HYPERBARIC OXYGENATION IN THE ACUTE STROKE

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Pressurized oxygen delivers free molecular oxygen immediately available for metabolic use to the cells without energy exchange, even in the absence of circulation
– *Edward Teller Ph.D.*
(Father of the Hydrogen Bomb)

Purpose

Suggestive Clinical work and data in the literature are that hyperbaric oxygenation may play an integral role in the treatment of early stroke. In 1998, a special meeting was convened in Washington, DC, to review this possibility and to devise a protocol (1) for further evaluation of said therapy. An abbreviated protocol will be included in this paper along with a biostatical analysis of the 1980 Neubauer and End paper (2).

Summary

Approximately 600,000 cases of stroke occur each year in the United States, i.e., one every fifty-three seconds. Medical bills and lost earnings of Americans who suffer stroke each year total forty-one billion dollars. Irrespective of all attempted therapies including thrombolysis, calcium channel blockers, glutamine antagonist, steroids, lazroids, etc., the basic deficit is that of oxygen reduction or deprivation. In our original paper (2) we were able to confirm previous observations that early intervention was critical for maximum improvement. Our early data strongly indicated that after four-to-six-hour window to approximately one week, hyperbaric oxygenation was not nearly as dramatic or effective as in the initial stages. Earlier intervention rendered a more pronounced effect on stopping or limiting the ischemic cascade (3) associated with multiple biochemical actions that take place as the body's defense against hypoxia. Our interpretation is that after the acute ischemic cascade, a settling process is mediated with the establishment of the ischemic penumbra. This is believed to be a zone surrounding the potentially irreparably damaged epicenter where cells are receiving enough oxygen to exist, but not enough to fire electrically. More potentially viable cells occur towards the periphery. It is not dissimilar to the atomic bomb where there is an epicenter of irreparable destruction, but fanning out towards the periphery, there is the possibility of viability. Basic research has demonstrated that the problem is more related to oxygen availability rather than blood flow (4). This paper relates only to acute ischemic thrombosic stroke treated within the first four hours prior to the established full ischemic penumbra. Yet, post mortem neurons are capable of transporting even eight hours after death (5). Much animal work has been performed substantiating this clinical approach (6). A later paper will discuss the potential reversibility of late stroke by identification and reactivation of the ischemic penumbra.

Introduction

One thousand cases of hyperbaric oxygenation therapy for acute stroke with intervention ranging from four hours to one week are in the literature. Work observation by Ingvar and Lassen (7) published the first report on the treatment of four stroke patients with hyperbaric oxygenation. The overall results showed a regression of EEG changes during treatment with hyperbaric oxygenation. Hayeman and Saltzman (8) published 22 of cases with some excellent results. Nighogossian (9) performed a double blind study utilizing a time factor of entry up to 24 hours. Anderson (10) in a control study showed that with a late entry the tendency toward poor results occurred with the hyperbaric oxygenation. The Russians (11) have done extensive work. A critical time factor of four hours and a specific protocol for hyperbaric oxygenation in the acute stroke were published in 1980.

Many of the above papers, with the exception of Hayeman and Saltzman, and Ingvaar, showed a delayed time of entry into the treatment. They were from 24-hours to a week. Appropriate pressures were not used. Frequency of treatments and the total number of treatments were also inadequate. Imaging data was not available. In the original paper (2) by Neubauer and End (a visionary genius of hyperbaric oxygen), they described the treatment of 122 acute and long-term stroke patients. Sixteen acute stroke patients were treated within the four-hour window. Of this group, 25-percent were discharged within 24-hours of hospitalization to continue outpatient hyperbaric oxygenation with PT (physical therapy), OT (occupational therapy) and speech therapy. This was the first paper to use a specific protocol suggesting that the pressure be 1.5-2.0 ata. End used a multistation chamber with masks, thus, 2.0 ata. Neubauer used 1.5ata monoplace plus pressurized with 100-percent oxygen, explaining the difference in the ata's. A specific protocol was suggested that the acute stroke patient be treated every six hours around the clock until stabilized with a total of 10-20 treatments for each patient.

It is noted that the four-hour time period is critical both for hyperbaric oxygenation, as well as for the thrombolysic drugs. This raises the point that perhaps many of the beneficial effects derived with each of the approaches may have been used in the patients with transient ischemic attacks (TIA). It must be noted that one, however, does not have the luxury to wait 24-hours to see the result. Recent imaging data suggest that the difference between a TIA and an acute thrombosic stroke may be ascertained within a six-hour period (12). Accepting the early time frame requires major education of the public to have the stroke patients brought to the hospital within such a short period. Only six-percent of the patients in the United States have received thrombolysis.

Besides the rapid discharge for the treated four-hour time window patients, the reduction was in disability, and the savings were significant. Another important observation was the fact that the patients receiving hyperbaric oxygenation had less nursing home care even in the later stroke. The original paper, Neubauer and End, was later revisited by Manly Boss, PhD, a bio-statistician from Florida Atlantic University. A control study clearly showed that although the morality rate was basically the same, the long-term care was significantly reduced. Again, a major factor in savings.

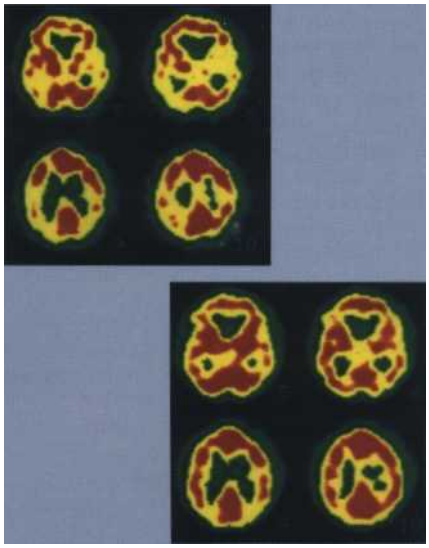
Materials and Methods

The current technique used at the Ocean Hyperbaric Center, Inc., is SPECT (Single photon emission computerized tomography) scanning before, and after hyperbaric oxygenation intervention. More work is being done with the diffusion weighted MRI's. Visualization and documentation are essential. The tracers used are Technetium-99m HMPAO (Ceretec) or (Neurolite), which cross the blood brain barrier and have 80-percent first extraction fraction. This measures not only blood flow, but also metabolism. With a split dose imaging before and after a single session of hyperbaric oxygenation, the predictability of stroke outcome may be almost immediate. Final results with thrombolysis may require three months.

Case Reports with Pictures

The case report presented here in this article hopefully will be substantiated with a large series. This was a mid-seventy year old white male with a left mid cerebral thrombosis (progressive right side weakness, dizziness, confusion and swallowing difficulties). Within two hours of ictus, he had his first SPECT scan using a split regime. One hour of hyperbaric oxygenation 1.5 atmospheres absolute (ata) in a monoplace chamber was accomplished. The remaining dose of Technetium was administered and the scan was repeated within two hours. SPECT scans clearly

showed deficit in the area of the left mid cerebral artery prior to the administration of hyperbaric oxygen. There is reduced flow in the left temporal lobe, basal ganglia and posterior occipital lobe on the right.



The frontal lobes were poorly perfused, being worse on the left. Following the hyperbaric oxygenation treatment, there is marked improvement in perfusion and metabolism throughout the entire distribution of the mid cerebral artery. The patient was treated as an outpatient with two hyperbaric oxygen treatments per day with a total of 16 treatments. At this time he had only minimal neurological deficits. A repeat scan three months later snoweu a normal pattern. With all stroke patients, it is important to incorporate modalities of PT (physical therapy), OT (occupational therapy), speech therapy, nutritional counseling, and bio-feedback.

SPECT scans: The pictures represent axial views before and after one hour of hyperbaric oxygenation. A description of the changes is in the above text. A clinical parallel was evident.

Conclusions

Because of certain rapid physiological effects of hyperbaric oxygenation, it may perhaps be a treatment of choice.

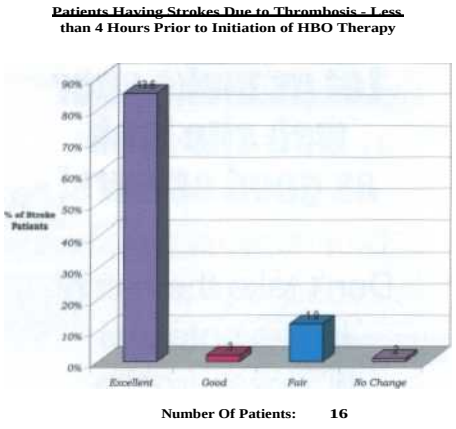
1) It reduces cerebral edema-focal and generalized.
2) It overcomes ischemia hypoxia, thus stopping or reducing the ischemic cascade.
3) It protects the integrity of the cell membrane and restores the integrity of the blood brain barrier.
4) It neutralizes toxic amines.
5) It neutralizes free radical.
6) It reduces the adhesiveness of the red cell and stickiness to the platelets to the endothelium.
7) It efficiently elevates the driving force for oxygen making increasing tissue space availability.
8) It reactivates dormant idling hypoxic neurons.
9) It reduces lactate peaks.

There is a strong suggestion in the literature that hyperbaric oxygenation may be an effective treatment for the acute ischemic thrombotic. Data from the original Neubauer and End paper are presented once again stressing the four-hour time window and suggesting that this may be a critical factor. Other publications are reviewed and the flaws are noted as to the time of intervention into the study, patient selection, protocols, etc. A brief review of the effects of hyperbaric oxygenation in acute stroke is noted. Finally, in order to ascertain the effectiveness of hyperbaric oxygenation in the acute stroke, Dr. James Toole, professor of Neurology at Bowman Gray University of Winston Salem, NC, convened several conferences with experts from around the world particularly relating to space and underwater medicine. A major meeting was held in Washington DC in 1988, at which time Drs. Virginia and George Howard, professors of bio-statistician at the University of Alabama, along with about 30 scientists and doctors, devised a protocol to attempt to ascertain the true effectiveness of hyperbaric oxygenation in early stroke. An abbreviated protocol is attached to this paper. Should these results be positive, formal grant applications will then be requested from NIH and MINDS. For information please see the last page of the protocol where the full instructions may be obtained.

PROTOCOL FOR STUDY

Specific Aims:

1. To evaluate if hyperbaric treatment has a neuroprotective effect with a potential reduction in morbidity measured by sequential SPECT imaging. This effect will be evaluated after a single hyperbaric treatment, after a comprehensive 5-day/12-treatment protocol, and after a 3-month follow-up period. In addition, differences between groups in the volume of infarcted tissue at 3-months by CT scan will be assessed.
2. To assess if there is a decreasing efficacy of hyperbaric treatment to spare brain tissue with increasing time after onset of stroke symptoms.
3. To assess if the use of tPA is associated with a differential efficacy of hyperbaric treatment to spare brain tissue.



4. To gather initial data on the impact of hyperbaric therapy on clinical outcome, survival (composite functioning scales (SSS, Barthel, Rankin), and development of subsequent stroke.
5. To assess logistic challenges and patient acceptability of hyperbaric treatment.

Eligibility: Inclusion: incident (first) ischemic stroke patients with a baseline NIH stroke scale of at least 13.

Exclusions: 1) patients unable to be treated with hyperbaric oxygen therapy in less than 24 hours. 2) age less than 45. 3) pulmonary disease that would contraindicate hyperbaric treatment (i.e., severe emphysema, evidence of blebs requires chest x-ray, etc). 4) unstable medical conditions requiring immediate access (cardiac arrhythmia, congestive heart failure, etc.). 5) life-threatening diseases limiting likelihood of evaluation of study outcome or life expectancy below 3 months.

Initial Evaluation: A CT will be performed at admission to rule out hemorrhage (required for tPA treatment also). For patients reaching the hospital within the time window to permit tPA treatment, the administration of tPA will be completed prior to the initiation of the hyperbaric study protocol. However, once the tPA has been administered, these patients will be screened for eligibility and if eligible, offered the hyperbaric protocol. Patients who refuse tPA, as well as those with a hospital admission outside of the tPA window, can proceed directly to the hyperbaric protocol.

As part of the eligibility work-up, prior to randomization, a SPECT scan and a baseline standardized neurological exam (activities of daily living scales and NIH stroke scale) will be performed.

Treatment Evaluation: Patients will be randomized to receive hyperbaric therapy plus best medical therapy versus best medical therapy alone. The initial hyperbaric therapy will be performed (1.5 ATA for 60 minutes) in those randomized to treatment. In all patients, a second SPECT scan and NIH stroke scale will be performed 3 hours after randomization (i.e., after the initial treatment for those randomized to treatment, and at a similar time among those randomized to best treatment.)

For those randomized to hyperbaric therapy, follow-up treatments (1.5 ATA for 60 minutes) will be performed at 8-hour intervals (2 per day) for the following three days. Hence, there is a total of 5 days of treatment incorporating 12 treatments. At the end of each day an NIH stroke scale will be performed for all patients. At the end of the 5 day treatment period discharge, a second SPECT scan, NIH stroke scale, and the activities of living scales will be performed in all patients. At three months, patients will return for a clinic visit, where a SPECT scan, a CT scan, the NIH stroke scale and evaluation of Activities of daily living will be repeated.

Analysis and Evaluation: Analysis will employ an intention-to-treat approach to assess differences in the volume measures from the SPECT scans, using a random-effect linear modeling approach. Differences in the efficacy at the follow-up times, the differential role of HBOT in tPA versus non-tPA patients, and the potential affect modification of demographic and risk factors will be assesses as interaction terms in these same models. The assessment differences in a composite score from the activities of daily living scales will use a similar approach, while time to subsequent stroke will use standard time-to-event analysis approaches. The sample size has not yet been determined.

Although Dr. James Toole is overseeing the project, Dr. Paul Harch will be the person in direct charge. Any centers interested in joining the study should be in contact with Dr. Harch.

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This paper is dedicated to my friend and mentor, the late Edgar End, MD (101511910-512311981),
A true visionary genius of Hyperbaric Oxygenation.