Stroke Research Directory

Hyperbaric Oxygen in the Treatment of Acute Ischemic Stroke

A Double-blind Pilot Study
N. Nighoghossian, MD; P. Trouillas, MD; P. Adeleine, MD; F. Salord, MD
Background and Purpose

The effects of hyperbaric oxygen (HBO) therapy on humans are uncertain. Our study aims first to outline the practical aspects and the safety of HBO treatment and then to evaluate the effect of HBO on long-term disability.

Methods Patients who experienced middle cerebral artery occlusion and were seen within 24 hours of onset were randomized to receive either active (HBO) or shaim (air) treatment. The HBO patients were exposed daily to 4 0 minutes at 1.5 atmospheres absolute for a total of 10 dives. We used the Orgogozo scale to establish a preatreatment functional level. Changes in the Orgo gozo scale score at 6 months and 1 yuear after therapy were used used to assess the therapeutic efficacy of HBO. In addition, we used the Rankin scale and our own 10-point scale to assess long term-disability at 6 months and 1 year. Two sample t tests and 95% confidence intervals were used to compare the mean differences between the two treatment groups. Student's two-tailed test was used to compare the differences between pretherapeutic and posttherapeutic scores at 6 months and 1 year in the two treatment groups.

Results Over the 3 years of study enrollment, 34 patients wer e randomized. 17 to hyperbaric treatment with air and 17 to hyperbaric treatment with 100% oxygen. There was no significant difference at inclusion between groups regarding age, time from stroke onset to randomization, and Orgogozo scale scores.

Neurological deterioration occured during the first week in 4 patients in the sham group, 3 of whom died; this worsening was clearly related to the ischemic damage. Treatment was also discontinued for 3 patients in the HBO group who experienced myocardial infarction, a worsening related to the ischemic process, and claustrophobia. Therefore, 27 patients (13 in the sham group and 14 in the HBO group) completed a full course of therapy.

The mean score of the HBO group was significantly better on the Orgogozo scal e at 1 year (P.02). However, the difference at 1 year between preth erapeutic and posttherapeutic scores was not significantly different in the two groups (P.16). Moreover, no statistically significant improvement was observed in the HBO group at 6 months and 1 year according to Rankin score (P.78) and our own 10-point scale (P.50).

Conclusions

Although the small number of patients in each group precludes any conclusion regarding the potential deleterious effect of HBO, we did not observe major side effects usually related to HBO. Accordingly, it can be assumed that hyperbaric oxygen might be safe. We hypothesize that HBO might improve outcome after stroke, as we detected an outcome trend favoring HBO therapy. A large randomized trial might be required to address the efficacy of this therapy. (Stroke. 1995;26:1369-1372.)

Hyperbaric oxygen might be of benefit in the treatment of ischemic stroke. An improved outcome has been demonstrated in experimental studies. Conversely, the effectiveness of HBO exposure in humans relies mainly on anecdotal or uncontrolled studies. Results from a recent double-blind trial9 that indicated an outcome trend favoring sham treatment raise the possibility that HBO might worsen outcome. We understood a pilot double-blind study of HBO in the early treatment of stroke in humans to outline the practical aspects of HBO treatment and evaluate long-term disability.

Received September, 21, 1994: final revision received April 20, 1995: accepted April 26, 1995. From the Department of Neurology, Cerebrovascular Disease and Ataxia Research Center (N.N., P.T.), and Department of Anesthesiology (F.S.), Neurological Hospital, and Laboratoire d'Informatique Medicale. UFR Alexis Carrel (P.A.). Lyon, France.

Correspondence to Dr. N. Nighoghossian, Service de Neurologie du Pr Trouillas (Urgenes Neurovasculaires et Centre de Recherches sur l'Ataxie). Hopital Neurologique, 59 Bd Pinel. Lyon 69003. France.

Subjects and Methods

Patients enrolled in the study had a neurological deficit highly suggestive of middle cerebral artery (MCA) occlusion and were between 20 and 75 years old. Radiological evidence on early or repeat CT scan of a recent ischemic stroke in the MCA territory was required. Inclusion into the trial was restricted to paitnets who presented within 24 hours of stroke onset. Patients who had a significant deficit (ie, a score <80 on the 100-point quantitative scale of Orgogozo10, in which 100 is normal) were enrolled. Informed consent was obtained from the patient or the next of kin. Patients were exclused if they had a history of stroke assessed by clinical and CT scan data; exhibited substantial improvement or resolution of the deficit within 1 hour after onset; were pregnant; experienced seizures at stroke onset; or had metabolic encephalopathy, significant pulmonary disease that contraindicated HBO exposure, congestive heart failure, or uncontrolled hypertension.

Patients were placed in a monoplace chamber. They were randomly assigned to receive either active (HBO) or sham (air) treatment. Pressure was raised at 0.2 atmospheres absolute (ATA) over 5 minutes in the sham group to mimic the HBO pressure effect. The patients were maintained at 1.5 ATA in the HBO group. Compression and decompression rates did not exceed 0.5 psi/min or those tolerated by the patients. A daily exposure of 40 minutes duration was required by both groups. Protocol was completed when 10 dives were performed. Dives were directly supervised by a physician and a neurological intensive care unit nurse trained in the administration of hyperbaric gases. The patients' electrocardiograms and blood pressures were continuously monitored during each dive.

TABLE 1. The Trouillas Disability Scale

Grade Description

1. No disability.
2. Neurological examination may disclose minor abnormalities, but the patient is able to either return to work or resume his previous activites.
3. Neurological examination may disclose minor abnormalities, and the patient either is unable to carry out his previous work and has been reassigned or is unable to resume his complete previous activites.
4. The patient is able to either work only part-time daily or look after himself without help.
5. The patient is unable to work, although he is able to look after himself without help.
6. Neurological examination may show significant abnormalities, but the patient is able to walk unassisted and needs no help in looking after himself.
7. The patient is unable to walk unassisted and needs temporary help in looking after himself.
8. The patient is unable to walk unassisted and needs permanent help in looking after himself.
9. The patient is dependent but able to move from wheelchair to bed.
10. The patient is bedridden and needs daily nursing and medical care.

11. Death related to cerebrovascular morbidity.

All patients received a standard therapy that combined low-dose heparin sodium (10 000 IU divided into two doses) for prevention of deep-vein thrombosis and supportive care (eg, nursing, rehabilitation, and speech and occupational therapy). Three scales were applied to assess neurological outcome at 6 months and 1 year. The Orgogozo scale (a 100-point quantitative scale in which 100 is normal), the Rankin disability scale, and our own 10-point scale (the Trouillas scale, described in Table 1) were used for functional assessment. Special attention was paid to recording side effects usually epxected with HBO treatment, such as difficulty clearing the ears, lung atelectasis, and seizures. Patients who had neurological deterioration associated with a comatose state at any time during the 10-dive course were withdrawn from the dives. Etiologic workup included neck ultrasonography, four-vessel angiography, electrocardiographic monitoring, and echocardiography. LArge-vessel disease was suspected as the cause of infarction when there was a stenosis of 50% or greater or an occlusion in the appropriate large atery. Potential cardiac sources of embolism were considered according to the results of cardiac monitoring and echocardiographic data. Infarct distribution within the MCA was defined with the Damasio template.

Statistical Methods

The design of this study was the classic two-group randomized experiment pretest-posttest design. Thus, the pretherapeutic and posttherapeutic measures were analyzed by the following methods: (1) comparison of the means of pretherapeutic and posttherapeutic scores in the two groups by Student's two-tailed test and (2) comparison of the differences of posttherapeutic scores observed at 6 months and 1 year. These differences were calculated by subtracting pretherapeutic scores from posttherapeutic scores. A comparison of these differences was made between the two treatment groups by Student's two-tailed test.

Results

TABLE 2. Characteristics of the Treatment Groups on Admission

Treatment Group

Characteristic	Air	HBO	
	(n=17>	(n=17)	P *
Sex (% male)	71	53	
Age, y	54 +/- 3	53 +/- 3	0.90
Time, h	18 +/- 3.2	19 +/- 2.7	0.24
Orgogozo scale score	31.5 +/- 5.3	42.5 +/- 5.1	0.15
HBO indicates hyperbaric oxygen. *By Student's two-tailed test.			

From December 1988 to March 1992, 34 patients were randomized, 17 to treatment with medical air (sham group) and 17 to hyperbaric treatment with 100% oxygen. We did not observe any significant difference at inclusion between the groups regarding age, time from stroke onset to randomization, and Orgogozo scale scores. Demographic data, average time from onset of symptoms until the first dive, and Orgogozo scale score values for both groups are listed in Table 2.

Dives were discontinued for 7 patients. The participation of 4 patients were terminated before completion in the sham group due to a worsening of neurological status that occured in the first week (3 of the 4 died). This worsening was clearly shown on CT scan to be related to ischemic damage. Additionally, dives were not completed in the HBO group by 3 patients who experienced myocardial infarction, worsening of neurological condition related to ischemic injury, and claustrophobia. We did not observe any patient from either group in a comatose state during therapy in the chamber. Therefore, only 27 patients completed a full course of therapy (13 control subjects versus 14 in the HBO group). Only 1 patient in the sham group had died at the 6-month follow-up. There was a significant difference between the two groups at the 1-year follow-up according to the mean scores on the Orgogozo ($P<.02$) and Trouillas ($P<.03$) scales, whereas the Rankin scale score did not show any difference ($P<.11$) (Table 3). Conversely, the comparison of the pretherapeutic and posttherapeutic differences in the two groups at 6 months and 1 year did not show any statistical significant whatever the scale we used (Table 4).

Etiologic workup was used to assess the potential mechanism of stroke in 14 patients in the sham group and 12 in the HBO group; it remained unknown in 8 patients (3 in the sham and 5 in the HBO groups). An atherothrombotic mechanism was suspected in 8 patients (3 in the sham and 5 in the HBO groups), whereas a cardioembolic mechanism was suspected in 16 patients (8 in the sham and 8 in the HBO groups). An arterial dissection was found in 2 patients (1 in the sham and 1 in the HBO groups).

The distribution of infarction within the MCA area is presented in Table 5.

Discussion

In 1960, Boerema et al observed that HBO enabled hemoglobin to deliver sufficient oxygen to the tissues to sustain life and neurological function. Clinical improvement during exposure to HBO in patients with ischemic stroke has been repeated by Ingvar and Lassen.

Holbach et al attempted to elucidate the metabolic effect of HBO and suggested that exposure to 1.5 ATA for 35 to 40 minutes had a favorable effect on the glucose or energy metabolism of the brain as well as on the clinical course. Moreover, some cerebral flow studies,have suggested that arterial oxygen content is a determining factor of blood flow velocity in the MCA. By enhancing tissue survival, HBO might also reduce the formoation of edema, whihc otherwise further compromises local perfusion.

Acute ischemic stroke treatment trais may have a narrow time window if potential beneficial effects are to be detected. The period of time that HBO can be utilized to delay the onset of symptomatic cerebral ischemic after arterial occlusion is limited by the onset of oxygen toxicity however, the threshold of oxygen concentration and the duration of exposure needed to produce deleterious effects of oxygen have yet to be determined. In addition, results of studies of stroke in humans suggest that the timining of the inital HBO exposure has yet to be determined, as an equaly high response rate has been reported with exposure during the subacute and chronic phases. In our study, however, we included patients within 24 hours after stroke onset, sooner than in previous studies.

Patients having large-vessel stenosis or occlusion with residual blood flow insufficient to support cerebral function are likely to respond favorably to HBO. Accordingly, we focused our selection on patients who had a clinical picture consistent with large-vessel thrombosis, in contrast to previous studies in which a distinction was not made between large- and small-vessel thrombosis.

Despite the promising experimental and clinical data, the major criticism to most HBO studies has been the lack of controlled prospective analysis in the early postischemic period. Recently, Anderson et a administered HBO or air in a double-blind protocol to 39 patients with ischemic cerebral infarction. The study was not completed, as a trend favoring the air-treated patients was observed. Conversely, our study did not share the same conclusion, and this discrepancy raises some controversy. Although the small number of patients in each group precludes any conclusion regarding potential deleterious effects of HBO, we did not observe major side effects clearly related to HBO. (One patient experienced claustrophobia, which is a complication more likely attributed to the use of a monoplace chamber.)

A trend favoring HBO treatment was observed at 1 year according to the mean scores on the Orgogozo and Trouillas scales; however, we did not find a significant difference in outcome between groups according to the pretherapeutic and posttherapeutic differences after the 1-year follow-up. Given the considerations, we hypothesize that HBO might improve the outcome after stroke; a large randomized trial would be required to address the efficacy of this therapy.

TABLE 3. Estimates of the Effect of Oxygen at 6 Months and 1 Year: Comparison of the Main Scores

	Group	Group			
	Air	HBO	Difference	95% Cl of	
Scale	(n=17	(n=19	(HBO - Air)	Mean Change	P *
Orgogozo					
Day 0	31.5 +/- 5.3	42.5 +/- 5.1	-	-	.15
6 mo	54.7 +/- 8.3	72.9 +/- 6.6	18.2 +/- 10.6	(-3.4, 39.9)	.10
1 yr	50.3 +/- 8.7	78.2 +/- 6.4	27.9 +/- 10.8	(6.0, 50.0)	.02
Trouillas					
6 mo	6.1 +/- 0.7	4.6 +/- 0.5	-1.5 +/- 0.9	(-3.3, 0.3)	.19
1 y	6.3 +/- 0.7	4.1 +/- 0.6	-2.2 +/- 1.0	(-4.2, -0.2)	.03
Rankin					
6 mo	3.2 +/- 0.3	2.6 +/- 0.2	-0.6 +/- 0.4	(-1.5, 0.2)	.13
1 y	3.0 +/- 0.3	2.4 +/- 0.2	-0.6 +/- 0.4	(1.5, 0.2)	.11
HBO indicates hyperbaric oxygen; Cl, confidence interval. Values are mean +/- SEM. *By Student's two-tailed test					

TABLE 4. Comparison of Pretherapeutic and Posttherapeutic Differences Between Treatment Groups

	Treatment Group				
Scale	Air	HBO	Difference	95% C1 of	P *
	(n=17)	(n=17)	(HBO - Air)	Mean Change	
Orgogozo					
	23.5	30.5			
Difference (6 mo - day 0)	+/-	+/-	7.1 +/- 10.6	(-14.6, 28.7)	.51
	7.7	7.3			
	19.1	35.9			
Difference (1 y-day 0)	+/-	+/-	16.8 +/- 11.6	(-6.9, 40.4)	.16
	9.2	7.1			
Trouillas					
	0.2	-0.4			
Difference (1 y-6 mo)	+/-	+/-	-0.6 +/- 0.5	(-1.6, 0.4)	.50
	0.4	0.2			
Rankin					
-0.3	-0.2				

Difference (1 y-6 mo)	+/-	+/-	0.1 +/- 0.2	(-0.3, 0.5)	.78
	0.1	0.1			
HBO indicates hyperbaric oxygen; Cl. confidence interval. Values are mean +/- SEM. *By Student's two-tailed test.					

TABLE 5. Infarct Distribution Within the MCA Territory

	Treatment Group	Treatment Group
Total MCA territory	8	6
MCA trunk	2	2
Ascendant trunk	5	6
Lenticulostriate arteries	2	3
MCA indicates middle cerebral artery; HBO, hyperbaric oxygen.		

Acknowledgements

The authors gratefully acknowledge the assistance of Mrs D. Durand in performing the hyperbaric treatments and the willingness of the patients to tolerate the discomfort and uncertainy involved in testing this treatment. Reprinted with Permission

References

1. Smith G, LAwson DD, Renfrew S, Ledingham IM, Sharp GR. Preservation of cortical activity by breathing oxygen at two atmospheres of pressure during cerebral ischemia. Surg Gynecol Obstet. 1961;113:13-16
2. Fusion RL, Moor JF, Smith WW, Brown IW. Hyperbaric oxygenation in exeperimental cerebral ischemia. Surg Forum. 1965;16:416-418.
3. Moor, GF, Fuson RL, Margolis G, Brown IW, Smith WW. Protective effect of hyperbaric oxygenation on the central nervous system during circulatory arrest. In: Brown IW, Cox BG, eds. Procreedings of the Third International Conference on Hyperbaric Medicine. Washington, DC: National Academy of Sciences; 1966:367-371.
4. Thomas AN, Hall AD, Blaisdell FW, Connolly JE. Survival after prolonged induced circulatory arrest, hyperbaric oxygenation, and hypothermia. In: Brown IW, Cox BG, edgs. Proceedings of the Third International Conference on Hyperbaric Medicine. Washington, DC: National Academy of Sciences; 1966:382-390.
5. Ingvar HD, Lassen NA. Treatment of focal cerebral ischemia with hyperbaric oxygen. Acta Neurol Scand. 1965;41:92-95.
6. Hart GB, Thompson RE. The treatment of cerebral ischemia with hyperbaric oxygen (OHB). Stroke. 1971:2:247-250.
7. Kapp, JP. Hyperbaric oxygen as an adjunct to acute revascularization of the brain. Surg Neurol. 1979;12:457-461.
8. Neubauer RA, End E. Hyperbaric oxygenation as an adjunct therapy in strokes due to thrombosis: a review of 122 patients. Stroke. 1980;11:297-300.
9. Anderson DC, Bottini AG, Jagiella WM, Westphal B, Ford S, Rockswold GL, Loewenson RB. A pilot study of hyperbaric oxygen in the treatment of human stroke. Stroke. 1991;22:1137-1142.
10. Orgogozo JM, Capildeo R, Anagostou CN, Juge O, Pere JJ, Dartigues JF, Steiner TJ, Yotis A, Rose FC. Mise au point d'un score neurologique pour l'evaluation clinique des infarctus sylviens. Presse Med. 1983;12:3039-3044.

Printed with Permission

Legal Disclaimer

The content and information provided within this site is for informational and educational purposes only. Consult a doctor before pursuing any form of therapy, including Hyperbaric Oxygen Therapy. The Information provided within this site is not to be considered Medical Advice. In Full Support of the F.D.A., Hyperbaric Oxygen Therapy is considered Investigational, Experimental, or Off Label.

Please consult with your Treating Medical Physician