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Hyperbaric Oxygen Therapy in the Treatment of Acute Severe Traumatic Brain Injury: A Systematic Review

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Abstract

There has been no major advancement in a quarter of a century for the treatment of acute severe traumatic brain injury (TBI). This review summarizes 40 years of clinical and pre-clinical research on the treatment of acute TBI with hyperbaric oxygen therapy (HBO_2) in the context of an impending National Institute of Neurologic Disorders and Stroke–funded, multi-center, randomized, adaptive Phase II clinical trial —the Hyperbaric Oxygen Brain Injury Treatment (HOBIT) trial. Thirty studies (eight clinical and 22 pre-clinical) that administered HBO_2 within 30 days of a TBI were identified from PubMed searches. The pre-clinical studies consistently reported positive treatment effects across a variety of outcome measures with almost no safety concerns, thus providing strong proof-of-concept evidence for treating severe TBI in the acute setting. Of the eight clinical studies reviewed, four were based on the senior author's (GR) investigation of HBO_2 as a treatment for acute severe TBI. These studies provided evidence that HBO_2 significantly improves physiologic measures without causing cerebral or pulmonary toxicity and can potentially improve clinical outcome. These results were consistent across the other four reviewed clinical studies, thus providing preliminary clinical data supporting the HOBIT trial. This comprehensive review demonstrates that HBO_2 has the potential to be the first significant treatment in the acute phase of severe TBI.

Keywords: Glasgow Coma Scale; Glasgow Outcome Scale; hyperbaric oxygen; normobaric hyperoxia; traumatic brain injury

Introduction

Traumatic brain injury (TBI) has enormous negative social and economic impacts across a large variety of populations. Nearly 4 million people in the United States suffer a TBI each year—of whom half require a visit to the emergency department, 500,000 are hospitalized, and 50,000 die from their injury.[1] The risk of death and long-term disability to a patient rises considerably with increasing injury severity and concomitant body trauma. It is estimated that 2% of the U.S. population (approximately 5.3 million people) are living with long-term disabilities related to their TBI.[2] The annual combined direct and indirect financial impact incurred by TBI in the United States is $76.5 billion.[3] Despite these physical and financial costs, however, there has been little advancement in the acute treatment of TBI since the 1990s,[4] and clinical outcomes have not improved. In fact, in the last 15 years, at least 25 clinical trials of therapeutics for TBI have failed.[5]

Many treatments administered in the immediate period following a TBI are focused on altering the acute pathophysiology. However, following the primary mechanical injury to the brain, secondary injury frequently develops. This secondary injury is precipitated by ischemia resulting from decreased cerebral blood flow (CBF) and is particularly likely to occur in the first 24 h after injury.[6,7] Because of decreased oxygen (O_2) delivery to brain cells,[8] the brain converts from aerobic to highly inefficient anaerobic metabolism, resulting in inadequate energy production in the brain and eventual cell death.

Hyperbaric oxygen therapy (HBO_2) targets TBI-induced ischemia by exposing patients to an environment that substantially increases the amount of O_2 inspiration (100% O_2 at >1 ATA), producing an increased O_2 concentration in the plasma and thus increased delivery of O_2 for diffusion to brain tissue. Despite the capacity of HBO_2 to protect against secondary ischemic damage, the use of HBO_2 for the treatment of TBI has been controversial. One concern regarding the use of HBO_2 for acute TBI arises from apparent conflicts in the literature about its efficacy. It is likely that injury heterogeneity, variable injury chronicity, and variability in study design have contributed to this perception. Additional

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concerns relate to O_2 toxicity and the logistics of widespread implementation of this therapy.

Consideration of HBO_2 for the treatment of acute TBI is warranted, as evidenced by the fact that a multi-center study across 15 U.S. academic centers was recently awarded National Institute of Neurological Disease and Stroke (NINDS) funding under the auspices of the Strategies to Innovative Emergency Care Clinical Trials Network. The rigorously designed adaptive Phase II Hyperbaric Oxygen Brain Injury Treatment (HOBIT) trial will enroll 200 TBI patients with a specific subset of pathology to assess the efficacy of HBO_2.[9] In this review, we summarize the pre-clinical and clinical studies utilizing HBO_2 for the treatment of acute TBI conducted to date. We also discuss the neuroprotective mechanism of HBO_2 and its potential clinical utility to treat acute severe TBI, the controversy surrounding its use, and briefly, the methodology of the HOBIT trial.

Methods

A PubMed literature search was performed on February 22, 2016, to identify primary articles on the acute use of HBO_2 or combined HBO_2 and normobaric hyperoxia (NBH; 100% O_2 at 1 ATA) for TBI in both the clinical and pre-clinical settings using the following search terms: ''hyperbaric oxygenation''[MeSH Terms] AND ''brain injuries''[MeSH Terms] AND (Clinical Trial[ptyp] AND ''humans''[MeSH Terms]); ''hyperbaric oxygenation''[MeSH Terms] AND ''brain injuries''[MeSH Terms] AND ''animals''[MeSH Terms:noexp]; ''brain injuries''[MeSH Terms] AND ''normobaric hyperoxia''[All Fields] AND ''humans''[MeSH Terms]; and ''brain injuries''[MeSH Terms] AND ''normobaric hyperoxia''[All Fields] AND ''animals''[MeSH Terms:noexp].

These PubMed searches revealed a total of 46 clinical and 77 pre-clinical studies. Studies that employed a treatment that combined HBO_2 with NBH were included. Studies were excluded if the total sample size of the treatment groups was less than six or an English translation was not readily available. Clinical studies were excluded if treatment was initiated >30 days post-injury and if participants with non-traumatic brain injuries (i.e., stroke, hypoxia, etc.) were enrolled, unless the authors included data on participants with isolated TBI. Pre-clinical studies were excluded if the treatment was given prior to the induced injury or if the induced brain injury did not model TBI (i.e., ischemic, cortical stab injury, anoxic, cryogenic, etc.). Studies included that were not found in the indicated searches were reviewed in an identical manner to papers obtained through PubMed.

Results

Twenty-two pre-clinical studies (20 that implemented HBO_2 and two that implemented combined HBO_2 and NBH) and seven clinical studies (six that implemented HBO_2 and one that implemented combined HBO_2 and NBH treatment) met the inclusion criteria for this review.

Pre-clinical studies

HBO_2 treatment. Twenty pre-clinical studies utilizing a wide range of methodologies employed HBO_2 to acutely treat induced TBI. Adult male Sprague-Dawley rats were used in 15 (75%) studies, whereas in the remaining five studies two used rabbits, two used Wistar rats, and one used mice. The TBI model most commonly used was cortical impact (eight studies), but dynamic cortical deformation (six studies), lateral fluid percussion (five studies), and blast (one study) also were utilized. Treatment regimens included pressures between 1.5 and 3 ATA for 30 to 90 min, and all but two studies initiated treatment within 6 h of the injury. Seven studies administered a single HBO_2 treatment, two studies administered two consecutive daily treatments, seven studies administered at least three daily treatments, and four studies administered multiple treatments per day for at least 3 days.

Physiologic outcomes. The pre-clinical models provided evidence for the neuroprotective effect of HBO_2 after TBI, reporting reduced lesion size,[10–13] lesion severity,[14] brain water content,[10,14–16] and apoptosis.[10,14,16–21] In fact, all seven of the studies that assessed neural apoptosis reported decreased apoptosis in animals treated with HBO_2 after induced injury, as measured by terminal deoxynucleotidyl transferase dUTP nick-end labeling cell staining. Further, these studies also reported reduced levels of apoptosis-related proteins (B-cell lymphoma 2 [Bcl-2]; B-cell lymphoma-extra-large [Bcl-xL]; bcl-2-associated X protein [Bax]; caspase-3; and caspase-9) in treated animals, providing further evidence of the neuroprotective effect of HBO_2. The transmembrane potential in mitochondria, measured by caspase-9 activity, was found to be significantly reduced after injury and was subsequently brought back to near-normal levels following HBO_2, thus reducing activation of the mitochondrial apoptotic pathway.[18,19]

Apoptosis within the hippocampus and general hippocampal neuronal integrity also has been repeatedly shown to benefit from HBO_2, potentially through an anti-inflammatory mechanism.[12,14,15,22] The inflammatory response of animals with an induced injury is consistently reduced after HBO_2, compared with both baseline measurements and those animals that do not receive treatment. This response has been shown through serum and cortex measurements of biomarkers, including neutrophil infiltration, tumor necrosis factor-alpha, transforming growth interacting factor, transforming growth factor-beta1, interleukin-1beta (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10), macrophage inhibitory protein-2, monocyte chemotactic protein-1, matrix metalloproteinase-9, hypoxia inducible factor-alpha, and myeloperoxidase activity.[10,15,16,23–26] Animals that displayed reduced inflammatory responses following HBO_2 had consistently better functional outcomes and reduced lesion volumes. Chen and colleagues[10] improved the mechanistic understanding of the positive anti-inflammatory effect of HBO_2 when they reported that mice injected with an anti-inflammatory protein, IL-10, following cortical impact had better functional outcomes, and that mice with an induced genetic anti-inflammatory defect (IL-10 knockout) had greater lesion volumes, elevated apoptosis, and worse functional outcomes than wild-type mice after CI.

Additional support for the neuroprotective effect of HBO_2 after TBI include findings of reduced blood–brain barrier (BBB) permeability and dysfunction[10,15,16,27] and infarction volume,[23,24,26] as well as increased neuronal density, neuronal integrity, neurogenesis, synaptogenesis, and axonal integrity.[11,16,18,24,28] Only one study reported neutral treatment effects, but its sole outcome measure was cerebral edema.[29]

Functional and cognitive outcomes. In pre-clinical studies, HBO_2 was shown to have a positive effect on functional and cognitive outcomes. Treatment-dependent improvements were seen in overall motor function,[23,26] cognitive and behavioral testing,[11,24] neurologic function,[14,27] and locomotor coordination,[28] as well as in specific tests such as the Morris water maze,[15,22] grip-strength test,[28] and beam-walk test.[12] Wang and colleagues[14] designed a study to determine the impact of the post-injury window (i.e., the

time between the injury and the initiation of treatment) and number of treatments on improvement in neurological function. The authors reported that a single treatment initiated within 12 h of injury led to improved neurologic outcomes, compared with a longer window of 24 h; no significant improvement was observed with a 72-h window before a single treatment. However, if the first HBO_2 treatment was initiated at 24 h post-injury, multiple HBO_2 treatments (either 3 or 5 consecutive days) were significantly more effective than a single treatment for decreasing both neurologic deficit scores and neuronal cell loss. Improvements were still seen if the first treatment was initiated within 48 h of injury and followed by additional treatments, although these improvements were less robust than those observed in response to a single treatment administered at 6 h. This data suggests that the optimal treatment paradigm for clinical studies may be a single treatment initiated within 24 h of the injury followed by treatments for 5 consecutive days.

Safety. Of the 20 studies reviewed, only one suggested a negative effect of HBO_2 treatment. Tinianow and colleagues[12] reported that four animals died from O_2 toxicity during their study, and some other animals temporarily lost motor function in the forepaw. The authors of this study initiated treatments with a 145-min dive that reached 2.5 ATA. This is an exceptionally high dose that would have caused the formation of reactive oxygen species across many organ systems, including the central nervous system, to levels that easily exceeded the body's antioxidant mechanisms, resulting in large-scale, unrepairable cellular damage (i.e., lipid peroxidation and DNA destruction) and inevitable fatality.

Combined HBO_2 and NBH treatment. Two pre-clinical studies combined HBO_2 and NBH into one treatment, both of which used a lateral fluid percussion model of TBI in adult male Sprague-Dawley rats.[30,31] Treatment was initiated 15 or 30 min after the injury. Zhou and colleagues[30] implemented HBO_2 (1.5 ATA) for 1 h prior to 3 h of NBH. Daugherty and colleagues used the same methodology in 1 group of rats, and NBH for 30 min prior to HBO_2 (1.5 ATA) on a second group. All animals in both studies were exposed to 1 treatment before sacrifice.

Physiologic outcomes. The brain tissue oxygen tension ($P_{bt}O_2$) of animals treated with NBH prior to HBO_2 increased from a mean baseline value of 37 mm Hg to 103 mm Hg during NBH and further to 247 mm Hg during HBO_2.[31] This combined HBO_2/NBH therapy–induced increase in $P_{bt}O_2$ corresponded to beneficial outcomes, including an increase in adenosine triphosphate (ATP) production, decreased hippocampal apoptosis, and increased mitochondrial redox potential.[30,31] An important finding in the study conducted by Daugherty and colleagues was the fact that mitochondrial function was not improved in injured animals after 1 h of HBO_2, but was significantly improved at 4 h (i.e., after the delivery of an additional 3 h of NBH). This finding suggests HBO_2 is acting as a signal transducer that improves mitochondrial function after HBO_2 administration and the subsequent administration of NBH enhances this effect.[31]

Functional and cognitive outcomes. The animals that received the combined HBO_2 and NBH treatment performed better in the Morris water maze than animals that did not receive treatment.[30]

Safety. Zhou and colleagues reported no abnormalities in mitochondrial free-radical formation in treated animals.[30]

Summary. The pre-clinical studies evaluating HBO_2 that have been conducted over the last 20 years using a variety of animal models have demonstrated benefits in mitochondrial function, neural integrity, lesion volume, and inflammatory response, as well as motor and cognitive outcomes. Thus, they provide clear proof-of-concept evidence supporting the use of HBO_2 in the acute treatment of TBI.

Clinical studies

HBO_2 treatment: Phase I. Of the eight trials that met the inclusion criteria for this review, two were Phase I trials. Rockswold and colleagues[32] recruited 37 patients with a severe TBI and a positive computed tomography scan. These patients underwent an average of five daily 60-min HBO_2 treatments at 1.5 ATA that were initiated within the first 24 h after injury.[32] Sukoff and colleagues[33] recruited 50 comatose patients without a surgically correctable lesion, and administered a clinically dependent number of 45-min HBO_2 treatments at 2 ATA. All treatments were instituted within 6 h of admission and were repeated every 8 h for 2 to 4 days.

Physiologic outcomes. Both studies found beneficial effects of HBO_2 treatment on intracranial pressure (ICP). Rockswold and colleagues reported that patients presenting with an ICP >15 mm Hg had significantly decreased ICPs at both 1 and 6 h after the HBO_2 sessions.[32] Sukoff and colleagues monitored ICP in 10 patients and found that ICP was reduced in all cases in the chamber.[33] In most cases, lower pressures were sustained for 2 to 4 h after HBO_2.

Cerebral blood flow is normally regulated by cerebral metabolism—so-called metabolic coupling—such that if cerebral oxidative metabolism increases, CBF also increases. Thus, it is of particular note that Rockswold and colleagues reported that HBO_2 improved metabolic coupling; HBO_2 significantly increased the cerebral metabolic rate of oxygen ($CMRO_2$) at 6 h post-HBO_2 treatment with a corresponding increase in relatively low pre-treatment CBF.[32]

Functional and cognitive outcomes. Sukoff and colleagues reported improvements in awareness and motor activity during treatment in 31 of the 50 patients studied.[33]

Safety. Rockswold and colleagues reported no permanent sequelae related to HBO_2 in any of the patients treated. Sukoff and colleagues found no pulmonary complications due to suspected toxic effects of HBO_2 and no decreased motor function or cognitive awareness, compared with patients who received standard care.

HBO_2 treatment: Phase II. The remaining six studies included in this review were Phase II trials, including patients with Glasgow Coma Scale (GCS) scores ranging from 3 to 12. Patients in these studies underwent between one and 42 treatments at a range of 1.5 to 2.5 ATA for a duration of 20 to 90 min. A majority of these six studies initiated treatment within the first few days after the injury.

Physiologic outcomes. Rockswold and colleagues reported positive metabolic treatment effects of HBO_2, compared with the standard of care in terms of improvements in $CMRO_2$, CBF,

and $P_{bt}O_2$, as well as dialysate lactate concentrations and the lactate pyruvate ratio (LPR).[34] This study replicated previous findings demonstrating a reduction in intracranial hypertension in HBO_2-treated patients, compared with those who received standard treatment.[32,35]

Functional and cognitive outcomes. There have been conflicting results regarding the functional outcome of patients who are treated with HBO_2. Lin and colleagues[36] found that Glasgow Outcome Scale (GOS) scores were improved at 6 months in a subset of patients treated with HBO_2, and Prakesh and colleagues[37] reported improvements in hospital stay, social behavior, and disability. Holbach and colleagues[38] reported improved mortality rates at Day 10 post-injury and larger rates of complete recovery in HBO_2 treated patients. Artru and colleagues[39] reported improvements in coma status at 1 month and mortality at 1 year for a subset of severely injured patients. Further, two studies found improved GCS scores between study groups.[36,37] However, Rockswold, and colleagues[35] reported no differences in favorable outcome as measured by dichotomized GOS scores at 6 months post-injury between those who received HBO_2 compared with the standard of care. In this prospective, randomized clinical trial, 84 patients served as a control group and 84 patients received HBO_2 at 1.5 ATA for 60 min. The HBO_2 treatments were given every 8 h for 14 days unless the patient began to follow commands or became brain dead. In retrospect, the protocol for this clinical outcome study was chosen arbitrarily, and while it was not shown to improve clinical outcome, it did result in a 50% relative reduction in mortality. This reduction in mortality was especially dramatic in patients with negative outcome predictors such as intracranial hypertension, evacuated mass lesions, and GCS scores of 4 to 6.

Safety. Rockswold and colleagues found no change in cerebrospinal fluid (CSF) F2-isoprostane (a marker of lipid peroxidation) or bronchial alveolar lavage IL-6 and IL-8 levels after HBO_2 treatment, indicating no cerebral or pulmonary O_2 toxicity resulting from treatment.[34] In addition, there was no increased incidence of pneumonia, FiO_2 requirements >50%, or positive end expiratory pressure (PEEP) >10 mm H_2O. Artru and colleagues interrupted individual treatments in five cases due to onset of pulmonary symptoms, but these symptoms were transient and may have correlated with improved post-treatment neurological condition.[39]

Combined HBO_2 and NBH treatment. One study investigated the combined effects of HBO_2 and NBH in the clinical setting.[40] Rockswold and colleagues, using the rationale based on the results of the experimental study described above,[31] randomized 42 patients with non-penetrating, severe TBI (GCS 3-8) and a Marshall classification of ≥2 to either a standard or HBO_2 treatment group. Three daily treatments were initiated within 24 h of the injury and each included 1 h of HBO_2 at 1.5 ATA followed by 3 h of NBH.

Physiologic outcomes. Brain tissue oxygen tension was elevated during treatment in both relatively uninjured brain tissue and pericontusional tissue, and remained elevated after treatment for 2.5 h, compared with patients who received the standard of care. Intracranial pressure, as well as cerebral dialysate concentrations of glycerol and lactate and dialysate LPR, were decreased in patients who received HBO_2, compared with those who received the standard of care. Overall, the reported physiologic outcomes showed positive metabolic effects of treatment in both relatively non-injured and pericontusional areas of brain.

Functional and cognitive outcomes. Both functional outcome and mortality were significantly improved at 6 months post-TBI in the treatment group, compared with patients who received the standard of care. The mortality rate at 6 months post-TBI was improved by an absolute 26% ($p = 0.04$), and a favorable outcome based on the injury severity-adjusted GOS score was improved by 38% ($p = 0.02$). The results indicate that combining HBO_2 and NBH into a single treatment has a potentially synergistic therapeutic effect.

Safety. This study reported reductions in microdialysate glycerol (a marker of phospholipid degeneration in neural tissue cell membranes) and CSF F2-isoprostane levels in those patients who received combined HBO_2 and NBH treatment, compared with control-treated patients. This finding is important because it signifies a protective effect against cerebral O_2 toxicity related to improved mitochondrial energy production. In addition, there were no reported increases in the incidence of pneumonia, FiO_2 requirements >50%, or PEEP >10 cm H_2O for the treated group, compared with the control group.

Summary. Overall, the clinical studies reviewed here provide evidence for the potential clinical utility of HBO_2 in the acute stage of severe TBI. These Phase I and II clinical trials demonstrate that increased O_2 availability results in reductions in intracranial hypertension and improvement in oxidative metabolic function, while definitive improvements in functional clinical outcome have been inconsistently demonstrated.

Discussion

Mechanism of HBO_2

During the acute phase of a severe TBI, the metabolic demands of the brain increase but O_2 delivery to the brain decreases due to a reduction in CBF, as well as barriers to O_2 diffusion caused by capillary endothelial edema, which is exacerbated by the neuroinflammatory response to trauma, capillary collapse, and increased ICP.[8] This O_2 deficiency forces a conversion to anaerobic metabolism, leading to the depletion of cellular energy (ATP) and eventually to cell death.[41] This phenomenon was observed in the studies reviewed above that report decreased $CMRO_2$, decreased ATP production, and increased lactate concentrations in both microdialysate and CSF. The cellular energy crisis resulting from inadequate O_2 delivery results in electrolyte imbalances stemming from the lack of energy for normal Na^+/K^+ ATP-ase pump function within neurons and glial cells. This imbalance leads to an increased calcium influx, resulting in an abnormally elevated release of excitatory neurotransmitters and further disruption of mitochondrial metabolism in a positive feed-forward manner that causes excessive free-radical buildup. As the neuroinflammatory response continues, apoptosis-mediator proteins such as bcl-2 and bcl-xL initiate the process of cell death.

This biochemical cascade resulting in potentially large-scale cell death demonstrates the need for providing an adequate O_2 supply following TBI in order to limit secondary ischemic injury. It is currently unclear whether the benefit seen with HBO_2 is due to a defined threshold of $P_{bt}O_2$ that must be reached (preliminary evidence suggests this threshold may be >200 mm Hg)[34] or an area under the curve of O_2 dosage that must be reached. Either way,

providing an adequate O_2 supply is a task that HBO_2 appears to accomplish. The effects of HBO_2 are mediated by increasing the O_2 dissolved in plasma, as opposed to the O_2 carried by hemoglobin. For example, the dissolved O_2 content (volume %) at room air (1 ATA) is 0.32. At 1.5 ATA, it is increased by a factor of 10.[42] When additional O_2 becomes available for diffusion across capillary endothelium, anaerobic metabolism converts back to aerobic metabolism, allowing mitochondria to restore depleted cellular energy.[31] This neuroprotective effect can be objectively observed in the traumatized human brain by improved $CMRO_2$ measurements following HBO_2 treatments, as mitochondrial metabolism accounts for >90% of O_2 consumption in the brain.[32,34] This neuroprotective increase in $CMRO_2$ leads to a number of physiologic benefits. First, returning to aerobic metabolism results in improved energy production and halts the cascade toward cell death described above. Second, the averted energy crisis allows for a return of normal autoregulation, which can normalize CBF and ICP.[32] Third, it decreases the neuroinflammatory response that leads to apoptosis.[23,25,43–46] Fourth, as ATP becomes available from restored mitochondrial function, the function of Na^+/K^+ ATP-ase pumps improves, allowing osmotic effects to alleviate endothelial swelling and edema. In turn, this reverses induced barriers to the diffusion of O_2 to the mitochondria.[47–49] Finally, the BBB stabilizes and there are increases in stem cell production.[24,47,48,50,51]

Hyperbaric oxygen therapy also has been proposed as a treatment for the chronic sequelae of TBI, but evidence to support HBO_2 for this purpose is weak. Previous review articles have suggested that issues with methodology and statistical analysis may be underlying reasons,[52] but the biochemical mechanism responsible for the benefits of HBO_2 in chronic mild TBI are not well documented in either clinical or pre-clinical work. In our review of the literature, we were able to identify only two pre-clinical studies evaluating HBO_2 for chronic TBI.[15,51] Notably, the mechanism for any benefit seen with HBO_2 in the treatment of chronic mild TBI is unlikely to be similar to that underlying the acute effect of HBO_2 because the acute mechanism relies on cascades relating to the energy crisis that occurs in the body within hours or days of a severe TBI.

Controversy surrounding the use of HBO_2

The biochemical mechanisms and physiologic benefits of acutely administered HBO_2 for severe TBI provide objective evidence supporting the use of this treatment in the clinical setting. However, controversy still exists due to safety concerns of an increased O_2 dose, how meaningful the benefits in functional outcome are, the feasibility of implementing these treatments, and the apparent inability to consistently replicate data.

Safety. One safety concern related to the therapeutic use of HBO_2 in TBI stems from O_2 toxicity, which is caused by oxidative stress and the formation of reactive O_2 species in the lungs and brain tissue after prolonged exposure to O_2.[34,53] Oxygen toxicity is commonly measured in increments of unit pulmonary toxicity dose (UPTD), which is a theoretical method for calculating relative O_2 doses.[54] One UPTD is equal to 1 min of exposure to 100% O_2 at 1 ATA, and appropriate conversion factors allow one to quantitate the pressure of O_2 exposure. In general, it is recommended that total O_2 exposure during a single treatment be limited to ≤615 UPTD. The extreme upper limit of a single O_2 exposure is 1425 UPTD, which will produce a predicted 10% decrease in vital capacity in a healthy individual. A treatment consisting of 60 min of HBO_2 at 1.5 ATA with compression/decompression at 2 feet/min generates 130 UPTD. At a pressure of 2.5 ATA, using the same procedure, the O_2 dose is 296 UPTD. Both paradigms are well below the accepted upper limit. It is important to note that interruptions in O_2 exposure between treatments have been shown to increase O_2 tolerance and improve safety; for example, 600 UPTD per day in two treatment sessions was administered for weeks without any evidence of accumulative pulmonary toxicity.[55]

Feasibility. Questions have been raised regarding the feasibility of HBO_2, because its use requires hospitals to purchase chambers. However, a higher-cost, multiple-occupancy, large compartment chamber requiring sophisticated operation is not necessary for most hospitals. A lower-cost monoplace chamber, which allows for the treatment of a single patient with external support, is entirely adequate and can be incorporated into a critical care area.[34,56] Further, it has the advantages of minimal physical space requirements and minimal operation demands (which can be met by training support staff already employed by the hospital), a lack of iatrogenic sickness to the support staff, and a lower cost of purchase and installation. Given the widespread demographic that TBI affects, the wide-scale implementation of an effective treatment option for these severely injured patients should be seen as an investment rather than a cost.

In addition to the expense, expanding this complex, labor-intensive treatment to multiple centers could be problematic. Experience at Hennepin County Medical Center has demonstrated that HBO_2 can be delivered to patients with severe TBI safely. Over 1900 HBO_2 treatments have been delivered to 167 patients over the course of four clinical trials without negative permanent sequalae.[32,34,35,40,56] As with any new medical procedure, the process has to be taught to other centers, but novel clinical trials can drive practice if new treatments show beneficial effects in randomized trials.

Mixed results. A major concern of implementing HBO_2 as a clinical treatment arises from the perception that the data are not consistently replicated in the literature. Two main factors may contribute to these inconsistencies. The first factor is the heterogeneous pathophysiology of TBI. Hyperbaric oxygen therapy may not be the best choice for all patients that present with a severe TBI. Studies using subgroup analyses have shown that some patients respond better to treatment than others, such as patients who have lower baseline CBF levels, higher ICP levels, those whose injuries are more severe, and those with mass lesions.[32,35,39] Second, suboptimal and inconsistent methodologies have been employed in HBO_2 studies; examples include studies of patients with injuries that vary substantially in severity, and those with poorly defined inclusion criteria, studies that do not consistently randomized patients or blind the analysis, and studies with a high risk for bias.[57] In fact, only one study has met the standards of a prospective, randomized controlled trial.[41] Further complicating this issue, treatment protocols have varied greatly from study to study, resulting in patients receiving variable O_2 dosages initiated at various timepoints following injury with sporadic frequencies.

Despite methodological inconsistencies and subsequent incapability to conduct a meta-analysis, this review summarizes data that indicate the positive potential of HBO_2 for the treatment of TBI during the acute post-injury period. However, optimal treatment paradigms are unable to be further delineated at present, because pre-clinical investigators working with TBI models and HBO_2 have used pressures varying from 1.5 to 3.0 ATA, and clinical investigators have used pressures varying from 1.5 to 2.5 ATA. In

addition, the lungs of severe TBI patients are frequently compromised by direct lung injury and/or acquired ventilator-associated pneumonia and are therefore susceptible to O_2 toxicity. Working with those constraints, it is essential to determine the most effective HBO_2 treatment paradigm without producing O_2 toxicity and clinical complications. The ideal HBO_2 treatment paradigm would include pressure (ATA) parameters and information regarding whether NBH delivered after HBO_2 treatment enhances clinical effectiveness. A recently funded randomized clinical trial, the HOBIT trial, will have two principal aims: 1) to select the combination of HBO_2 treatment parameters that is most likely to demonstrate improvement in good neurological outcome at 6 months following severe TBI in a subsequent confirmatory trial, and 2) to determine whether there is a >50% probability of the selected HBO_2 treatment demonstrating significant improvement in good neurological outcomes at 6 months following severe TBI in a subsequent confirmatory trial.[9] Based on the previous work described in this review, a targeted subset of patients with severe TBI will be enrolled in the trial.

Conclusion

This systematic and comprehensive literature review demonstrates that, despite the controversy surrounding HBO_2 for the treatment of TBI, this therapy has significant clinical potential. Nearly 50 years of pre-clinical and clinical research demonstrate a possible beneficial effect of this treatment, yet acutely administered O_2 therapy is still considered an experimental procedure. Because of this, the HOBIT trial, a recently NINDS-funded, adaptive Phase II clinical trial is warranted, and it is anticipated that an optimal treatment paradigm for potential efficacy will be established from these data.

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