

# Hyperbaric Oxygen Therapy in Acute Ischemic Stroke

## Results of the Hyperbaric Oxygen in Acute Ischemic Stroke Trial Pilot Study

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**Background and Purpose**—Hyperbaric oxygen therapy (HBO) has promise as a treatment for acute stroke. This study was conducted to evaluate the efficacy, safety, and feasibility of using HBO in acute ischemic stroke.

**Methods**—We conducted a randomized, prospective, double-blind, sham-controlled pilot study of 33 patients presenting with acute ischemic stroke who did not receive thrombolytics over a 24-month period. Patients were randomized to treatment for 60 minutes in a monoplace hyperbaric chamber pressurized with 100% O<sub>2</sub> to 2.5-atm absolute (ATA) in the HBO group or 1.14 ATA in the sham group. Primary outcomes measured included percentage of patients with improvement at 24 hours (National Institutes of Health Stroke Scale [NIHSS]) and 90 days (NIHSS, Barthel Index, modified Rankin Scale, Glasgow Outcome Scale). Secondary measurements included complications of treatment and mortality at 90 days.

**Results**—Baseline demographics were similar in both groups. There were no differences between the groups at 24 hours ( $P=0.44$ ). At 3 months, however, a larger percentage of the sham patients had a good outcome defined by their stroke scores compared with the HBO group (NIHSS, 80% versus 31.3%;  $P=0.04$ ; Barthel Index, 81.8% versus 50%;  $P=0.12$ ; modified Rankin Scale, 81.8% versus 31.3%;  $P=0.02$ ; Glasgow Outcome Scale, 90.9% versus 37.5%;  $P=0.01$ ) with loss of statistical significance in a intent-to-treat analysis.

**Conclusions**—Although our HBO protocol appears feasible and safe, it does not appear to be beneficial and may be harmful in patients with acute ischemic stroke. (*Stroke*. 2003;34:571-574.)

**Key Words:** brain infarction ■ brain ischemia ■ cerebrovascular accident ■ hyperbaric oxygenation

Hyperbaric oxygen therapy (HBO) represents a possible therapy for acute ischemic stroke. Potential benefits include increased oxygen delivery,<sup>1</sup> decreased cerebral edema,<sup>2</sup> decreased lipid peroxidation,<sup>3</sup> inhibition of leukocyte activation,<sup>4</sup> and maintenance of blood-brain barrier integrity.<sup>5</sup> HBO has been shown in animal models of both focal and global ischemia to reduce the volume of brain infarction and improve outcome.<sup>6-8</sup>

There have been >400 cases of ischemic strokes in humans treated with HBO, with more than half of these cases claiming improvement on clinical or experimental grounds.<sup>9-12</sup> Despite this result, there have been only 2 controlled pilot studies in humans, both using multiple treatments at 1.5-atm pressure absolute (ATA).<sup>13,14</sup>

We conducted a pilot study to prospectively assess the efficacy, safety, and feasibility of a 1-time treatment with hyperbaric oxygen at 2.5 ATA in patients with acute ischemic stroke.

### Methods

This study was a prospective, sham-controlled, double-blind pilot study comparing HBO with sham in the treatment of ischemic stroke. This study was approved by the Methodist Hospital Institutional Review Board, with patient or proxy consent obtained before enrollment.

### Participants

Participants included adults >18 years of age presenting to an emergency department within 24 hours after stroke onset with a measurable deficit on the National Institutes of Health Stroke Scale (NIHSS) and without evidence of hemorrhage on CT scan. Patients waking up with symptoms had time of onset defined as the time they went to sleep. Patients were excluded if they received thrombolytics, had a seizure at onset, had a stroke within 3 months, had improvement on the NIHSS score before treatment, or had an NIHSS score >22. Patients were also excluded if they had risk factors for HBO, including a history of severe chronic obstructive pulmonary disease, pneumothorax, bowel obstruction, sickle cell disease, or evidence of cardiac arrhythmia deemed by an investigator as potentially mandating emergent intervention.

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## Interventions

Subjects were stratified on the basis of time since symptom onset (0 to 12 or 12 to 24 hours) and subsequently randomized to receive either HBO or sham treatment. The HBO group underwent a 1-time treatment for 60 minutes in a monoplace HBO chamber (Sechrist Industries, model 2500B) pressured with 100% oxygen to 2.5 ATA (50 ft of seawater). The sham group underwent similar treatment except with a pressure of 1.14 ATA (4.48 ft of seawater). The sham group treatment was designed to simulate pressure changes within the tympanic membrane.

## Outcome Measures

The primary outcomes measured were the percentage of patients with good outcomes at 24 hours and 90 days. Good outcome at 24 hours was defined as an NIHSS score of 0 or an improvement of >4 points from baseline. Outcomes at 90 days involved 4 stroke scales with good outcomes defined as follows: an NIHSS score  $\leq 1$ , a Barthel Index score of 95 or 100, a modified Rankin Scale score  $\leq 1$ , and a Glasgow Outcome Scale score of 5.

Secondary efficacy end points included mortality by 90 days and treatment complications, including ear pain, tympanic membrane rupture, claustrophobia, seizure, or known development of a pneumothorax.

## Randomization and Blinding

Subjects were randomized within their time stratum to receive either HBO or sham treatment. Treatment designation was placed in a sealed envelope and seen only by the hyperbaric nurse at the time of treatment, with both investigator and study participant blinded to the treatment given. Dials of the HBO chamber were covered, and different investigators measured baseline and 24-hour assessment.

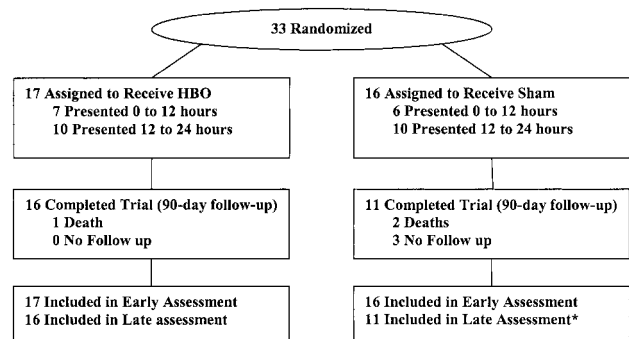
## Statistical Analysis

Secondary to being a pilot study, a sample-size calculation was not performed. Rather, we sought to enroll 20 subjects into each treatment arm divided evenly between those presenting within 12 hours and those presenting between 12 and 24 hours of symptom onset. Baseline patient characteristics were compared through the use of either the Wilcoxon rank-sum test or Fisher's exact test. The percentage of subjects with good outcomes at 24 hours and at 3 months and mortality and complication rates was compared between groups with Fisher's exact test. The strength of the association of treatment effect was quantified by estimating the odds ratio (OR) and a 90% CI for the OR. Three-month outcomes included only those subjects who completed assessment. A secondary intent-to-treat analysis of the 3-month outcomes was also performed using all subjects enrolled in the study, with subjects who died or were lost to follow-up given the worse possible scores on all stroke scales. Given the exploratory nature of this study, a significance level of  $\alpha=0.10$  was used in determining statistical significance. SAS version 8.2 (SAS Institute) was used to perform all statistical analyses.

## Results

From November 1999 to November 2001, 33 patients were randomized, 17 to HBO and 16 to sham (the Figure). The treatment groups were well matched with respect to baseline characteristics (Table 1).

Treatment compliance was excellent, with all study patients undergoing the full 60-minute treatment at the chosen depth. All patients in both groups underwent 24-hour testing. Ninety-four percent of the HBO group and 68.7% of the sham group underwent testing at 3 months. One study participant in the sham group did not undergo 3-month NIHSS testing, but the modified Rankin Scale, Barthel Index, and Glasgow Outcome Scale scores were obtained from a relative who was their primary caregiver. Median 3-month follow-up was 109 days (range, 89 to 174 days).



Hyperbaric Oxygen in Acute Ischemic Stroke Trial. \*One patient refused the 3-month NIHSS, but other stroke scales were obtained from the caregiver.

There were no statistical differences detected between the 2 groups in the number of patients with early improvement (sham, 31.3%; HBO, 17.7%;  $P=0.44$ ). At 3 months, the percentage of patients with good outcomes was greater in the sham group compared with the HBO-treated group, reaching significance in 3 of the 4 scales (Table 2). A similar trend was seen in the intent-to-treat analysis but failed to reach significance for any of the stroke scales (Table 2).

Complications of HBO were similar to those of sham ( $P=0.66$ ), with 3 patients in the sham group (claustrophobia) and 2 in the HBO group (ear pain, claustrophobia) having complications. The 1 patient with ear pain did not require pain medications or suffer any tympanic membrane damage. All patients who complained of claustrophobia were treated with either a single dose of diazepam (5 mg) or midazolam (2 mg). No complications resulted in suspension of treatment.

Three patients died before the 3-month follow-up period (1 HBO, 2 placebo;  $P=0.60$ ), with only 1 in the placebo group related to the stroke.

**TABLE 1. Baseline Characteristics**

	Sham (n=16)	HBO (n=17)	P
Age, median (range)	68 (43–85)	75 (50–87)	0.23
Female, %	37.5	29.4	0.81
Race, %			0.91
White	75.0	58.8	
Black	25.0	41.2	
Hours elapsed from symptom onset to treatment (n)			
0–3	0	0	
3–6	3	2	
6–12	3	5	
12–24	10	10	
NIHSS score, median (range)	7 (1–21)	8 (3–16)	0.90
NIHSS score (n)			
0–3	3	3	
4–6	5	4	
7–10	2	4	
11–15	4	4	
16–22	2	2	

**TABLE 2. Percent of Subjects With Good Outcomes at 90 Days**

	Sham (n=11)	HBO (n=16)	Odds Ratio (90% CI)	P
Barthel Index, n (%)	9 (81.8)	8 (50.0)	0.22 (0.05, 1.02)	0.12
Modified Rankin score, n (%)	9 (81.8)	5 (31.3)	0.10 (0.02, 0.48)	0.02
Glasgow Outcome score, n (%)	10 (90.9)	6 (37.5)	0.06 (0.01, 0.41)	0.01
NIHSS, n (%)	8 (80.0)*	5 (31.3)	0.11 (0.02, 0.55)	0.04
Intent-to-Treat Analysis				
	Sham (n=16)	HBO (n=17)	Odds Ratio (90% CI)	P
Barthel Index, n (%)	9 (56.3)	8 (47.1)	0.69 (0.22, 2.19)	0.73
Modified Rankin score, n (%)	9 (56.3)	5 (29.4)	0.32 (0.10, 1.08)	0.17
Glasgow Outcome score, n (%)	10 (62.5)	6 (35.3)	0.33 (0.10, 1.08)	0.17
NIHSS, n (%)	8 (50.0)	5 (29.4)	0.42 (0.13, 1.39)	0.30

\*n=10.

### Discussion

The results of this study suggest that HBO therapy at 2.5 ATA for 60 minutes in patients with acute ischemic stroke is not likely to be efficacious and may be harmful. A comparison of the 2 groups at 3 months showed that patients treated with HBO were between 31% and 53% (absolute) less likely to have a good outcome compared with sham.

Our study supports prior work suggesting that HBO has few complications in acute stroke patients, with only 1 patient in the current study complaining of any barotrauma symptoms (ear pain) and no patients suffering from oxygen toxicity.

Compared with prior studies with 15 and 10 dives in which 70% and 20% of patients had protocol violations,<sup>13,14</sup> our protocol was feasible, with 100% of patients completing the treatment protocol.

The major limitation in interpreting these data is that this study was designed as a pilot study with a small number of patients, making its generalizability difficult. Although we originally proposed to enroll 20 patients in each group, with 10 in the 0- to 12-hour time frame and 10 in the 12- to 24-hour time frame, we stopped the study early at 24 months secondary to recruitment problems. In addition, all 3 of the patients lost to 3-month follow-up were in the sham group. One of these patients entered a nursing home after her stroke. When finally located 8 months after study enrollment, the patient's stroke scores would not have placed her in the good outcome category. Another patient refused to come in but according to her family was doing well, although no formal testing was done. The third patient relocated without leaving a forwarding address. Including patients who either died or were lost to follow-up, only 68% of the sham group were available for the 3-month follow-up. This is reflected in the loss of significance in the intent-to-treat analysis.

There are several possible explanations for the results presented here. Patients with ischemic stroke may have a narrow therapeutic time window in which HBO is beneficial. In our study, patients were treated within 24 hours of symptom onset, with only 15% of them receiving treatment

within 6 hours of symptom onset. In animal models of ischemic stroke, Weinstein et al<sup>15</sup> showed that the benefit conferred by HBO was lost in those animals treated >4 hours after artery occlusion. In the 2 prior human studies of HBO for stroke, the average times to treatment were 51.8 and 18 hours.<sup>13,14</sup> Neither of these studies demonstrated any benefit, although the study by Nighoghossian et al<sup>14</sup> did show a trend toward benefit in the HBO group at 1 year. Other explanations may be that the pressure used in this study was too high. Although data exist suggesting that patients with primarily traumatic brain lesions had impaired glucose utilization at pressures of 2.0 ATA compared with 1.5 ATA,<sup>16</sup> we chose 2.5 ATA on the basis of animal data showing decreased lipid peroxidation, decreased leukocyte activation,<sup>4</sup> and improved integrity of the blood-brain barrier<sup>5</sup>; animal studies have shown that treatment pressures of 2.5 ATA result in improved outcome and smaller infarctions.<sup>3,7</sup> Because HBO has been shown to increase free radical formation in the rat brain,<sup>17</sup> it is possible that it may contribute to worsening reperfusion injury. Animal studies, however, have shown that HBO did not increase brain lipid peroxidation, a byproduct of free radicals interaction with neuron membrane phospholipid.<sup>3</sup>

In conclusion, our protocol of HBO therapy at 2.5 atm for 60 minutes, while safe and feasible, does not appear to be an efficacious treatment for acute ischemic stroke. From these results, we will not pursue the use of our protocol in a larger clinical trial.

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