

# HYPERBARIC OXYGEN THERAPY FOR MULTIPLE SCLEROSIS RELAPSE

## Protocol

Amendment # 2  
Protocol Version 2/24/15

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**A. Specific Aim 1:** To determine whether use of hyperbaric oxygen improves clinical parameters at baseline versus 6 months. The clinical parameters to be evaluated are:

- 1a) Kurtzke Expanded Disability Status Scale (EDSS)
- 1b) Multiple Sclerosis Functional Composite (MSFC)
- 1c) Symbol Digit Modality Test (SDMT)
- 1d) Low Contrast Visual Acuity

**Specific Aim 2:** To determine whether use of hyperbaric oxygen impacts MRI parameters. MRI parameters will be evaluated at baseline and 6 months to determine:

- 2a) Thalamic volume loss
- 2b) Magnetization transfer ratio (MTR) change in baseline lesions.
- 2c) Magnetization transfer (MT) histogram whole brain and normal appearing brain tissue change (white matter and gray matter).
- 2d) Accumulation of new T2 and CE lesions.
- 2e) T2 brain lesion volume change.

**Specific Aim 3:** To determine whether use of hyperbaric oxygen improves patient reported outcomes. (PROs). The PROs to be evaluated during the study are:

- 3a) Fatigue impact scale change.
- 3b) Beck depression scale.
- 3c) MSIS-29.

## **B. Background and Significance/Preliminary Studies**

Previously hyperbaric oxygen has been studied for treatment of MS with very mixed results. These preliminary studies suggest a positive, though transient effect of HBO on advanced multiple sclerosis which warrants further studies (3). Hyperbaric oxygen is not currently a proven therapy for MS, although a number of patients use it and anecdotally report benefit. In a Cochrane analysis review (1), it is clear that prior randomized studies of hyperbaric oxygen focused on progressive MS, used it as monotherapy, and looked mainly for an impact on EDSS disability and symptoms. These studies also used higher atmosphere oxygen than 1.5, which could actually be detrimental. This study focused on sensitive MRI techniques will evaluate the impact of hyperbaric oxygen on relapsing MS. No prior study examined the benefits of hyperbaric oxygen to treat acute MS relapses, as an adjunct to standard steroids. Therefore this study will chart new territory. It will use new outcomes, and will evaluate patients by very sensitive nonconventional imaging techniques, as well as by clinical evaluation and self-report.

There is accumulating data that MS may have a vascular component, with association of macroscopic lesions to small venules, endothelial pathology, and blood brain barrier leakiness. Hyperbaric oxygen improves both mitochondrial metabolism and tissue oxygenation, and has shown neuroprotective effects in traumatic brain injury models (5). HBO can also stimulate expression of trophic factors and improve neurogenesis and gliosis (2). It is possible that it could have a benefit at the time of an acute MS relapse, when there is increased permeability, edema, and local brain disruption. Previous studies have also shown that hyperbaric oxygen improves immunological parameters in multiple sclerosis patients including total and helper T lymphocyte counts (4). A similar pilot study to the one being proposed showed that HBO therapy combined with intravenous edaravone was effective for the treatment of patients with acute embolic stroke (6). Another study involving stroke patients showed that HBO improved neurological function and quality of life, along with clinical improvement confirmed by SPECT imaging (7).

Given the encouraging results involving different neurologic issues and the use of hyperbaric oxygen, along with the need for more data to be collected involving relapsing MS and HBO, this is a study with great potential.

## **C. Research Design and Methods**

### **1. Rationale/Overview**

This is a pilot (proof of principle) study which will explore the potential benefit of hyperbaric oxygen for relapsing MS. This is a 6 month study. It is estimated to last 18 months, with recruitment over the first year. Outcomes will be compared between the group who receives the hyperbaric treatment vs. those who do not. Analysis of covariance will be used to compare baseline score changes based on group assignment.

## 2. Research Sites

Patients will be seen by Dr. Coyle at Stony Brook University's MS Comprehensive Care Center for their study visits. Patient MRIs will be conducted at the Zwanger & Pesiri facility located in Stony Brook. MRIs will be done at Zwanger & Pesiri because of their three 3T machines in the area along with a guaranteed rapid screening while the patient is relapsing. Patient MRIs will be sent to SUNY Buffalo for a blind reading. If a patient is randomized to receive hyperbaric oxygen therapy they will go to Hyperbaric Medical Solutions located in Medford or Woodbury.

## 3. Study Sample

This study will enter 30 patients with relapsing forms of MS. Patients will be randomized to receive adjunctive hyperbaric oxygen treatment (n=15), or not (n=15). All 30 patients will undergo baseline and 6 month analysis.

## 4. Screening

### **Inclusion criteria:**

- Patients will meet International Panel 2010 diagnostic criteria
- Relapsing form of MS
- Disease duration 10 years or less
- Age 18 to 50 years.
- Chest x-ray within the last 12 months with results
- Negative pregnancy test in females of childbearing potential
- Willing to commit additional time if randomized to Hyperbaric Oxygen (Initial interview/physician/safety lecture; 1 hour per day, 5 days per week, for 4 weeks)

### **Exclusion criteria:**

- Unable or unwilling to undergo hyperbaric oxygen therapy, or MRI scan.
- Significant comorbidity that would make it difficult to participate in the study and/or judge treatment response (congestive heart failure, cardiac or respiratory disease, tympanic membrane injury/ear disease/cataracts.)
- Kidney disease
- Implanted devices (i.e. pacemaker)
- Unable or unwilling to remove the following for hyperbaric oxygen treatments:
  - a. Deodorant
  - b. Lotion (petroleum based hair or body products)
  - c. Perfume or cologne
  - d. Mousse, gel, or hairspray
  - e. Makeup
  - f. Jewelry

- g. Watches or any metal objects
  - h. Hair accessories
  - i. Hearing aids
  - j. Contact lenses
  - k. Thermacare heat wraps/warmers
  - l. Dentures
  - m. Prostheses
  - n. Food, gum, candy, alcohol(within 8 hours), carbonated beverages
  - o. Petroleum based products or sulfamylon dressings
  - p. Acrylic nails, silk wrap nails, nail polish
  - q. Silk tape
  - r. Transderm medication patches
  - s. Velco products
  - t. No hair dye within 48 hours
- IV medication cannot be used during hyperbaric oxygen treatments. If you are on IV medication and you are unable or unwilling to stop your IV therapy you will be excluded from the study.

Patients being considered for the study will be screened by the study coordinator/Dr. Coyle to see if they meet eligibility criteria. Eligible patients will be offered entry, and if they agree will sign the consent.

## **5. Procedures**

After the patient is consented, the baseline assessment will involve physical and neurologic examination including EDSS, MSFC, SDMT, low acuity vision testing, completion of PROs (Fatigue impact scale, Beck depression scale, MSIS-29), and baseline brain MRI with and without contrast. Following MRI completion, the study coordinator will randomize the patient to hyperbaric oxygen or no oxygen (patients are unblinded). Dr. Coyle and the MRI reading site will be blinded to treatment arms.

The hyperbaric oxygen therapy will consist of an initial safety lecture, interview and brief physical lasting 30 minutes, followed by 20 sessions (5 per week) at 1.5 atmospheres for 1 hour each. These sessions allow patients to breathe 100% pure oxygen in a private pressurized acrylic chamber, allowing more oxygen to flow through the bloodstream to improve healing. Patients who are randomized to receive hyperbaric oxygen treatment will sign an additional consent form.

It is expected that most patients will be on MS disease modifying therapy (DMT). It is possible that DMT therapy will be started, or switched, during the study. DMT therapy status will be recorded, but will not influence randomization or study conduct.

Patients will return at 24 weeks for a brief physical examination, EDSS, MSFC, SDMT, low acuity vision testing and the PROs. Dr. Coyle will evaluate and treat all patients but remain blind to the randomized group. The study coordinator will screen and evaluate all patients,

and be in monthly contact throughout the study. The 24 week final visit will include a repeat brain MRI with and without contrast.

## D. Statistics

### 1. RANDOMIZATION:

Using a computerized random number generator, participants will be assigned in consecutive order to one of two groups using a one to one ratio. The first group will receive adjunctive hyperbaric oxygen (n = 15); the second group will not (n = 15). The randomization scheme will be limited so that no more than three consecutive participants can be placed in the same group. Randomization will be non-stratified.

### 2. CLINICAL ANALYSIS (as defined by Specific Aims)

Specific Aim 1: To determine whether use of hyperbaric oxygen improves clinical parameters. The clinical parameters to be evaluated are:

1a) Kurtzke Expanded Disability Status Scale (EDSS) at 6 months compared to baseline.

**For each patient, EDSS at baseline will be compared to EDSS at 6 months. Patients will be categorized as improved (negative delta), stable (0 delta), or worsened (positive delta). Proportions for each of the categories will be compared using chi square. An additional analysis will compare the proportion persons in each group who improve to those who have not (either stable or worsened).**

1b) Multiple Sclerosis Functional Composite (MSFC) at 6 months compared to baseline.

**For each patient, MSFC at baseline will be compared to MSFC at 6 months. Patients will be categorized as improved (negative delta), stable (0 delta), or worsened (positive delta). Proportions for each of the categories will be compared using chi square. An additional analysis will compare the proportion persons in each group who improve to those who have not (either stable or worsened).**

1c) Symbol Digit Modality Test (SDMT) at 6 months compared to baseline.

**For each patient, SDMT at baseline will be compared to SDMT at 6 months. Patients will be categorized as improved (negative delta), stable (0 delta), or worsened (positive delta). Proportions for each of the categories will be compared using chi square. An additional analysis will compare the proportion persons in each group who improve to those who have not (either stable or worsened).**

1d) Low Contrast Visual Acuity at 6 months compared to baseline.

**For each patient, Low Contrast Visual Acuity at baseline will be compared to Low Contrast Visual Acuity at 6 months. Patients will be categorized as improved (negative delta), stable (0 delta), or worsened (positive delta). Proportions for each of the categories will be compared using chi square. An additional analysis will compare the proportion persons in each group who improve to those who have not (either stable or worsened).**

Specific Aim 3: To determine whether the use of hyperbaric oxygen improves patient reported outcomes. (PROs). The PROs to be evaluated during the study are:

3a) Fatigue impact scale change.

3b) Beck depression scale change.

3c) MSIS-29 change.

**Data for each of the outcomes 3a through 3c will be evaluated at 0 and 6 months, and analyzed using ANCOVA (analysis of covariance) controlling for baseline values.**

### 3. MRI ANALYSIS:

Image analysis will be performed at the Buffalo Neuroimaging Analysis Center (BNAC); see <http://www.bnac.net>. The operators will be blinded to patients' clinical characteristics and clinical status. Analysis will be performed on a Gentoo GNU/Linux workstation (Kernel Version 2.6.7; Gentoo Technologies, Inc. Boston, MA, USA). At all stages of manual, semi-automated and automated analyses, quality-control montage imaging output analyses files will be examined by an expert observer. If a value is missing at baseline, or if no post-baseline value is available for a subject, then the mean value will be calculated at the specified visit using all available data.

#### 3.1. LESION ACTIVITY ANALYSIS:

All number and activity analysis will be performed at time points 0 and 24 weeks.

##### Gd lesions:

A new Gd-enhancing lesion will be defined as a typical area of hyperintense signal on post contrast T1-WI according to the guidelines by Barkhof et al. ([Barkhof et al., 1997](#)). Other Gd-based MRI lesion activity outcomes will include the number of total Gd-enhancing lesions per patient and the number of persistent Gd-enhancing lesions (enhancing lesions also present on the previous scan) ([Zivadinov et al., 2004](#)).

##### T2 lesions:

A new or newly enlarging lesion on T2-weighted images will be defined as a rounded or oval lesion arising from an area previously considered normal appearing brain tissue (NABT) and/or

showing an identifiable increase in size from a previously stable-appearing lesion according to the guidelines by Filippi et al. ([Filippi et al., 1998](#)).

Other T2-based MRI lesion activity outcomes will include the number of new active lesions (the number of new enhancing lesions plus the number of new or newly enlarging, non-enhancing lesions on T2-WI), as well as the number and percent of active scans showing one or more new enhancing or new or newly enlarging T2 lesions and the number of persistent T2 lesions (T2 lesions also present on the previous scan). An active scan will be defined as a scan showing any new, enlarging or recurrent lesion on post contrast T1- and T2-WI.

### 3.2. QUANTITATIVE LESION ANALYSIS:

All lesion volume (LV) analyses will be performed for Gd lesions at 0 and 24 weeks.

Data will be analyzed using JavaImage (version 4.0, Xinapse Systems, Northants, UK, <http://www.xinapse.com>).

#### Gd-LV:

For analysis of hyperintense T1 post-contrast lesion volume T1-WI will be used. We will determine the volume of Gd-enhancing lesions on the post-contrast T1-WI ([Zivadinov et al., 2004](#)).

#### T2-LV:

For analysis of hyperintense T2 lesion volume (LV) FLAIR images will be used. Our method of quantifying the total brain hyperintense LVs has been previously described in detail ([Zivadinov et al., 2001a](#); [Zivadinov et al., 2001b](#)). Briefly, the T2-LVs will be calculated using a highly reproducible semiautomated local thresholding technique for lesion segmentation. The T2 lesions will be outlined on T2 images on each axial slice. In a previous study, mean COV for T2-LV was 1.1% (range 0.9 to 3.5) for inter-observer reproducibility and 1.5% (range 1.0 to 4.1) for intra-observer reproducibility ([Zivadinov et al., 2001a](#); [Zivadinov et al., 2001b](#)).

### 3.3. QUANTITATIVE THALAMUS ATROPHY ANALYSIS:

All thalamus volume analyses will be performed at months 0 and 24 weeks.

We will use FMRIB's FIRST software to segment high resolution 3D T1-weighted images (<http://www.fmrib.ox.ac.uk/fsl/first/index.html>) at 0, 6 and 12 months. Briefly, FIRST is a model-based segmentation/registration program that uses shape/appearance models constructed from manually segmented images. The manual labels are parameterized as surface meshes and modeled as a point distribution model. Deformable surfaces are used to automatically parameterize the volumetric labels in terms of meshes; the deformable surfaces are constrained to preserve vertex correspondence across the training data. Normalized intensities along the surface normals are sampled and modeled. The shape and appearance model is based on multivariate Gaussian assumptions. Shape is then expressed as a mean with modes of variation (principal components). Based on the learned models, FIRST searches through linear combinations of shape modes of variation for the most probable shape instance given the observed intensities in the

input image. Volumetric data for thalamus will be acquired, as previously described. ([Zivadinov et al., 2012](#)) We will then obtain absolute and percent changes of these volumes between baseline to 24 weeks.

#### 3.4. QUANTITATIVE MAGNETIZATION TRANSFER ANALYSIS:

Proton density (PD), and proton density with a magnetization saturation pulse (PT+MT) will be used in our study to measure magnetization transfer ratio (MTR). The analysis requires several rigid body registration steps performed by a software program (FLIRT) (Smith et al., Neuroimage 2002). In these steps, all images—mfast segmented mask, PD+MT, and pseudo FLAIR—are registered to the PD image, and transformation matrices are saved for subsequent use. The mfast segmentation of the native space is performed. The output segmentation map of the mfast program is then retrofitted to match PD space using the transformation matrix created earlier (FLIRT). Lesions, which are traced by trained operator, are then transformed to correspond to lesion areas on PD using the pseudo FLAIR transform matrix. The segmentation mask is then split into 3 component images—GM, WM and CSF—and each is made into a binary mask. The CSF image is dilated by 1 pixel, decreasing partial volume effects [[ImageJ-http://rsb.info.nih.gov/ij/](#)], and applied to both GM and WM masks, minimizing the erroneous inclusion of CSF in the parenchyma. An algebraic sum of GM and WM masks is applied to the PD image to generate a whole brain mask, where all extra-parenchymal tissues and CSF are removed. The lesion mask is then applied to the PD image, creating a PD image indicative of NABT. This image is saved, and used to generate two additional images in which only NAWM and NAGM are saved. Lastly, a mask consisting of only pseudo FLAIR lesions is applied to the PD. Five different PD images are used to calculate five different MTR maps for NABT-MTR, NAWM-MTR, NAGM-MTR, and Gd and T2 lesion MTR. For each image, our algorithm automatically saves histogram characteristics of mean MTR. To calculate these values, the PD and PD+MT images are algebraically combined to create an MTR map by performing the following calculation on a voxel-by-voxel basis:  $MTR = [(M0 - MS) * 100] / M0$ , where M0 represents the proton density signal intensity and MS represents the PD signal intensity with the magnetization saturation pulse. The above calculation is performed on each variant PD image using the JavaImage software. A montage image showing each slice of the MTR images is created for quality control checking. In the previous study (Zivadinov et al. Hum Mol Gen, 2007) the scan-rescan coefficient of variation (COV) was 0.1% for WB-MTR, 0.3% for NAGM-MTR, 0.4% for NAWM-MTR and 0.3% for NABT-MTR.

#### **E. Funding Status/Details**

This study will be funded by the Cure MS Foundation of New York.

#### **F. Human Subjects Research Protection From Risk**

##### **Risks to Subjects**



- For the MRI scan, subjects will have a contrast agent (gadolinium) injected into a vein. Gadolinium causes some people to experience a metallic taste, nausea, dizziness, headaches and on rare occasions, kidney damage. Some people feel claustrophobic during the MRI and lying still may be uncomfortable. There is a potential risk of nephrogenic systemic fibrosis (NSF) in patients with renal failure. Therefore, patients with kidney disease should be excluded. Subjects should not have an MRI if they have devices or implants such as pacemakers, metal bone pins, baclofen pump, cerebral aneurysm clips or have had a heart valve replaced, or if they have had any other type of device placed inside their body for medical reasons, they should inform you as they may not be able to have an MRI.
  
- For subjects randomized to receive hyperbaric oxygen there are minimal risks associated with treatments. These risks will be explained in full detail during the initial safety lecture at Hyperbaric Medical Solutions. They include:
  - Barotrauma (Pain in the ears or sinuses)
  - Cerebral air embolism and pneumothorax (air in the lungs)
  - Oxygen toxicity
  - Risk of fire
  - Risk of worsening near-sightedness
  - Temporary improvement in far-sightedness
  - Maturing or ripening cataracts
  - Fluid in the ears
  - Numb fingers
  - Ingestion of chemicals into the body which may affect the efficacy and success of hyperbaric treatment may occur if you smoke cigarettes, pipes, cigars, or any other form of tobacco or chewing tobacco.
  - Upset stomach as a result of carbonated beverages before treatment
  - Pressure intolerance due to a permanent implanted device (pacemaker, insulin pump, implanted pain pump, etc.)
  - You should let the technician know of the following as they may put you at risk:
    - if you have any cold or flu symptoms, fever, sinus, or chest congestion
    - if there is a chance you are pregnant
    - if there has been a change in your medication
    - if you have been recently hospitalized
    - if you did not eat before your treatment
    - if you are a diabetic and did not take your insulin
    - if you have any concerns at all

### **Adequacy of Protection Against Risks**

Patients will be monitored closely by Dr. Coyle and the study coordinator. Dr. Coyle will remain blind to the randomized group and the study coordinator will be in monthly contact with the study patients. Dr. Coyle will continue to treat these patients for any unscheduled visits if it becomes necessary. These visits will be facilitated and documented through the study coordinator. All risks that exist in this study are characterized as minimal.

### **Potential Benefits of Proposed Research to Subjects and Others**

This study will look at hyperbaric oxygen therapy to see if there is an improvement in clinical parameters. It is possible that hyperbaric oxygen lesson ongoing damage to the central nervous system. Based on properties of hyperbaric oxygen that would improve oxygen delivery to central nervous tissue there is a possibility that clinical status will improve and tissue damage will be less with hyperbaric oxygen therapy. If the preliminary data is promising and shows that hyperbaric oxygen improves MRI and clinical parameters, additional studies will be done. If no benefit is seen from the use of hyperbaric oxygen, it will not be worthwhile to study further.

### **Importance of the Knowledge to be Gained**

MS is a major neurological disorder effecting young adults. It involves ongoing injury. Treatments that decrease disease damage would be extremely beneficial and might offer a new therapy.

## **H. Data Safety Monitoring Plan**

Data will be collected and recorded by the study coordinator under the supervision of the PI. Data will be stored in a locked, secure location by the study coordinator. As results are collected throughout the study, any adverse events will be identified and reported to the principle investigator. Adverse events will be categorized according to the Common Terminology Criteria for Adverse Events (CTCAE). Adverse events will also be reported to the IRB upon annual study renewal. The principle investigator will determine the relationship of the event to the study and decide course of action for the study participant. If an event is deemed to be a serious adverse event by the PI the IRB will be notified immediately along with other necessary study personnel including the sponsor, institutional officials, and coordinating research sites (SUNY Buffalo, Hyperbaric Medical Solutions, Zwanger & Pesiri). If a subject is experiencing a serious worsening of their MS, another serious illness, or side effects as a result of participation in the study it may be determined by the PI that it is in their best interest to stop participating.

Monitoring will be conducted monthly via internal audits. Dr. Lauren Krupp (444-2599) will be responsible for these safety reviews based on her Multiple Sclerosis expertise and extensive experience with clinical trials. She will be responsible for monitoring the following:

- only subjects who meet the inclusion/exclusion criteria are enrolled
- no study procedures are taking place prior to obtaining informed consent
- data is being collected and analyzed according to the protocol
- adverse events are being reviewed promptly and reported appropriately
- privacy and confidentiality of subjects is being maintained according to the informed consent form
- data is being stored securely
- any dropouts/early terminations have been documented

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