Hyperbaric oxygen for neurologic indications. Action plan for multicenter trials in: stroke, traumatic brain injury, radiation encephalopathy and status migrainosus

Tlenoterapia hiperbaryczna we wskazaniach neurologicznych. Plan badania wieloośrodковego w przypadkach udaru, pourazowego uszkodzenia mózgu, encefalopatii popromiennej i stanu migrenowego

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A B S T R A C T

Introduction: There is great interest in using hyperbaric oxygen (HBO) to treat neurological disease. The exquisite sensitivity of neural tissue to hypoxia makes increased oxygenation attractive as a therapy for disease processes that induce ischemia, edema, and, more recently, apoptosis. Four things specifically exist as targets for future projects and clinical trials: (1) stroke (2) traumatic brain injury (3) radiation induced necrosis and (4) status migrainosus. Methods: Specific aims: Stroke: determine if the use of HBO in the treatment of acute ischemic stroke is effective at improving outcomes. TBI: determine whether use of HBO in the acute state after traumatic brain injury is effective at improving outcomes and reducing elevated ICP. RIN: determine whether HBO treatment of radiation necrosis of brain results in improvement of neurological function and reduction of necrosis. Migraine: determine whether use of HBO will relieve headache pain in status migrainosus. Results: Stroke: there is evidence from animal studies that focal cerebral ischemia may improve after HBO treatment. TBI: the interest in using HBO to treat TBI is based upon the premise that hypoxia, edema and apoptosis play significant roles in the pathophysiology of the disease. RIN: the evidence suggests that in cases where either the patient is not improving on medical therapies or when surgical resection is not possible, HBO should be considered as a treatment option. Migraine: there is some evidence looking at HBO as an effective treatment of acute migraine attack. Summary: Each is discussed further with proposed study design and justification for their respective parameters. As our action plan moving forward, it is our goal to investigate in each area with multidisciplinary, multi-centered, case controlled double blind crossover studies.

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Introduction

Since the early days of hyperbaric medicine, there has been interest in using HBO₂T to treat neurological disease. The exquisite sensitivity of neural tissue to hypoxia makes increased oxygenation attractive as a therapy for disease processes that induce ischemia, edema, and, more recently recognized apoptosis. Four conditions were specifically targeted for future projects and clinical trials: (1) stroke (2) traumatic brain injury (3) radiation induced necrosis and (4) status migrainosus.

Each is discussed and presented as a proposed study design with justification for study parameters. It is our goal to present this publicly to stimulate further discussion and to aid in the development of multidisciplinary, multi-centered, controlled, blinded trials in each of these important areas of investigation.

As such, we specifically ask for reader comments on the trials proposed.

Stroke

Specific aim

To determine if the use of HBO₂T in the treatment of acute ischemic stroke is effective at improving outcomes.

The largest body of evidence involving the use of hyperbaric oxygen for neurologic illness is found in the field of cerebral ischemia, which was reviewed by Helms et al. [1]. At the center of an infarct, blood flow is completely absent, causing neurons to die within a matter of minutes. This area, therefore, may not be amenable to treatment after the start of symptoms. The region of the brain that draws the most interest is the penumbra, where evidence has shown that blood flow is diminished, but not absent. The cells in this region remain viable for a prolonged period, and can be saved if adequate perfusion is restored [2]. The only FDA approved therapies for acute ischemic stroke include tPA, and interventional intra-arterial treatments aimed at restoring blood flow to the ischemic penumbra [3–6], but must be used within the first few hours of the onset of symptoms [7, 8]. There is also evidence that a percentage of the cells subjected to prolonged ischemia will inevitably undergo apoptosis, either after prolonged ischemia or due to reperfusion injury in the case of temporary ischemia [9–12]. As a result, there has been great interest in using HBO₂T for the added benefit of its anti-inflammatory and anti-apoptotic properties [13–18].

There is reasonable evidence from animal studies, involving mice, rats, gerbils, and cats that damage from focal cerebral ischemia is ameliorated after treatment with HBO₂T (1). Several human trials investigating the use of HBO₂T for ischemic stroke have also been performed. Most of these lacked controls, as well as uniform standards for inclusion criteria and outcome measurement. There have been three prominent randomized controlled studies that have evaluated HBO₂T in ischemic stroke, none of which where able to demonstrate statistically significant benefit [19–21]. One might conclude from this that HBO₂T is an ineffective treatment for ischemic stroke, however, it should be noted that these studies enrolled patients well after the therapeutic window of 6–12 h suggested by previous animal studies. Additionally, two of the three also used lower doses of HBO₂T than was found effective in animal studies. Based on our present understanding of ischemia, one would not expect improvement in measured outcomes under these conditions.

It seems therefore reasonable to assess patients presenting for potential HBO₂T for a pattern of penumbra as this provides the strongest evidence of recoverable tissue. As the ischemic penumbra represents the area which is expected to be most salvageable, it is reasonable to determine whether a penumbra is or is not present in patients undergoing experimental treatment with HBO₂T On MRI, penumbra is represented by perfusion–diffusion mismatch [6]. More simply stated, we must find the area of brain which is dying in hope that HBO₂T can still save it before it is dead. This is called ischemic penumbra. In the rat model of focal ischemic stroke produced via thrombotic occlusion of the MCA, MRI revealed perfusion–diffusion mismatch which persists up to 6–12 h after the occlusion. In patients such mismatch is usually present during the first 6 h after stroke [22]. Noticeably, HBO₂T was effective against experimental stroke if administered when a penumbra is typically present in the brain [23]. HBO₂T administered at a time when penumbra is usually gone (e.g. at 23 h) may even be harmful [24]. The clinical trials done with HBO₂T so far did not follow this paradigm, which creates the most important discrepancy between experimental and clinical work. We propose that the evaluation of patients in any future clinical trial should include separate subgroup analyses of patients with and without confirmed penumbra as the impact on outcomes may be different in these two groups.

As the accepted standards of stroke care are paramount in treatment of any patient presenting with acute stroke, patients presenting within the therapeutic window for tPA should be treated with tPA but should be considered for HBO₂T as well if they have persistent neurologic deficits on physical examination and can be treated within the time window. This is because even in cases of temporary ischemia HBO₂T has shown benefit in animal studies through decreases in reperfusion injury [25].

Study design

Subjects presenting to the ED with a presumed diagnosis of stroke will be evaluated by a neurologist. Inclusion requires the determination of anterior circulation ischemia by the clinical judgment of the examiner, meaning that the stroke is restricted to the middle or anterior cerebral artery territory. Both males and females at least 18 years-old with onset of symptoms less than 6 h will be evaluated by a certified examiner using the National Institute of Health Stroke Scale (NIHSS) [26]. While this may seem a very high standard in terms of timing, this is consistent with the recommendations of the American Stroke Association recommending that assessment and treatment of acute stroke patients commence within 60 min of presentation to the emergency department [27].

A minimum score of four on the NIHSS is needed for inclusion. The premorbid modified Rankin scale score (mRS) will be evaluated by discussing with the patient/family as
Traumatic brain injury

Specific aims

To determine whether use of HBO₂T in the acute state after traumatic brain injury is effective at improving functional and mortality outcomes.

To determine whether use of HBO₂T in the acute state after traumatic brain injury is effective at reducing elevated intracranial pressure (ICP).

Traumatic brain injury (TBI) is one of the leading causes of disability in the United States, affecting more than 1.4 million people yearly [41]. Although the primary injury to the brain sustained at the time of the trauma is usually not reversible, it is the secondary injury occurring in the hours and days following the initial injury that provides more opportunities for treatment to preserve tissue and function. In addition to the initial injury, a large contributor to morbidity and mortality is cerebral ischemia resulting from post-traumatic hypoxia and hypotension [42]. On a microscopic level, abnormalities of calcium and potassium homeostasis, mechanical membrane disruption, excitotoxicity, and altered glucose metabolism also contribute to cellular damage, which in turn cause edema and neuronal cell death [43]. Cell death in the form of both necrosis and apoptosis occurs in the areas surrounding the primary injury, but can also occur at more distant areas [44]. Increased intracranial pressure from edema, as well as from contusions and hemorrhages, contributes to secondary injury by increasing ischemia, and derangement of cellular metabolism, and can lead to herniation and death [45, 46].

The interest in using HBO₂T to treat TBI is based upon the premise that hypoxia, edema and apoptosis play significant roles in the pathophysiology of the disease. Only a few studies have directly compared HBO₂T to standard of care in acute TBI. Most recently Rockswold et al. [47] published a treatment effect in acute TBI lowering intracranial pressure for 3 days using 60 min of HBO₂T at 1.5 ATA. In 1974, Holbach alternated 99 patients in coma after TBI for an average of 4.5 days after their injuries, and treated them at 2.5 ATA for 60 min daily over 10 days with a 4 day break repeated versus standard of care. At one year, the study showed non-significant trends towards shorter coma and higher rate of consciousness in the HBO₂T group. Mortality was not affected. The only significant improvements were in a subgroup of young patients with brainstem injury who had higher rates of consciousness at one month, (HBO₂T 67% vs control 11%). In 1974, Holbach alternated 99 patients in coma with acute midbrain syndrome to either standard care or HBO₂T at 1.5 ATA and saw significant improvements in mortality (53% vs 74%) and good outcome on the Glasgow Outcome Scale (33% vs 6%) [49]. More recently, Rockswold et al. randomized 168 TBI patients between 6 and 24 h after injury with GCS of 9 or less to HBO₂T at 1.5 ATA for 60 min every 8 h for 2 weeks versus standard care [50]. At 12 months, blinded examiners saw no change in outcome among survivors, but there was a significant decrease in mortality (17% vs 32%) at one year. A small more recent trial randomized patients at day 3 with a GCS of less than 9 to HBO₂T at 2.5 ATA for 400–600 min every 4 days for 3 or 4 treatments versus standard care [51].
A markedly larger percentage of patients in the treatment group achieved a good outcome at 6 months (83% vs 30%). A recently published clinical study of a subacute TBI population included patients who had an initial GCS score of 3–12. Subjects were treated initially at an average of 28 days post-insult/injury with 20 treatments lasting 90 min each of 2.0 ATA. Despite enrollment at such a late time, they were able to demonstrate a significant benefit from 20 lasting 90 min each of 2.0 ATA HBO₂T when baseline comparisons were made at 6 months post-treatment in the number of patients achieving a Glasgow Outcome Scale level of 4 (moderate disability) subgroup of the patients was evaluated [52].

At first glance this data might lead one to question why HBO₂T is not now standard care for TBI. The problem with the above studies is that none were blinded, there were no sham controls, and there was extreme variability in criteria of inclusion, time of enrollment, and type of treatment given.

Therefore, because these studies were so poorly controlled, it is impossible to say whether there was any overall benefit in the number of those who returned to reasonable cerebral function.

Study design

Patients arriving to the Emergency Department with a presumed diagnosis of diffuse axonal injury by history will be evaluated by a neurologist or neurosurgeon. Inclusions in the study require the patient, either male or female, be at least 18 years-old and have a Glasgow Coma Score (GCS) of 8 or less at time of presentation. HBO₂T must be initiated within 6 h of the traumatic event. Past medical history including mRS, will be gathered from family if present to assess for possible contraindications. If this information is unavailable the patient will be excluded. Patients with a premorbid mRS > 1 will also be excluded. Patients who require other intervention such as surgical hematoma evacuation or medical therapy including administration of agents to reduce ICP will not be excluded provided that HBO₂T is initiated within 6 h of the trauma.

An MRI with diffusion weighted imaging will be obtained at presentation to confirm type and extent of injury, and to assess for intracranial pathology that would warrant exclusion, as well as for comparison at a later date. ABC will be drawn and chest X-ray will be done to assess for underlying pulmonary disease which could be a contraindication for HBO₂T.

If no exclusion exists, the patient will be randomized immediately to HBO₂T or standard of care treatment. HBO₂T will consist of 100% oxygen at 2.4 ATA for 90 min daily for one week. Multiple dose therapy is selected because of the time course of secondary injury associated with TBI.

Myringotomy or temporary grommets will be at the discretion of the HBO₂T physician.

Patients will have a repeat MRI at 72 h for comparison. All patients enrolled will undergo mRS, Barthel index and Glasgow outcomes scale assessment at 7 days. These assessments will be repeated at 6 and 12 months. All evaluations will be done by examiners blinded to treatment status.

Primary outcomes will be modified Rankin scale score and mortality. Secondary outcomes will include Barthel index score, Glasgow outcome scale score, MRI appearance and need for ICP lowering therapy. Total doses of ICP lowering therapeutic agents or number of episodes of increased ICP will be tracked.

Secondary analyses should take into account the age of the patient at the time of injury as treatment with HBO₂T, an anti-apoptotic regimen, may have some deleterious effects on very young patients who are still undergoing planned apoptosis as part of normal brain development [53]. For similar reasons, there may also be some benefit, particularly in patients under age 25, to prolonged monitoring past one year for optimal outcome measures.

Radiation induced cerebral necrosis

Specific aim

Determine whether HBO₂T treatment of radiation necrosis of brain results in improvement of neurological function and reduction of necrosis.

Radiation induced cerebral necrosis (RICN) is a dreaded complication associated with the treatment of various brain pathologies (metastases, arteriovenous malformations) with radiotherapy or radiosurgery. The neurologic signs and symptoms that result are often progressive and can be difficult to distinguish from tumor recurrence [54]. The most common presentations involve headache and other signs of elevated intracranial pressure, but can also include cognitive changes such as short term memory loss, poor concentration, personality changes, and focal neurologic abnormalities such as hemi-paresis and aphasia [55].

Radiation necrosis tends to be a delayed toxicity from radiation and is often detected as a result of abnormal contrast enhanced imaging within the radiated field [56]. This is presumed to be due to radiation damage to the vasculature such that capillaries leak contrast dye. This effect also results in increased edema in the brain that can lead to signs and symptoms of elevated intracranial pressure. Although steroids may also have a stabilizing effect on the necrotic tissue, they tend not to reverse the radiation necrosis itself [57].

Various imaging studies have been performed to distinguish necrosis from tumor recurrence, as tumor recurrence would need further treatment and necrosis may be treated symptomatically with non-surgical interventions. MR spectroscopy, PET scanning, SPECT scanning and MR perfusion studies have been largely unsuccessful with insufficient sensitivity such that the gold standard of diagnosis is still surgical excision [58–60].

Treatment of radiation necrosis of the brain is difficult. Steroids tend to provide symptomatic relief and at the expense of significant side effects such as myopathy, hyperglycemia, osteoporosis and psychological manifestations. Surgical resection may stop progression, however, at the expense of a major operation. Often patients with metastatic disease are too sick to undergo such procedures and treated with prolonged steroids as the alternative [61]. HBO₂T has been very successful in treating radiation injuries in other tissues in
the body, such as the bladder and rectum. Given that endothelial cell damage and microvascular ischemia are considered to be part of the injury cascade in such soft tissue radiation injuries, hyperbaric oxygen therapy may be a viable treatment alternative for RIN as well [62].

There has been only one small, phases I–II randomized controlled study investigating the use of HBO2T in RIN. Hulshof et al. [63] randomized 7 patients with cognitive deficits at least 1.5 years after brain irradiation to receive either 30 HBO2T treatments at 3.0 ATA for 115 min, or no treatment. Using a battery of neuropsychological tests as outcome measures, they found a trend towards improved function at three months in the treatment group, but this result was not statistically significant. There have also been numerous anecdotal reports of efficacy and a few short uncontrolled series reporting positive results [64–67]. In the largest series, reported only in abstract form, Warnick et al. [68] included 29 patients with RIN of the brain receiving HBO2T at 2.5 ATA over 90 min for 20–60 treatments. All of the patients in the study had focal, progressive neurological deficits with increasing steroid requirements and an MRI showing a ring-enhancing mass with surrounding edema consistent with necrosis. In this series, 27 of the 29 patients showed improvement or stabilization of symptoms, decreased steroid requirement, and improved MRI appearance. The 2 patients who worsened were shown to have tumor progression. Interestingly, the greatest benefit was noted in a subset of 4 patients with benign underlying pathology (meningioma and AVM), Chuba et al. [69] also reported benefit in a group of 10 pediatric patients who underwent HBO2T after a diagnosis of RIN and failure of traditional steroid therapy. All ten patients showed clinical improvement or stabilization both initially and at follow-up, while 5 of the 6 surviving patients showed continued improvement. The 4 deaths in this group were attributed to tumor progression.

The evidence suggests that in cases where either the patient is not improving on medical therapies, such as steroids, or when surgical resection is not possible, HBO2T could be considered as a treatment option. Due to the lack of studies currently available in this field, there is a definite need for both more and larger randomized trials utilizing HBO2T for the treatment of RIN.

If no exclusion exists, the patient will be randomized to HBO2T or standard of care treatment. HBO2T will consist of 100% oxygen at 2.4 ATA for 90 min daily, at least 5 days per week, for 30 treatments. The selection of this regimen is based both on the safety and efficacy observed in other FDA approved uses including radiation necrosis of non-neural soft tissues.

All patients will be monitored throughout their treatment period for progression of symptoms and their steroid requirement. They will also receive repeat MRI scans of the head after completion of the treatment protocol (30 days) and again and at 90 days following completion of treatment protocol. Formal neuropsychological evaluation will be done at enrollment and repeated at 90 days post-treatment. Quality of life measures, such as the EORTC QLQ-C30 and BN 20 will be administered at enrollment and 90 days as well [70, 71].

Primary outcomes will be progression, stabilization or resolution of symptoms measured by the neurologist, as well as progression, stabilization, or resolution of the lesions on MRI imaging where RECIST (response evaluation criteria in solid tumors) criteria will be applied [72]. Secondary outcomes will include change in neuropsychological measures and, the steroid requirement as compared to control. All measures will be assessed at 90 days post-treatment.

## Migraine

### Specific aim

To determine whether use of HBO2T will relieve headache pain in status migrainosus.

Migraine is a common disorder. One-year prevalence is approximately 18% and 7% for American woman and men, respectively [73]. Status Migrainosus, as defined by The International Headache Society’s International Classification of Headache Disorders, 2nd edition [74], is a migraine attack lasting more than 72 h that is typical of previous attacks except in duration, and that cannot be attributed to another disorder. While usually felt to be a rare phenomenon, in a recent retrospective study, 20% of migraineurs reported episodes which met these criteria [75]. Current knowledge suggests that primary neuronal dysfunction leads to intracranial and extracranial changes that account for migraine [76]. Those prone to migraine have a genetic migrainous threshold that leaves them susceptible to acute attacks, dependent on the balance of excitation and inhibition at various levels of the nervous system. Genetic and environmental factors both play a role [77]. Nevertheless, it is believed that vasodilatation still plays an integral part in the severe throbbing pain characteristic of migraine, likely secondary to instability in the central neurovascular control mechanism [78]. It has been suggested that prolonged dilation of blood vessels is associated with an increased risk of stroke [74]. Additionally, it has been theorized that release of nitric oxide by nerves, vessels, or brain tissue may be part of the trigger of migraine pain [79]. Hyperbaric oxygen causes cerebral vasoconstriction, likely though scavenging of nitric oxide [80] and thus the effect of HBO2T might improve pain directly through decreases in NO as well as through vasoconstriction and anti-inflammatory mechanisms.
There is some evidence that HBO₂T is an effective treatment of acute migraine attack. Wilson et al. [81] assigned female subjects with confirmed migraine to either 100% oxygen at normal pressures, or hyperbaric oxygen. They found that subjective pain was significantly reduced in the group receiving hyperbaric oxygen, but not following control treatment. They concluded that HBO₂T is effective for migraine pain, and the patient’s subjective pain assessment was the best indicator of relief. In a double blind, placebo-controlled study by Eftedal et al. [82] the prophylactic effect of HBO₂T on migraine was investigated. Forty patients were randomly assigned to a treatment group receiving three sessions of hyperbaric oxygen, or a control group receiving three hyperbaric air treatments. Patients kept a standardized migraine diary for eight weeks before and following treatments. Thirty-four patients completed the study. Their primary measure of efficacy was the difference between pre- and post-treatment hours of headache per week. The results showed a non-significant reduction in hours of headache between groups. Levels of endothelin-1 in venous blood pre- and post-treatment showed no difference between the hyperbaric oxygen and control groups. They concluded that the tested protocol does not show a significant prophylactic effect on migraine and does not influence the level of endothelin-1 in venous blood. Bennett et al. [83] conducted a meta-analysis on randomized trials comparing HBO₂T or normobaric oxygen with placebo or no treatment in patients with migraine headache or cluster headache. Nine small trials were included which involved 201 participants. Five trials compared HBO₂T vs sham therapy for migraine. Pooling data from three trials suggested that HBO₂T was effective in relieving migraine headache compared to sham (relative risk (RR) 5.97, 95% confidence interval (CI) 1.46–24.38, P = 0.01). However, no evidence was found for prophylactic use. No reduction in the incidence of nausea and vomiting was seen. Neither was there a reduction in rescue medication requirements. We are not aware of data looking at HBO₂T as a therapy for status migrainosus.

Study design

Patients arriving to the Emergency Department with a presumed diagnosis of status migrainosus by history will be evaluated by a neurologist. Inclusion in the study requires that the patient, either male or female, be at least 18 years-old and have prior history of migraine consistent with current headache except in duration. Headache must have been present for a minimum of 72 h, with no period of time being pain free greater than 4 h. Past medical history will be gathered to assess for possible contraindications. Other causes of headache will be ruled out with appropriate imaging and laboratory studies. Patients with headache possibly attributed to other cause will be excluded. Patients without prior migraine, with sudden onset pain (i.e. thunderclap headache), with focal neurologic deficits (other than visual field changes), or other evidence of underlying neurologic pathology will be excluded. Head pain must be refractory to current standard or care treatment for status migrainosus. If pain responds to treatment, as defined by a 50% reduction in pain on a 10 point visual analog pain scale, the patient will be excluded.

A CT of the head at presentation will be obtained to assess for intracranial pathology that would warrant exclusion. Subjects should be screened to exclude significant risks for undergoing an extended course of HBO₂T including ejection fraction of <35%, an ABG, and radiographic evidence of pulmonary blebs or bullae. Prior to treatment the patient will report subjective level of pain based on the visual analog pain scale, due to prior studies showing this measure was the best indicator of relief.

If no exclusion exists, the patient will be randomized to HBO₂T or sham treatment. Only the technician administering the therapy will be aware of which treatment the patient receives. HBO₂T will consist of 100% oxygen at 2.4 ATA for 90 min for one treatment.

Post-treatment the patient will again be assessed for pain based on visual analog pain scale. A positive response will be defined as a 50% pain reduction using a 10 point visual analog pain scale which will serve as the primary outcome of the study. Patients will also be assessed, directly or by phone, at 24 and 48 h for duration of the effect of the therapy and frequency of recurrence of migraine pain.

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According to order.

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None declared.

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