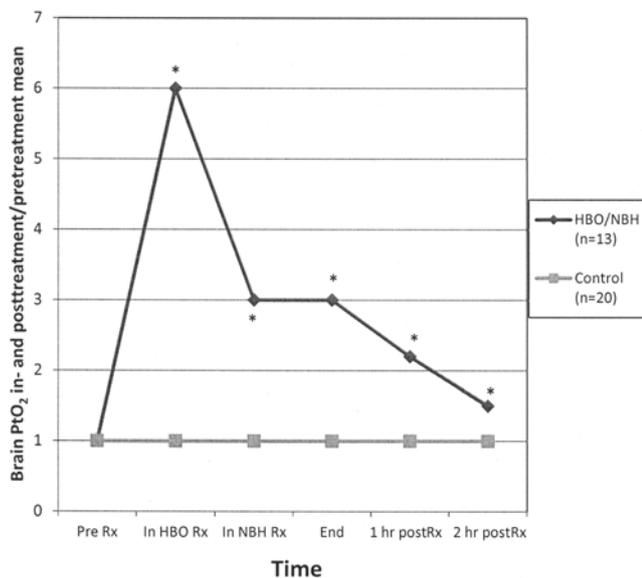


FIG. 1. Graph showing brain tissue PO₂ with both in-treatment/pretreatment and posttreatment/pretreatment ratio means. A value > 1 indicates the in- or posttreatment value is greater than the pretreatment value, and a value < 1 indicates the in- or posttreatment value is less than the pretreatment value. The graph also depicts the overall comparison of changes among the treatment arms. In comparison with the control group, there was an increase of ~ 600% in brain tissue PO₂ during the HBO₂ portion of the treatment. During the NBH portion of the treatment, the brain tissue PO₂ remained 300% higher than in the control group until the end of treatment. For 2.5 hours after the combined HBO₂/NBH treatment, the brain tissue PO₂ remained significantly higher than that in the control group by ~ 50%. *p < 0.0001 in comparison with the control group. Significance is based on the mixed-effects linear model. Rx = treatment.

There were no significant differences in the levels of microdialysate glucose in either noninjured or pericontusional brain when the combined HBO₂/NBH treatment and control groups were compared.

Intracranial Pressure

The ICP in the combined HBO₂/NBH group was significantly lower than that of the control group during the O₂ treatment (p < 0.0003), and the improvement continued until the next treatment session (p < 0.0006). Patients who started with an ICP greater than 15 mm Hg before treatment showed the largest decrease (p = 0.0019). Figure 4 shows the mean difference of ICP from pretreatment to posttreatment for this patient subgroup. The posttreatment effect was the same for all 3 days. The TIL score was decreased significantly from pretreatment to posttreatment for patients in the combined HBO₂/NBH group as compared with the control patients (p < 0.0001).

Oxygen Toxicity

The combined HBO₂/NBH group's levels of microdialysate glycerol were significantly decreased in comparison with those of the control group in both the noninjured and pericontusional brain (p < 0.001). The combined HBO₂/NBH group's levels of CSF F₂-isoprostane were decreased by approximately 10% after treatment in comparison with the control group and this decrease almost

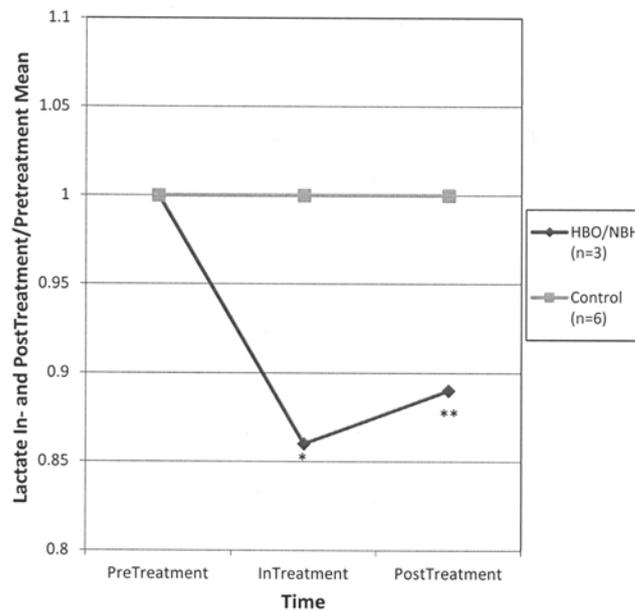


FIG. 2. Graph showing microdialysate lactate in pericontusional brain with both in-treatment/pretreatment and posttreatment/pretreatment ratio means. A value > 1 indicates the in- or posttreatment value is greater than the pretreatment value, and a value < 1 indicates the in- or posttreatment value is less than the pretreatment value. This figure also depicts the overall comparison of change between the treatment arms. In patients in the combined HBO₂/NBH group, microdialysate lactate was decreased by 14% during the treatment and by 6% for 12 hours after the treatment in comparison with control group levels. As a significant time*group interaction was not found in the statistical model, only the global pre- to posttreatment ratio means are shown. *p = 0.0003 and **p = 0.0193 in comparison with the control group. Significance is based on the mixed-effects linear model.

reached statistical significance (p = 0.0692). The post-treatment BAL levels of IL-6 and IL-8 cytokines in the HBO₂/NBH group did not significantly differ from levels in the control group.

One patient in the combined HBO₂/NBH group had his treatment stopped as a result of increased baseline FiO₂ requirements and chest radiograph changes. There was no increased incidence of pneumonia, FiO₂ requirement of 50% or more, or PEEP > 10 cm H₂O for the combined HBO₂/NBH group as compared with the control group.

Clinical Outcome

One patient from the combined HBO₂/NBH group and one patient from the control group were lost to follow-up at 6 months; therefore the 6-month outcomes are based on 19 patients in the combined HBO₂/NBH group and 21 control patients, for a total of 40 patients.

The mortality rate was 16% for the combined HBO₂/NBH group as compared with 42% for the control group. This 26% reduction (absolute percentage) in mortality for the combined HBO₂/NBH group as compared with the control group was statistically significant (p = 0.0482).

The statistical analysis also showed that 8 (38%) of the 21 patients in the control group and 14 (74%) of the 19 patients in the combined HBO₂/NBH group had a favorable outcome based on the sliding dichotomized GOS.

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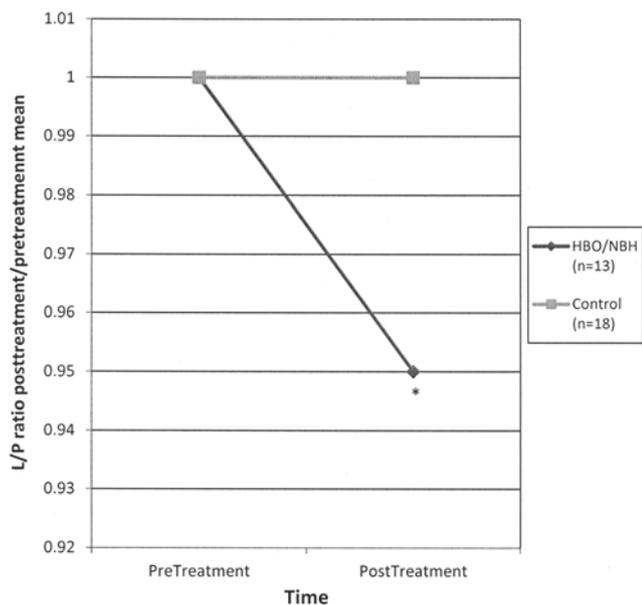


Fig. 3. Graph showing microdialysate L/P ratio in “uninjured” brain with posttreatment/pretreatment ratio means. A value > 1 indicates the posttreatment value is greater than the pretreatment value, and a value < 1 indicates the posttreatment value is less than the pretreatment value. This figure also depicts the overall comparison of change between the treatment arms. Posttreatment microdialysate L/P ratios were decreased by 5% for patients in the HBO₂/NBH group in comparison with control group levels. As a significant time*group interaction was not found in the statistical model, only the global pre- to in-treatment and the pre- to posttreatment ratio means are shown. *p = 0.0078 in comparison with the control group. Significance is based on the mixed-effects linear model.

This difference represents an absolute 36% improvement in favorable outcome and is statistically significant (p = 0.0239). Based on the dichotomized GOS, 7 (33%) of 21 patients in the control group and 11 (58%) of the 19 patients in the combined HBO₂/NBH group had a favorable outcome. This is a 25% absolute improvement, which almost reached statistical significance (p = 0.077).

Discussion

This is the first report on a prospective, randomized Phase II clinical trial combining HBO₂ and NBH as a single treatment and comparing its effect in terms of surrogate markers of oxidative metabolism, ICP, and O₂ toxicity as well as clinical outcome to results in a control group of patients treated with standard care. In addition, the effect of the treatment on cerebral metabolism was studied in both relatively noninjured brain and pericontusional brain tissue. The perilesional area or “traumatic penumbra” has biochemical signs of cerebral energy failure and cell membrane degradation with the capacity to regain a normal metabolic pattern.⁵¹ There is a significant difference between the energy metabolism of pericontusional tissue and that of relatively noninjured brain tissue in the same patients.¹⁶ Cerebral energy metabolism is severely decreased in the pericontusional area while being much closer to normal outside of this zone. Combined HBO₂/NBH treatment appears effective in improving cerebral

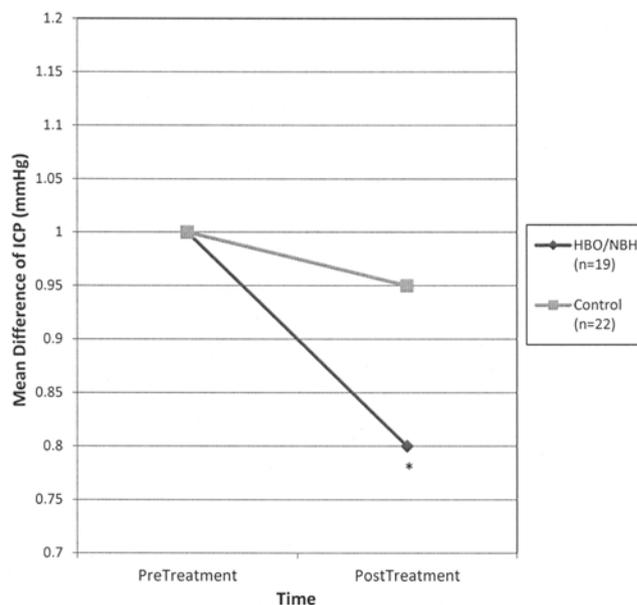


Fig. 4. Graph showing the mean pre- to posttreatment difference in ICP resulting from the statistical model when ICP was greater than 15 mm Hg before treatment. The difference in pre- to posttreatment values was used for ICP instead of the ratio of pretreatment values to posttreatment values because of 0 values. This figure also depicts the overall comparison of change between the treatment arms. The combined HBO₂/NBH group's difference in ICP from pre- to posttreatment was significantly lower than the control group when ICP was greater than 15 mm Hg prior to treatment. As a significant time*group interaction was not found in the statistical model, only overall pre- to posttreatment mean differences are shown. *p = 0.0019 in comparison with the control group. Significance is based on the mixed-effects linear model.

metabolism in both areas of the traumatically injured brain. In addition, the combination of HBO₂ and NBH therapy appears to have increased therapeutic efficacy as compared with the 2 treatments in isolation.

Mechanism of HBO₂

Hyperbaric O₂ therapy appears to have several protective mechanisms of action in severe TBI, likely increasing its potential effectiveness. These mechanisms have been demonstrated in both experimental and clinical investigations and include improved oxidative metabolism and mitochondrial function and reductions in intracranial hypertension, apoptosis, neuroinflammation, and free radical-mediated damage.^{9,38,39,41,44–46,50,52,58–61,65} The results of the present randomized clinical trial help to support these findings.

Reduced cerebral blood flow is particularly critical in decreasing substrate delivery in the first 24 hours following severe TBI.^{5,6,57} Studies of cerebral blood flow have revealed a pericontusional zone of low blood flow, which often corresponds to the hypodensity seen on CT scans.²⁰ In addition, diffusion barriers reduce cellular delivery of O₂ following TBI and decrease the ability of the brain to increase O₂ extraction in response to hypoperfusion.³¹ The phenomenon is particularly operative in pericontusional areas. Studies have shown that local brain tissue PO₂ levels are significantly correlated with ischemia and outcome.^{54,55} Hyperbaric O₂ therapy clearly leads to

a remarkable increase in the amount of O₂ delivered to relatively uninjured brain tissue in patients with TBI.⁴⁵ The present study documents that O₂ delivery is also significantly increased to pericontusional areas under hyperbaric conditions.

Our previous investigations of HBO₂ in the treatment of severe TBI support the theory that the combination of HBO₂ and NBH therapy potentially has a synergistic effect.^{44,45} During those studies, markers of cerebral metabolism such as the cerebral metabolic rate of O₂, microdialysate lactate, and microdialysate L/P ratio did not improve during the actual HBO₂ treatment but did improve during the next 6–24 hours following HBO₂ treatment. When the combined HBO₂/NBH treatment paradigm was used, the markers for cerebral metabolism, ICP, and oxygen toxicity improved in-treatment, especially in the pericontusional brain. This improvement is likely secondary to the fact that the in-treatment measurements were taken 1 hour after the HBO₂ treatment, while the patients were still receiving NBH. The data suggest that HBO₂ enables the brain to use increased FiO₂ in the post-treatment period. Experimental investigations also support the concept of using HBO₂ followed by continued increased O₂ at normobaric pressures as a single treatment.⁹ Daugherty et al.,⁹ in a lateral fluid percussion TBI rat model with 1 hour of HBO₂ treatment at 1.5 ATA followed by 3 hours of NBH, have documented significant improvement in mitochondrial function as measured by redox potential at the completion of the 4 hours of treatment but not at completion of 1 hour of HBO₂. These data indicate that mitochondrial function is depressed after TBI but there is a potential for mitochondrial functional recovery and that the combination of HBO₂ and NBH can enhance this recovery. In addition, another experimental study, using the same treatment paradigm, showed that elevated brain tissue O₂ favorably influences the binding of O₂ in the mitochondrial redox enzyme system leading to significantly reduced cell loss in the CA2–3 region of the hippocampus and improved mitochondrial function and ATP production.⁶⁵ A significant improvement in functional recovery as measured by a Morris water maze test also was shown. This effect was not seen in the NBH-treated or control animals.⁶⁵ The results of these studies corroborate the findings that HBO₂ used in combination with NBH enhances cellular metabolism by increasing intracellular O₂ levels, thereby improving mitochondrial function, which results in enhanced O₂ utilization post-treatment.

Further experimental studies have found that HBO₂ restores the loss of the mitochondrial transmembrane potential and that the reduction of apoptotic cell death mediated by HBO₂ is achieved by a mitochondrial protective effect.^{39,50} The investigators theorize that the increased intracellular O₂ bioavailability resulting from HBO₂ may contribute to the preservation of mitochondrial integrity and reduce the activation of the mitochondrial pathway of apoptosis. Clinical trials have shown increased global O₂ consumption lasting for at least 6 hours after HBO₂ treatment.^{44,45} This increase appears to be secondary to improved mitochondrial function. In addition, the effect is seen for at least 5 days postinjury in human TBI pa-

tients treated with HBO₂. Thus, HBO₂ improves oxidative metabolism during the period of prolonged posttrauma hypometabolism.

Experimental studies have shown that energy failure after trauma in the region of a contusion activates monovalent cation channels in penumbral capillary endothelial cells resulting in capillary fragmentation allowing extravasation of blood and progressive hemorrhage associated with worse clinical outcomes.^{48,49} Hyperbaric O₂ has decreased the size and the amount of brain destruction in a cerebral contusion rat model.^{38,58} The present study documents that with improved brain tissue O₂ delivery to pericontusional areas, markers of cerebral metabolism improve. Improved energy production would prevent the activation of monovalent cation channels in penumbra capillary endothelial cells, providing a mechanistic rationale for the observation that HBO₂ reduces the size of hemorrhagic contusions.

Acute inflammation in the perilesional area, while important to the repair process, contributes to secondary neuronal death.^{8,64} Neutrophils contribute to secondary injury by causing microvascular occlusion, releasing free O₂ radicals, proteolytic enzymes, and proinflammatory cytokines.^{8,25,59} Matrix metalloproteinases are a group of enzymes that have been demonstrated to be upregulated in experimental TBI. Neutrophils are the primary source of MMPs which, in turn, contribute to brain damage. The effect of HBO₂ on neuroinflammation and on the expression of MMP-9 was studied in a cortical contusion rat model.⁵⁹ Neutrophils were revealed by myeloperoxidase staining, and immunohistochemical staining for MMP-9 was performed. The HBO₂-treated group had a significant decrease in neutrophilic inflammatory infiltration compared with the control group. The expression of MMP-9 also was significantly lower in the HBO₂ group. These results demonstrated that HBO₂ decreased the extent of secondary cell death in reactive neuroinflammation in a cortical contusion TBI model compared with controls. Decline of MMP-9 expression after HBO₂ may also contribute to protection of brain tissue in the perilesional area.

Oxygen Toxicity

As in previous clinical trials performed at our institution,^{41,44,45} there were no signs of cerebral or pulmonary O₂ toxicity in the present trial. Brain tissue is especially vulnerable to lipid peroxidation because of its high rate of O₂ consumption and higher content of phospholipids.^{12,13,23} Cerebrospinal fluid F2-isoprostanes are a unique series of prostaglandin-like compounds formed in vivo from the free radical-catalyzed peroxidation of arachidonic acid and have been used to assess peroxidation in patients with severe TBI.^{3,4,17,35} Glycerol is an end product of phospholipid degradation in neural tissue cell membranes and is a marker of cell damage whether caused by O₂ toxicity via free radical formation and lipid peroxidation or secondarily from ischemia.^{16,19,32} Levels of CSF F2-isoprostanes as well as microdialysate glycerol were significantly decreased following combined HBO₂/NBH treatment. These findings may not only signify that there were no signs of O₂ toxicity from the combined HBO₂/NBH treatment, but, in

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fact, that there was a protective effect against neuroinflammation and free radical-mediated damage.

The lung is the organ most commonly damaged by hyperoxia, since O_2 tension in the surface area exposed to O_2 in the lungs is substantially higher than in other tissues.²⁶ When the inhaled O_2 exceeds the protective capacity of antioxidants present in the lungs, acute pulmonary pneumonitis associated with the release of proinflammatory cytokines by alveolar macrophages, specifically IL-8 and IL-6, develops.^{10,11} The amount of these proinflammatory cytokines in the BAL is associated with acute lung injury and pulmonary infection similar to acute respiratory distress syndrome.^{15,36} In the combined HBO₂/NBH group, patients' BAL levels of IL-6 and IL-8 cytokines did not significantly differ posttreatment from the control group levels. Correspondingly, there was no increased incidence of pneumonia, FiO_2 requirements greater than 50%, or PEEP > 10 cm H₂O compared with the control group.

Intracranial Pressure

Intracranial hypertension is the major cause of deterioration and death in the 1st week following severe TBI.^{24,37} Again, in this smaller trial, intracranial hypertension was significantly reduced by the combined HBO₂/NBH treatment and that improvement continued until the next treatment session. The TIL score (used to assess the aggressiveness of intracranial hypertension) was correspondingly reduced.

Clinical Outcome

The clinical outcome of the combined HBO₂/NBH treatment was significantly improved at 6 months compared with controls in this relatively small group of patients. There was an absolute 26% reduction in mortality, as well as a 36% improvement in favorable outcome using the sliding dichotomized GOS and a 25% improvement using the dichotomized GOS. This outcome is significantly better than our prior experience using HBO₂ as a single treatment or reports from the literature using NBH.^{41,53} This improvement in clinical outcome may be due to the synergistic effect of combining HBO₂ and NBH treatments. There was significant improvement in markers of cerebral metabolism and oxygen toxicity as well as ICP during the NBH portion of the combined HBO₂/NBH treatment. The combined HBO₂/NBH treatment also significantly improved markers of cerebral metabolism in pericontusional brain tissue as well as "normal" areas posttreatment for several hours as compared with values in the control group. Normobaric hyperoxia following an HBO₂ treatment increases the baseline O_2 available for mitochondria. The continued increased O_2 bioavailability enhances the effect of HBO₂ treatment. There have been several studies in the literature that show that improvement in markers of cerebral metabolism and ICP correlate with clinical outcome.^{14,24,27,33,34,40,47,55}

In addition to improving cerebral metabolism and ICP, the combined HBO₂/NBH treatment significantly improved markers of cerebral oxygen toxicity. It is possible that the increased intracellular O_2 bioavailability resulting from the combined HBO₂/NBH treatment may

result in the neuroprotection of mitochondrial integrity and reduce the activation of the mitochondrial pathway of apoptosis, and the treatment may reduce free radical-mediated damage as shown in experimental studies.^{38,39,50,58–61} This neuroprotective action of the combined HBO₂/NBH treatment could lead to the preservation of viable but nonfunctioning mitochondria, which would in turn improve clinical outcome.

A major limitation of the clinical outcome portion of this study is the relatively small number of patients. This trial was not designed or powered to be an outcome study, as the primary focus was on cerebral metabolism, ICP, and oxygen toxicity. Therefore, the outcome results need to be interpreted with caution. However, they point toward the need for a Phase III trial to determine if the combined HBO₂/NBH treatment could become a significant treatment for patients suffering a severe TBI.

Statistical Methods

Mixed-effects models, such as those used here and accomplished using the restricted maximum likelihood technique, are highly recommended for analyses in which data are obtained repeatedly but not necessarily at regular or identical times from a cohort of study participants.⁵⁶ Vespa et al.⁵⁶ have stated that mixed-effects models should be used by all researchers studying interdependent serial physiological data. The mixed-effects model controls for the interrelatedness of sequential hourly values within each patient. These models take into account the differences in group sizes and correct for differences in pretreatment values (such as the difference in BAL IL-8 levels) in the calculation of significance.

Generalizability of the Treatment Protocol

Safe treatment of severe TBI patients with HBO₂ requires institutional expertise in the management of severe TBI as well as in critical care hyperbaric medicine.^{21,42} The HBO₂ chamber and its environment must become an extension of the ICU to allow safe care of the patient with severe TBI. The expertise of appropriate personnel must be as readily available in the HBO₂ environment as it is in the ICU. A monoplace chamber has a relatively small physical space footprint and can be incorporated in or placed adjacent to a critical care support area.⁴⁵ The delivery of HBO₂ treatments is relatively labor intensive. It requires transport of the patient to and from the chamber, and proximity of the HBO₂ chamber to the ICU minimizes transportation time. Monitoring of the ventilatory status of the patient with severe TBI during transport is critical and includes pulse oximetry and portable end-tidal CO₂ monitoring. The monoplace chamber has to be specifically designed to adequately monitor the patient and administer appropriate fluids and medications during the treatment.²¹ Intermittent HBO₂ treatments at 1.5 ATA for 60 minutes have resulted in a very low incidence of complications, all of which were reversible. When a monoplace chamber is used, the patient is physically isolated from health care providers, but the chamber can be decompressed in approximately 2 minutes and rapid access to the patient achieved. Our institution has delivered 1984

HBO₂ treatments in 3 prospective clinical studies, and an emergency decompression has never been required.^{41,44,45} If a proper treatment paradigm is maintained, our experience documents that HBO₂ treatment can be safely delivered to patients with severe TBI in monoplace as well as multiplace chambers.

Blast Injuries and HBO₂

Blast injuries to the brain represent a spectrum of severity similar to traditional TBI. Armonda and other investigators have documented that the severe injuries are characterized by edema, vasospasm, and intracranial hemorrhage.^{1,2} In severe cases the onset of edema has been rapid and life threatening, requiring emergent decompressive craniectomy. Vasospasm of the internal carotid and anterior cerebral arteries is frequently related to intracranial hemorrhage resulting from penetrating fragments. To the authors' knowledge, no investigations using HBO₂ have been applied to this type of injury. However, the HBO₂ neuroprotective mechanisms discussed earlier in preclinical and clinical investigations of severe TBI could well be beneficial to patients with severe explosive blast brain injuries. There have been investigations of HBO₂ therapy for blast-induced postconcussion syndrome and posttraumatic stress disorder.²² The patients experienced their injuries at least 12 months prior to HBO₂ treatment. The preliminary report by Harch et al.²² suggests that HBO₂ should be studied in a larger catchment of patients. The mechanism of action of HBO₂ in this setting has not been clearly delineated. It is hypothesized that the potential improvement in neurological function relates to improved cerebral blood flow, particularly to the hippocampus.^{2,63}

In summary, the treatment of blast-induced TBI with HBO₂ is at a preliminary stage but deserves further investigation.

Conclusions

Data in this study can be summarized by the following key points: 1) The combined HBO₂/NBH treatment significantly improved markers of oxidative cerebral metabolism in relatively uninjured brain tissue but, importantly, also in pericontusional tissue. 2) The combined HBO₂/NBH treatment reduced intracranial hypertension and thereby decreased the therapeutic intensity of treatment of intracranial hypertension. 3) There was no evidence of O₂ toxicity either in the brain or lungs, and there was actual demonstrated improvement in markers of cerebral toxicity. 4) Combining HBO₂ and NBH into a single treatment potentially has a synergistic therapeutic effect. 5) The combined HBO₂/NBH treatment reduced mortality and improved favorable outcome as measured by the GOS at 6 months. This improvement was significantly better than past clinical outcomes observed with either of the treatments used separately. The clinical outcome portion of this study is limited by a relatively small number of patients.

Disclosure

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