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INFORMATION PAPER

MCMR-DCV-ADR
2 June 2015

SUBJECT: Hyperbaric Oxygen for Traumatic Brain Injury (TBI): State of the Science

BLUF

Hyperbaric oxygen (HBO₂) therapy has been used for more than 80 years to treat injuries and diseases associated with hypoxia or hypoxemia. Recently it has been advocated as a treatment for traumatic brain injury (TBI). In patients with severe TBI, where there is evidence of cerebral hypoperfusion and ischemia, several investigators have found improved blood flow and metabolism after HBO₂ treatments. A recent meta-analysis of HBO₂ randomized, controlled trials on TBI patients of all severities concluded that HBO₂ may reduce the risk of death and improve the level of consciousness after brain injury. However, there is no evidence to support that HBO₂ improves the quality of life for TBI patients. Additionally, the FDA has issued a statement in the last year that HBO₂ treatment has not been proven clinically effective for a number of conditions, including brain injury.

Several clinical studies have demonstrated HBO₂ effectiveness in reducing post-concussion symptoms months to years after mild TBI. The results of these studies must be interpreted with caution, as the lack of subject randomization, treatment group blinding, and control groups weakened their scientific rigor and potentially induced experimenter and selection bias. Recent randomized controlled trials provide no evidence for the efficacy of HBO₂ interventions compared to shams for improving post-concussion symptoms in mild TBI patients. This is true both immediately after and three months post-intervention. These negative results may reflect the contribution of non-specific factors towards a positive response in both treatment and placebo groups, such as fluctuation of symptoms in chronic patients and the improvement in patient outcomes due to expectation, conditioning, and/or the psychosocial context of treatment (i.e., clinician-patient interactions). The National Institutes of Health is funding a study to develop a set of measures that will determine the association of the treatment response with patient attitudes, expectancies, and the perception of clinician-patient interactions and the treatment environment. This tool will be important for use in future clinical trials of hyperbaric oxygen, and may help reveal what aspects of the treatment environment could be enhanced to maximize improvements in patient outcomes.

Whether treatments should be used to produce a placebo effect is a controversial and contradictory topic. An ethical principal in clinical practice is that sham treatments should only be used when there are no alternative treatment options available. Until the benefit of HBO₂ treatment for post-concussion symptoms is demonstrated through high

quality, controlled clinical trials, conventional symptom-based treatments are the most appropriate recommendation for TBI patients. The most common post-concussion symptoms include headaches, sleep problems, dizziness, and cognitive difficulties. There are well-defined and effective treatments for all of these sequelae.

Background

Hyperbaric oxygen therapy is defined as the medical application of oxygen at concentrations and pressures greater than normal to increase the saturation of oxygen in the blood and tissues of the body. The first report of this type of therapy was in 1662 when a British clergyman and physician known only as Henshaw created the first hyperbaric chamber for therapeutic purposes (1). The chamber was a sealed room with a system of bellows and valves to alter the internal air pressure. Henshaw theorized that with pressure changes the room would modulate in his “domicilium” and thereby ameliorate both acute and chronic illnesses.

Over a century later, Joseph Priestley was the first to chemically isolate and characterize oxygen in 1775. Shortly thereafter were reports of the toxic effects of hyperbaric oxygen on the central nervous system (seizures associated with cell damage) and lungs (oxidative damage to cell membranes and collapse of alveoli and respiratory distress). As a result, the use of HBO₂ fell out of favor until 1936 when Behnke and Shaw investigated its use to treat decompression sickness (2). Based on this discovery, HBO₂ chambers were widely used by the military in the 1940’s to treat deep-sea divers who suffered from decompression sickness. During the next several decades there were reports of the successful use of HBO₂ to enhance the radiosensitivity of tumors, for improving outcomes in cardiac surgery, and for the treatment of carbon monoxide poisoning and clostridial gas gangrene.

Treatment typically involves the patient breathing 100% oxygen while in a sealed chamber that has been pressurized from 1.3 to 2.8 times that of normal atmospheric pressure (room air at normal atmospheric pressure is made up of 21% oxygen). The treatment can last anywhere from 30 minutes to two hours. HBO₂ can be done in single or multi-person chambers that can hold more than a dozen people at a time. A single-person chamber or *monoplace* consists of a metal or plastic tube about seven feet long. The patient lies on a padded table that slides into the tube. The chamber is sealed and gradually pressurized with 100% oxygen. Patients are asked to relax and breathe normally during treatment. They may experience ear popping and mild discomfort. At the end of the session technicians slowly depressurize the chamber. Immediately after an HBO₂ session patients often feel lightheaded and tired.

In general, complications with clinical use are lessened if pressures within the hyperbaric chamber stay below three times the normal atmospheric pressure and sessions last no longer than 2 hours. Mild problems associated with HBO₂ include claustrophobia, fatigue, and headache. More serious complications include myopia (short-sightedness) that can last for weeks or months, sinus damage, ruptured middle ear, and lung damage (3). Rarely oxygen toxicity can result in seizures, pulmonary

edema, and even respiratory failure. The treatment is generally contraindicated for those with severe congestive heart failure. Pregnant women should be treated with HBO₂ only in serious situations where there are no other options. Hyperbaric oxygen is also contraindicated for those receiving chemotherapy with bleomycin, doxorubicin, or cisplatin, as well as those treated with disulfiram (Antabuse) or using sulfamylon cream. Fires or explosions in hyperbaric chambers have caused approximately 80 deaths worldwide.

There are several hundred HBO₂ locations throughout the US in both free standing facilities and within hospitals. The typical charge is between \$100-\$300/session. Charges are lowest for those who receive multiple, shorter duration sessions.

The Undersea and Hyperbaric Medical Society, founded in 1967, formed a Committee on Hyperbaric Oxygenation which has become recognized as the authority on evidence-based applications of hyperbaric oxygen treatment. From 2008 to 2013, the following diseases have been endorsed by the Committee, claiming there is good evidence they respond to HBO₂ treatment:

- Decompression sickness
- Arterial gas embolism
- Carbon monoxide poisoning (with or without cyanide poisoning)
- Delayed radiation injury of the soft tissue or bones, including osteoradionecrosis
- Gas gangrene
- Skin grafts and flaps that are not healing well with standard treatment
- Soft tissue infections in which tissues are necrotic
- Anemia due to severe blood loss (when transfusions are not an option)
- Crushing injuries in which there is evidence of ischemia
- Certain wounds that are not healing with standard treatment
- Thermal burns
- Abscess in the brain or head
- Osteomyelitis that does not respond to standard treatment
- Blockage of the retinal artery

The U.S. Food and Drug Administration (FDA) has also approved HBO₂ for treatment of these diseases, with expenses reimbursed by Medicare/Medicaid and most major insurance companies. In addition, HBO₂ is thought of by some as an alternative therapy for multiple sclerosis, cerebral palsy, cancer, autism, chronic fatigue syndrome, Lyme disease, AIDS, stroke, traumatic brain injury and migraines. At present, there is insufficient scientific evidence to support the efficacy of HBO₂ for these conditions. Accordingly, the FDA has sent a warning letter to at least one manufacturer about promoting unproven uses for HBO₂ treatment. The FDA considers oxygen to be a drug, therefore it must be prescribed by a physician or licensed health care provider to treat illnesses or health conditions.

Use of HBO₂ for TBI

Rationale

There is abundant evidence that TBI (at least severe) is associated with a reduction in aerobic metabolism. Clinical reports document cerebral blood flow levels 30-50% below normal within 2-3 hours after injury (4). Brain injuries are also associated with elevated tissue lactate/pyruvate ratios, increased absolute lactate levels, and other metabolic evidence of mitochondrial failure (5,6). Post-mortem studies find histologic evidence of ischemia in 80-92% of those who die following TBI (7).

Mechanism of effect

In rodent studies HBO₂ reduces TBI-induced microglial activation, Tumor Necrosis Factor (TNF- α) expression, and neuronal apoptosis. This suggests that in the acute phase of TBI, HBO₂ may attenuate microgliosis and the expression of the pro-inflammatory cytokine TNF- α , resulting in a neuroprotective effect (8). Clinical studies of patients with severe TBI indicate that HBO₂ improves aerobic metabolism. Sukoff et al. reported that seven, 60 min sessions at 1.5 atmospheres absolute (ATA), resulted in a significant increase in the cerebral metabolic rate for oxygen (CMRO₂) and a decrease in cerebrospinal fluid (CSF) lactate levels one and six hours after treatment (9).

In another study, Rockswold et al. found that HBO₂ raised both cerebral blood flow (CBF) and CMRO₂ levels in patients with initially low CBF at one and six hours after treatment (10). Arterial-jugular venous differences in oxygenation (AVDO₂) remained constant, but levels of CSF lactate and intracranial pressure values (>15 mm Hg) decreased at the one and six hour marks. However, Rockswold et al. also found that the effects of each treatment did not last until the next session in the hyperbaric chamber.

Nakamura et al. documented a significant decrease in jugular venous lactate levels and in the mean pulsatility index in seven patients with severe TBI after they were treated with five sessions of HBO₂ at 2.7ATA/60 min (11). Rockswold et al. also found a decrease in CSF lactate levels, an increase of in-tissue pO₂, and lower intracranial pressure (ICP) when severe TBI patients were treated with HBO₂ for one hour followed by normobaric hyperoxia (NBH) for 3 hours (10). However, Puccio et al. did not find any change in levels of CSF lactate or F2-isoprostane (markers of oxidative stress) with just NBH treatment. This discrepancy suggests that HBO₂ may be critical for improving aerobic metabolism rather than just an increase in ambient pO₂ (12).

Outcomes

The most compelling evidence for efficacy of HBO₂ is in the treatment of severe TBI. Rockswold et al. treated 42 subjects with three HBO₂ sessions, each 1.5ATA/60 min, followed by 100% fraction of inspired oxygen (FIO₂) at 1.0 ATA for 3 hours (13). At six months after treatment they found a 26% decrease in mortality and a 36% increase in favorable outcomes compared to matched controls. Ren et al. treated 35 severe TBI

patients with three HBO₂ sessions and noted an improvement in the Glasgow Coma Scale (GCS) score from 5.1 to 14.6 at follow-up (14). However, the control patients in this study may have done worse than expected because they were treated with dehydration and steroids, two therapies that are not advocated by evidence-based guidelines. Sahni et al. reported that 20 patients with severe TBI improved on Ranchos Los Amigos Scale scores after 30 HBO₂ sessions (15). Lin, et al., found a significant improvement in Glasgow Coma Scale (GCS) and Glasgow Outcome Scale (GOS) scores in 22 patients after they were treated with HBO₂ for six months (16).

Some clinical studies of patients with mild TBI and persistent post-concussive symptoms have found positive results. Boussi-Gross et al. treated 56 patients with 40 HBO₂ sessions (1.5ATA /60 min) and evaluated them at 10 days, then three weeks after treatment. They found significant improvements in cognitive and self-report quality of life measures as well as improved blood flow on post-treatment SPECT scans (17). Harch et al. also documented improved cognition, quality of life, and improved SPECT blood flow in 16 service members with blast induced TBI evaluated one week after 40 HBO₂ sessions at 1.5 ATA/60 min (18). Long-term outcomes (3-6 months after treatment) were not reported for either study, so the durability of the treatment effect is unknown.

In contrast, other studies have not found HBO₂ treatments to be effective on mild TBI patients with persistent symptoms. In a randomized, double-blind, sham-controlled trial (RCT), Wolf et al. treated 50 mild TBI patients for 30 sessions at 2.4 ATA/60 min. They found no difference between treatment and sham conditions on Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) or the Post-traumatic Stress Disorder Checklist – Military (PCL-M) six weeks after treatment (19). In a series of three papers from the same RCT, Cifu et al. also reported HBO₂ produced no effect on post-concussive symptoms compared to a sham treatment. Also a RCT, Cifu et al. treated 61 service members with 40 HBO₂ sessions (2.0 ATA/60 min) and three randomly assigned oxygen fractions: 10.5%, 75%, and 100%. Breathing 10.5% oxygen at 2.0 ATA is equivalent breathing normal air and functioned as the sham. The 75% and 100% conditions were treatments. Cifu et al. found no change compared to sham controls on the Rivermead Post-concussion Symptom Questionnaire (RPQ) and the PCL-M immediately (20) or three months after treatment (21). In addition, one week post-intervention measures of psychomotor and neuropsychological function revealed no differences between the treatment and sham groups (22).

In the latest RCT to address HBO₂ therapy, Miller et al. evaluated 40 sessions on 72 military service members with mild TBI (23). Participants were randomly assigned to HBO₂ (1.5 ATA/60 min) and sham conditions (1.2 ATA/60 min). They were evaluated at pre-treatment, mid-point, and post-treatment using the RPQ, Neurobehavioral Symptom Inventory (NSI), and the Automated Neuropsychological Assessment Metrics (ANAM). Symptom change scores were calculated for both treatment and sham groups. While symptom scores improved over the course of the intervention, they did not differ between treatment and sham groups.

In the above studies, randomization procedures were clearly described, sham groups were employed, and outcomes were assessed by clinicians blinded to the treatments. As such, they represent the highest standard in clinical investigation. The results suggest HBO₂ treatment offers no purchase beyond sham compression and any clinical benefits may be due to placebo. However, one argument against this conclusion is that the above trials do not employ a true sham. Hyperbaric oxygen shams, even with normal air (21% O₂, 78% N) and at low pressures (1.1 – 1.2 ATA), may raise the concentration of oxygen in blood and tissues. If this is the case, the sham is not truly inert and its associated outcomes may not differ from those of the treatments.

A recent meta-analysis published as a Cochrane Database Review looked at all randomized studies comparing the effectiveness of therapeutic regimens with and without HBO₂ on individuals with traumatic brain injury (24). Seven studies met the minimum clinical trial quality standards according to the Consolidated Standards of Reporting Trials (CONSORT) Guidelines. Overall, they included 571 people, 285 receiving HBO₂ and 286 in the control group. The results of two studies indicate that use of HBO₂ results in a statistically significant decrease in the proportion of people with an unfavorable outcome, as measured by the GOS, one month after treatment (relative risk (RR) for unfavorable outcome with HBO₂ 0.74, 95% CI 0.61 to 0.88, $p = 0.001$). Pooled data from final follow-up showed a significant reduction in the risk of dying after HBO₂ treatment (RR 0.69, 95% CI 0.54 to 0.88, $p = 0.003$). Two trials suggested favorably lower intracranial pressure in people receiving HBO₂. Two small trials reported a significant improvement in GCS scores for patients treated with HBO₂ although those trials showed considerable heterogeneity. Two studies reported a 13% incidence of significant pulmonary impairment in the HBO₂ group. In general, the studies were small and carried a significant risk of bias. None described adequate randomization procedures or allocation concealment and none of the patients or treating staff were blinded to treatment. It was concluded that while the addition of HBO₂ may reduce the risk of death and improve the final GCS score, there was little evidence that the survivors have a good outcome.

Treatment of Post-concussion Symptoms: Conventional Care vs HBO₂

Symptom management following mild TBI is the standard of care in the Military Health System (MHS). Headaches are the most common of the post-concussion symptoms. The current treatment of post-traumatic headaches in U.S. Army soldiers was recently evaluated (25). In that study a 23% (significant) decline in headache frequency was observed when subjects were treated with topiramate. Triptan class medications were found to be highly effective in aborting severe headaches and headache related disability declined by 57% among those who were treated. Other research has found spinal manipulation or transcutaneous electrical nerve stimulation to be effective therapies (26).

Another common component of post-concussion symptoms is sleep disturbances, most commonly insomnia. In addition to good sleep hygiene, stimulus control and

medication, investigators have shown that cognitive-behavioral treatments and cognitive processing therapy with prolonged exposure can significantly improve sleep quality and duration. This approach is especially effective if the insomnia is related to post-traumatic stress disorder (PTSD) (27). Studies of cognitive behavioral therapy in particular demonstrate very large treatment effects for insomnia severity and sleep quality (28).

Dizziness and vestibular dysfunction are also common post-concussion symptoms. Vestibular physical therapy is the most commonly prescribed therapy. One study of nearly 50 patients found significant improvement, on both subjective and objective measures, in patients receiving a mean of five sessions of vestibular therapy (29).

Regarding the cognitive deficits associated with post-concussion symptoms, there is some evidence that specialized programs of cognitive rehabilitation may help improve memory and attention deficits. Prospective studies of cognitive rehabilitation are currently ongoing. Conversely, six recent prospective trials of HBO₂ for concussion have been published (17, 19, 20, 21, 22, 23) and only one found possible improvement in cognition at 1-3 weeks following treatment (17). Interestingly, one of the studies looked at the effect of HBO₂ on headaches, dizziness, and sleep disturbances found that the sham control subjects, but not the HBO₂ treated subjects, had significantly less severe headaches at six weeks after treatment. In addition, they found no benefit of HBO₂ for dizziness or sleep problems (19).

Placebo effect in randomized, controlled treatment trials

Clinical trials of some types of interventions, including trials of complementary and alternative medicine, frequently fail to detect a true interventional effect compared to sham controls. The negative results of randomized controlled trials of HBO₂ for mild TBI (19, 20, 21, 22, 23) may be due to inefficacy of the treatment, or they may reflect a positive response to other, non-specific contextual factors in both treatment and placebo groups. This may include the natural course of the disease being studied; fluctuation of symptoms; and improvements in measured outcomes due to expectation, conditioning, and/or the psychosocial context of treatment (i.e., clinician-patient interactions) (30). However, the possibility that the sham treatments in these studies are not inert raises the question of their validity. Alternative methods of executing a sham and careful dosing experiments are needed to address the efficacy of HBO₂ and any factors that may produce a placebo effect.

The National Center for Complementary and Alternative Medicine, of the National Institutes of Health, is funding a study to develop a set of measures that can be used by clinicians and researchers to assess these factors and determine any association of the treatment response with the therapeutic environment, patient attitudes, expectancies, and the perception of clinician-patient interactions (31). This tool could improve the methodology of clinical trials on HBO₂ and be useful in determining what aspects of the treatment environment maximize improvements in patient outcomes.

Controversial or unresolved issues

1. Optimal Dose: HBO₂ involves four different treatment variables-ATA, FiO₂, treatment duration, and number of treatments. Most clinical trials have used 1.5 ATA, 100% FiO₂, 60 minutes of treatment, and 40 sessions. But there have been no large clinical trials that have compared different dosing protocols so it remains unclear if one is superior (or toxic).
2. Legitimacy of sham controls: treatment of a patient with HBO₂ at as little as 1.2ATA and a FiO₂ of room air will still result in a higher partial pressure of oxygen (PaO₂) than if the patient is at ambient pressure. Patients can tell if they are in a hyperbaric environment, so they would not otherwise be blinded to their therapy without some increase in ATA.
3. Durability of treatment: Studies in severe TBI patients that have looked at the metabolic effects of treatment have found improvement in CBF, CMRO₂, and CSF Lactate levels at 1 and 6 hours but not 24 hours after treatment. The recent Boussi-Gross study of mild TBI (17) found benefit at 10 days to 3 weeks, while the Cifu study (20) did not find any benefit 3 months after treatment.
4. Using HBO₂ for the primary purpose of inducing a placebo effect: Until HBO₂ is shown to be effective for treating post-concussion symptoms after mild TBI, conventional, symptom-based treatments are most appropriate and recommended for these patients.
5. Long term effects of mild TBI: what role would/could hyperbaric oxygen have for long term neurodegenerative conditions? The DoD currently has three initiatives to look at long term effects; (Appendix A) however the role of hyperbaric oxygen is not part of current protocols.

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Appendix A:

Three key DoD initiatives to better understand the long-term effects of TBI:

- a. DoD's 15 Year Longitudinal Study on the effects of TBI from OEF/OIF/OND will document the natural history of recovery from TBI of all severities for up to 15 years post-injury, determine the association of TBI and co-morbidities, and provide information on the long term health care and rehabilitation needs of service members and Veterans with TBI, including co-morbidities with mild TBI. The study is in its 4th year. Initial findings thus far reveal that a high proportion of Service members who sustain mild, moderate and severe TBIs continue to report significant symptoms and problems within the first five years post-injury, requiring continued care and support. Data collection will continue through 2026.
- b. DoD and Department of Veterans Affairs (VA's) jointly sponsored the Chronic Effects of Neurotrauma Consortium, to understand the chronic effects of mild TBI, determine what neurodegenerative processes may be associated with mild TBI, and to identify diagnostic and prognostic indicators of those processes. The study groups will also develop and advance methods to treat and rehabilitate those with chronic neurodegenerative disease. The studies are currently being launched.
- c. An interagency National Research Action Plan was developed by the DoD, VA, Department of Health and Human Services and the Department of Education to identify evidence-based therapies that are effective in maximizing short and long term health and function, community participation and reintegration for persons with TBI in civilian and military populations, including service members, Veterans, and their families. Interagency coordination and collaboration are occurring to share vital information across federal agencies.

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