Acta Neurochir Suppl (2008) 101: 145–149

Printed in Austria

Effect of hyperbaric oxygen on patients with traumatic brain injury

J. W. Lin[1,2], J. T. Tsai[3,4], L. M. Lee[5,6], C. M. Lin[1,2], C. C. Hung[7], K. S. Hung[1], W. Y. Chen[1], L. Wei[1], C. P. Ko[1], Y. K. Su[1], W. T. Chiu[1,6]

[1] Department of Neurosurgery, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[2] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[3] Institute of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan
[4] Department of Radiation-oncology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[5] Department of Urology, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan
[6] Graduate Institute of Injury Prevention and Control, Taipei Medical University, Taipei, Taiwan
[7] Department of Neurosurgery, Taipei Medical University Hospital, Taipei, Taiwan

Summary

Hyperbaric oxygen therapy (HBOT) is the medical therapeutic use of oxygen at a higher atmospheric pressure. The United States Food and Drug Administration have approved several clinical applications for HBOT, but HBOT in traumatic brain injury (TBI) patients has still remained in controversial. The purpose of our study is to evaluate the benefit of HBOT on the prognosis of subacute TBI patients. We prospectively enrolled 44 patients with TBI from November 1, 2004 to October 31, 2005. The study group randomly included 22 patients who received HBOT after the patients' condition stabilization, and the other 22 corresponding condition patients were assigned into the matched control group who were not treated with HBOT. The clinical conditions of the patients were evaluated with the Glasgow Coma Scale (GCS) and Glasgow Outcome Scale (GOS) before and 3 to 6 months after HBOT. The GCS of the HBOT group was improved from 11.1 to 13.5 in average, and from 10.4 to 11.5 ($p < 0.05$) for control group. Among those patients with GOS = 4 before the HBOT, significant GOS improvement was observed in the HBOT group 6 months after HBOT. Based on this study, HBOT can provide some benefits for the subacute TBI patients with minimal adverse side effects.

Keywords: Traumatic brain injury; hyperbaric oxygen; Glasgow Coma Scale (GCS); Glasgow Outcome Scale (GOS).

Introduction

Traumatic brain injury (TBI) is a major cause of death and disability. Every year in the United States, there are about one million head-injured people treated in hospital emergency rooms, and roughly 50,000 people die from TBI [8], 230,000 people are hospitalized, and 80,000 survive with significant disabilities. Because of the enormous medical expenditure resulting from such injury, many efforts have been devoted to minimize the influence of TBI.

Clinically, there are two mechanisms directly related to the TBI outcome. The first one is the primary insult, which results from the impact itself, and all the neuronal damages are determined by the impact. As this insult has already occurred before the patient comes to hospital, there is little that a medical team can do for the patient. The second mechanism is the delayed non-mechanical, which results from tissue edema after the impact followed by ischemic change inside the brain. This theoretically preventable or treatable condition is the principal target of treatment for TBI. All the medical treatment should therefore be devoted to minimize edema and facilitate cerebral blood flow, to enhance cerebrovascular autoregulation, to reduce cerebral metabolic dysfunction, and to adequately maintain cerebral oxygenation [7]. Furthermore, excitotoxic cell damage and inflammatory process resulting from ischemia may also lead to increased cell death [12]. Generally speaking, about 80% of deaths in TBI result from hypoxia. Consequently, oxygen supplement in the initial resuscitation of a TBI patient is of paramount importance.

Hyperbaric oxygen therapy (HBOT) is the medical use of oxygen at a pressure exceeding atmospheric pressure (ATA). The mechanism of HBOT consists in drastically increasing oxygen partial pressure of the tissues,

Correspondence: Wen-Ta Chiu, M.D., Ph.D., Department of Neurosurgery, Taipei Medical University-Wan Fang Hospital; Graduate Institute of Injury Prevention and Control, Taipei Medical University; 111, Section 3, Hsing-Long Road, Taipei 116, Taiwan.
e-mail: wtchiu@tmu.edu.tw

and facilitating the oxygen transport by plasma. As a result, HBOT can improve oxygen supply to the injured brain and diminish the volume of brain that will necrotize during ischemia [5, 11].

Materials and methods

In this prospective cohort study, we intended to study the impact of HBOT on moderate to severe TBI patients. The protocol of this study was approved by the Investigation Review Board-Wanfang Medical Center (approval no. F950305). All the patients were enrolled under the regulation of inclusion and exclusion criteria, and the criteria were as follows.

Inclusion criteria

1. Age ≥16 y/o (Pediatric patient was excluded).
2. The patients were diagnosed to have moderate to severe TBI. (Glasgow Coma Scale (GCS) from 3 to 12).
3. TBI condition stabilization.
4. Stable vital sign and spontaneous respiration without endotracheal intubation or mechanical ventilation (tracheotomy was eligible for the enrollment).
5. No active infection or leucocytosis.
6. A hyperbaric oxygen department physician was consulted, and he (she) agreed to treat the patient with HBOT.
7. Informed consent could be obtained from the patient's family.

Exclusion criteria

1. Medical history with central nervous system disease (e.g. Parkinson disease, dementia, congenital anomaly, stroke... etc.)
2. Systemic disease history (e.g. diabetes, coronary artery disease, renal insufficiency, COPD... etc.)
3. Multiple traumas (e.g. Chest contusion, abdominal blunt injury, internal bleeding, pelvic fracture... etc.)
4. Skull base fracture with CSF rhinorrhea or otorrhea.
5. Smoking or alcoholism.
6. Hemoglobin ≤10 gm/dl for female or ≤12 gm/dl for male patients.

When the patients were enrolled, the assignment will be decided. If one patient was chose randomly to be a study group candidate then there will be another patient with corresponding condition (e.g. age, sex, clinical course, severity and condition... etc.) chose to be the matched control group patients. If the patient was chose to be the study candidate, the potential risk and benefit will be explained to the family for the obtaining of the treatment consent. From Nov. 1, 2004 to Dec. 31, 2006, there were total 62 patients enrolled into his study. Finally, there were 44 complete patients' data available for the further analysis.

In this research, we used a multi-user pressurized chamber (Model no.: BTG/875/PV/02GOC-100, Apex Process Technologies (S) PTE LTD, Singapore) to treat patients. The HBOT protocol was to apply two-hour, two ATA pressures in the process. We increased the air chamber pressure slowly to 2 ATA over 15 min and maintained this pressure for 90 min. Patients were given 100% oxygen with O_2 masks. Then we depressurized to normal ATA over 15 min. The full treatment course was defined as once a day for 20 days over a 4 week period. [9] During the HBOT the patients' condition and vital sign were closely monitored. If there was any complication (e.g. hypotension, short of breath, seizure, unstable vital sign (blood pressure increased or decreased larger than 20 mmHg), hypoxia ($SaO_2 < 95\%$)... etc.) happened during HBOT, the treatment for this patient will be discontinued, and this patient and the corresponding controlled one will be excluded. The purpose of our study was to clarify the influence on HBOT in subacute TBI patients by analyzing patients' demographic information, GCS changes, and comparing variables such as the GCS, the injury severity, and the length of time of HBOT, with regard to the subacute TBI outcome. And the TBI outcomes were evaluated with the Glasgow Outcome Scale (GOS) consisting of 5 levels (1: Death, 2: Vegetative status, 3: Severe disability, 4: Moderate disability, and 5: Good recovery).

After data collection, we analyzed the result with SPSS 11.0 software. We compared the two groups by means of demographic information, including sex, age, body weight, injury timing, the severity of head injury, duration of hospital stay, treatment with received surgery or that without surgery, and length of HBOT treatment time. We compared the GCS and GOS scores of both groups at different times with the Chi-square test to assess difference between the two groups. The patients were stratified with different GOSb levels (GOS level before the HBOT) (GOSb = 2, GOSb = 3, and GOSb = 4). There was no GOSb = 1 and the GOSb = 5 patients enrolled because GOSb = 1 patients died before the

Table 1. *Demographic information for patients*

	HBOT group	Control group
Total	22	22
Sex		
M:F	19:3	19:3
Age		
Below 24	7	5
25–64	13	16
Above 65	2	1
Body weight (kg)	61.75	65.12
GCS		
9–12	10	10
3–8	12	12
Diagnosis		
EDH	3	2
SDH	5	6
ICH	4	5
SDH+ICH	5	4
SAH	3	4
DAI	2	1
Surgery		
With	16	20
Without	6	2
GOSb		
4	7	6
2–3	15	16

GCS The patient initial GCS during admission.
GOSb The patient's GOS before HBOT or the same time for the control group (mean 27.5 days after head trauma).
All variables have $p > 0.05$.
EDH Epidural hematoma, *SDH* subdural hematoma, *ICH* intracerebral hemorrhage, *SAH* subarachnoid hemorrhage, *DAI* diffuse axonal injury.

Table 2. *GCS improvement for the patients after HBOT*

	GCS mean on arrival	GCS mean before HBOT	GCS mean after HBOT
HBOT group	8.0	11.1	13.5
Control group	7.9	10.4	11.5*

* $p < 0.05$ with significant difference.

Table 3. *GOS outcome for the patients 3 and 6 months after HBOT*

		GOS3a without improvement	GOS3a with improvement	GOS6a without improvement	GOS6a with improvement	Total
GOSb = 2	HBOT	8	3	7	4	11
	control	8	2	7	3	10
GOSb = 3	HBOT	2	2	2	2	4
	control	4	2	3	3	6
GOSb = 4	HBOT	3	4	1	6*	7
	control	3	3	3	3	6
Total		28	16	23	21	44

GOSb The patient's GOS before the HBOT or the same timing for the control group.
GOS3a The patient's GOS at 3-month post injury or at the same timing for control group.
GOS6a The patient's GOS at 6-month post injury or at the same time for control group.
* $p < 0.05$ with significant difference.

HBOT and there was nothing could be improved for GOSb = 5 patients. We recorded the GOS scores before (GOSb) and 3 (GOS3a) and 6 (GOS6a) months after HBOT or at the same time for the control group patients to evaluate performance of the patients.

Results

As showed in Table 1, 22 patients were enrolled in each group. The M:F sex ratio was the same: 19:3 in both groups. Most of the patients were aged between 25 and 64 years, which was also the most common range of age for head injury. The average interval from injury to receiving HBOT was 27.5 ± 5.8 days. This was also the timing for the first GOS evaluation for both groups. If the patients received HBOT, the average treatment times were 24.4 ± 7.8 times. In this table, no significant difference was found in age, sex, body weight, GCS severity, presence or absence of surgical intervention, or GOS severity between HBOT and control groups (all $p > 0.05$).

The average initial GCS scores for both groups' patients on arrival were 8.0 and 7.9, respectively. After admission, surgical and/or medical treatments were applied to these patients, and the GCS recovery from 8.0 to 11.1 and from 7.9 to 10.4, respectively. We applied HBOT to the patients after their traumatic condition stabilization, and there was considerable improvement in the HBOT group, from 11.1 to 13.5. In the control group, GCS improved only from 10.4 to 11.5. Even in this subacute stage of TBI, HBOT showed beneficial effects on GCS improvement for moderate or severe TBI patients ($p < 0.05$) (Table 2).

The patients in both groups were stratified with the GOSb level (GOSb = 2, 3, and 4) to evaluate the HBOT effects on TBI patients. The outcome at the third and sixth months after the HBOT was evaluated and analyzed. In third month evaluation (Table 3), even though there was some improvement in patients with HBOT, the numbers were not sufficient for drawing significant difference and conclusion between study and control groups.

In sixth month evaluation (Table 3), there were 12 patients with improvement in the HBOT group, and 9 patients in the control group, but the difference did not reach statistically significance ($p > 0.05$) for GOSb = 2 or 3 patients. However, there was a significant difference between these two groups among patients with GOSb = 4, and as a whole the GOS6a (6 months after HBOT) improvement was greater in the HBOT group than in the control group ($p < 0.05$).

Adverse event

Two patients developed seizures during the first week of HBOT, and the convulsions were controlled with anticonvulsants. Then the patient resumed HBOT 2 weeks later. Two patients experienced severe ear pain, and received tympanostomy. Thereafter the ear pain subsided, and the patient completed the full course of HBOT successfully. No pulmonary adverse event, unstable vital sign, or cataract occurred during HBOT or within 6 months follow-up. However, all these 4 study candidates and their corresponding control patients were excluded.

Discussion

The US Food and Drug Administration have approved several clinical applications for HBOT. They included certain non-healing wounds, radiation necrosis of soft tissue and radiation osteonecrosis, carbon monoxide poisoning, decompression sickness, acute arterial ischemia, and some sports injuries. These approvals did not include TBI. However, in the literature review; we found reports showing some supports for HBOT application to TBI patients.

In 2004, the Agency for Healthcare Research and Quality reviewed two fair-quality trials [1, 10], showing fair evidence that HBOT might reduce mortality or the duration of coma in severe TBI patients. But in one of the trials, HBOT also implicated an increased chance for poor functional outcome. Therefore, the evidences were conflicting. Although these two trials are cited frequently, the methodologies of these two trials are also criticized [6]. In the past, HBOT was used under the concepts of improving TBI patients' outcome and mitigating social economical expenditure [2]. Previous studies have been focused on the immediate use of HBOT after head trauma. However, during the initial period of TBI, patients are often ventilator-dependent and may have other associated injuries, such as lung contusion. Under such situation, it is not convenient to treat TBI patients with HBO early. With SPECT to show blood flow improvement and to analyze them with different age groups, Golden et al, reported that HBOT could improve cerebral metabolism in the chronic stage of TBI [4]. There are only limited data in the literature to support beneficial effects of HBOT on TBI patients with different degrees of severity.

In some animal study [7], using 2.5 ATA HBOT could reach maximum microcirculatory hemoglobin oxygen saturation and 2 fold of normal hemoglobin circulation but there was also higher complication, such as pulmonary system barotrauma, cataract, glaucoma, seizure ... etc. [6, 10, 11]. The Rockswold *et al.* reported that using 1.5 ATA HBOT for 60 min is relatively safe without any oxygen toxicity [5, 11]. In our series, we used HBOT with 2 ATA for 90 min every day for a total 20 times. What the optimal oxygen atmospheric pressure and duration used in HBOT is need further clarification.

The timing of using HBOT around one month (27.5 ± 5.8 days) after TBI is more practical in clinical condition. At that stage, patients have become more stable for their cardiopulmonary function and often have received intensive rehabilitation. As a consequence, the frequency of HBOT-related respiratory complications will be reduced. Furthermore, the synergistic effect of rehabilitation with HBOT conceivably triggers the improvement of the patient's GOS in the sixth month.

The adverse events in this trial were rare. Only two patients had seizures during the initial period of HBOT, and another two had middle ear barotrauma. The seizure incidence in the previous reports was 2.4 per 10,000 patient-treatments [13]. Because the population base was different between our results and this report, and we focused on the head trauma patients only, there should be higher incidence of seizure attack during the HBOT. Besides, the sample size of our patients was too small for statistical comparison. The tympanic membrane tear is common in HBOT [3]. However, in our HBOT center, tympanoplasty was not routinely performed before HBOT; this simple procedure should be considered and performed before the HBOT to reduce the patient's suffering. As the minor side effects, such as tinnitus, aural fullness, disequilibrium, and vertigo and or nausea, these side effects were all well tolerated by the patients [9].

In this trial, we demonstrated that the GCS of TBI patients in the HBOT group recovered significantly better than in the control group ($p<0.05$) (Table 2). This result would indicate that HBOT has a positive benefit in GCS recovery of TBI patients. For the GOS improvement, there was no obvious difference, especially for the 3 months follow-up (Table 3). Why did GCS improve so much, and GOS did not? GOS is widely applied for TBI patient outcome evaluation, but the intervals used for GOS scores are too rough. In recent studies, an extended GOS was used to evaluate the outcome of the TBI patients, and more detailed evaluation might help our future study.

For the patients receiving HBOT, there was no improvement of GOS in the third month follow-up, but 6 months after HBOT, GOSb = 4 group got some improvement (Table 3). This situation could be explained by the delayed effect of HBOT. That means HBOT needs some more time to express the effects.

The TBI patients with GOSb = 4 showed significant GOS improvement six months after HBOT in the study group ($p<0.05$, Table 3). But there was no such difference in the GOSb = 2 or GOSb = 3 groups. In GOSb = 2 (vegetative state) and GOSb = 3 (severe disability) patients, there should be severe parenchymal damages in the cerebral cortex. HBOT can not regenerate necrotic neurons, but can only improve reoxygenation of the brain parenchyma. With incorporation of rehabilitation, HBOT can help patients with mild neurological deficits to recover and return to normal life. In this prospective study, we can conclude that HBOT can help TBI patients in GCS recovery and also help patients with mild functional disability to lead a better life.

Acknowledgements

The authors would like to acknowledge the grant from the Department of Health, Executive Yuan, Taiwan (DOH-TD-B-111-002), the grant

(NHRI-EX97-9707PI, NHRI-CN-HD9503S) from National Health Research Institute, Taiwan, the grant (NSC 96-2314-B-038-010-MY2) from National Science Council, Taiwan, and the grant (96001-62-010) from Department of Health, Taipei, Taiwan.

References

1. Artru F, Chacornac R, Deleuze R (1976) Hyperbaric oxygenation for severe head injuries: preliminary results of a controlled study. Eur Neurol Res 14: 310–318
2. Bennett MH, Trytko B, Jonker B (2004) Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. Cochrane Database Syst Rev Oct 18(4): CD004609
3. Fiesseler FW, Silverman ME, Riggs RL, Szucs PA (2006) Indication for hyperbaric oxygen treatment as a predictor of tympanostomy tube placement. Undersea Hyperb Med 33(4): 231–235
4. Golden ZL, Neubauer R, Golden CJ, Greene L, Marsh J, Mleko A (2002) Improvement in cerebral metabolism in chronic brain injury after hyperbaric oxygen therapy. Int J Neurosci 112(2): 119–131
5. Hardy P, Johnston KM, De Beaumont L, Montgomery DL, Lecomte JM, Soucy JP, Bourbonnais D, Lassonde M (2007) Pilot case study of the therapeutic potential of hyperbaric oxygen therapy on chronic brain injury. J Neurol Sci 253(1–2): 94–105
6. McDonagh M, Helfand M, Carson S, Russman BS (2004) Hyperbaric oxygen therapy for traumatic brain injury: a systematic review of the evidence. Arch Phys Med Rehabil Jul 85(7): 1198–1204
7. Meirovithz E, Sonn J, Mayevsky A (2007) Effect of hyperbaric oxygenation on brain hemodynamics, hemoglobin oxygenation and mitochondrial NADH. Brain Res Rev S4: 294–304
8. NIH, Traumatic Brain Injury: Hope Through Research 2002
9. Horn CE, Himel HN, Selesnick SH (2005) Hyperbaric oxygen therapy for sudden sensorineural hearing loss: a prospective trial of patients failing steroid and antiviral treatment. Otol Neurotol Sep 26(5): 882–889
10. Rockswold GL, Ford SE, Anderson DC, Bergman TA, Sherman RE (1992) Results of a prospective randomized trial for treatment of severely brain-injured patients with hyperbaric oxygen. J Neurosurg 76: 929–934
11. Rockswold SB, Rockswold GL, Defillo A (2007) Hyperbaric oxygen in traumatic brain injury. Neurol Res 2: 162–172
12. Werner C, Engelhard K (2007) Pathophysiology of traumatic brain injury. Br J Anaesth 99(1): 4–9
13. Yildiz S, Aktas S, Cimsit M, Ay H, Toğrol E (2004) Seizure incidence in 80,000 patient treatments with hyperbaric oxygen. Aviat Space Environ Med 75(11): 992–994