Hyperbaric oxygen for severe traumatic brain injury: a randomized trial

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Abstract

Objective: The present study aimed to explore the effects of hyperbaric oxygen therapy on the prognosis and neurological function of patients with severe traumatic brain injury.

Methods: A prospective study was carried out in 88 patients diagnosed with severe brain injury at our hospital and they were enrolled as research participants and randomly assigned to control and experimental groups (n = 44 per group) using a random number table method. Both groups underwent routine treatment. Patients in the experimental group were administered hyperbaric oxygen therapy approximately 1 week after admission when their vital signs had stabilized.

Results: No significant intergroup differences were observed in the Glasgow Coma Scale (GCS) and U.S. National Institutes of Health Stroke Scale (NIHSS) scores before treatment. However, after oxygen treatment, compared with the control group, the experimental group showed higher GCS and lower NIHSS scores. The GCS score at admission, tracheotomy status, and first hyperbaric oxygen therapy duration were independent prognostic factors in patients with severe traumatic brain injury.

Conclusion: Hyperbaric oxygen therapy may promote recovery of neurological function and improve the cognitive function and prognosis of patients with severe traumatic brain injury.

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Introduction
Brain injury is commonly associated with systemic trauma. This type of injury accounts for approximately 20% of the overall trauma incidence in the entire body and is the most common form of disability. According to its severity, brain injury can be categorized as mild, moderate, or severe. The latter category includes extensive brain contusion and/or skull fracture, brainstem injury, diffuse axonal injury, and intracranial hematoma. Because severe brain injury is characterized by severe symptoms, rapid progression, sequelae, and high disability and mortality rates, it seriously threatens the survival and quality of life of affected patients. Accordingly, severe brain injury is a focus of neurosurgical treatment.

Most patients with mild, moderate, or severe brain injury mainly receive non-operative treatments, including mild hypothermia therapy and dehydration therapy. Hyperbaric oxygen therapy has previously been used to treat some types of brain injury. This therapy can rapidly correct and relieve brain anoxia and craniocerebral edema, reduce intracranial pressure, and improve the neurological function, prognosis, and quality of life of patients. However, few reports have discussed the efficacy of hyperbaric oxygen therapy in patients with severe brain injury and its effects on their neurological function.

Therefore, the present study primarily investigated and analyzed the efficacy of hyperbaric oxygen therapy for patients with severe brain injury by comparing its clinical efficacy with that of routine treatment and comprehensively analyzing the factors affecting the efficacy of hyperbaric oxygen therapy. These findings provide an experiential reference regarding the application of hyperbaric oxygen therapy for severe brain injury.

Materials and methods
Participants
A prospective study was carried out in 88 patients diagnosed with severe brain injury at our hospital from May 2016 to December 2018 and they were enrolled as research participants and were divided into control and experimental groups (n = 44 per group) using a random number table method. Patients in both groups underwent routine treatment. Patients in the experimental group received hyperbaric oxygen therapy approximately 1 week after admission when their vital signs had stabilized. The patients enrolled comprised 47 males and 41 females aged between 18 and 60 years (mean age, 45.19 ± 7.71 years). The following inclusion criteria were applied: a diagnosis of severe brain injury and Glasgow Coma Scale (GCS) score (measured when admitted to the hospital and when the patient was treated with hyperbaric oxygen for 2 weeks) between 3 and 8 points; stable vital signs observed within 1 week after surgery during hospitalization, with no active cranial bleeding as indicated by a computed tomography (CT) examination; and the provision of signed informed consent by the participant or their family. This study was approved by the Ethics Committee of Shenzhen People’s Hospital.
The Second Clinical Medical College of Jinan University (approval number: ChiCTR1800015678; approval date: December 2018). The following exclusion criteria were applied: a history of cerebral hemorrhage, cerebral infarction, and/or brain injury; concurrent organ diseases, such as heart, liver, and kidney disease, or combined tumor, acute infection, diabetes, severe organ failure, mental disease, or physical disability; death within 2 weeks after the trauma event; transfer to another hospital; and pregnancy.

Treatment methods

Both groups were intensively and continuously monitored during the early post-admission period. All patients underwent decompressive craniectomy. The care administered to the control group included electrocardiographic, intracranial pressure, cerebral blood flow, and oxygen saturation monitoring. When necessary, patients in the control group received oxygen via positive pressure delivery, sputum aspiration, reinforced dehydration, preventive hemostasis, digestive system protection, antibiotics for pathogen infection prevention, and other supportive or drug treatments, such as neural nutrition, to maintain brain cell activity or complementary energy and fluid supplementation. Patients in the control group who required tracheotomy underwent this procedure within 4 days after surgery. Patients whose disease status remained stable at 1 week after surgery underwent treatment with thromboembolism prophylaxis after a repeat CT examination confirmed the absence of active cranial bleeding. In addition to the above-mentioned treatments, patients in the experimental group received 30 treatments in a hyperbaric oxygen chamber (Yantai Moon Oxygen Chamber Co., Ltd.) starting at approximately 1 week after admission when their vital signs had stabilized. A chamber pressure of 0.20 to 0.25 MPa was chosen, followed by pressurization for 20 minutes, oxygen inhalation with constant pressure for 80 minutes, and decompression for 20 minutes. Both groups of patients were treated once a day for 2 weeks. During hyperbaric oxygen therapy, professional nurses closely monitored the patients and immediately suspended treatment if a serious adverse reaction or an event reflecting intolerance of hyperbaric oxygen therapy occurred.

Observation indices

Primary endpoints: The systolic peak flow velocity (Vs), mean velocity (Vm), pulsatility index (PI), and intracranial pressure of the cerebral middle artery were measured in patients of both groups using a transcranial Doppler analyzer (KJ-2V6M Nanjing KeyGen Biotech Co., Ltd., Nanjing, China); moreover, blood oxygen saturation (SaO2), blood oxygen pressure (PaO2), and blood hemoglobin (Hb) were detected using blood samples that were simultaneously collected. Thereafter, the brain oxygen uptake rate was calculated using the Fick equation, which is based on the SaO2, PaO2, and Hb values.

Secondary endpoints: The GCS and U.S. National Institutes of Health Stroke Scale (NIHSS) scores of each patient were determined at admission and 2 weeks after hyperbaric oxygen therapy. GCS scores ranged from 0 to 15 points: 15 points indicated clear consciousness; 12 to 14 points indicated mild disturbance of consciousness; 9 to 11 points indicated moderate disturbance of consciousness; and 8 points indicated coma. Accordingly, a lower score indicated a more severe disturbance of consciousness, whereas a higher score indicated less severe coma. NIHSS scores included assessments of consciousness, staring, facial paralysis, upper extremity strength, lower limb muscular strength, ataxia, aphasia, dysarthria,
sensation, visual field, negligence, and distal limb function and ranged from 0 to 42 points. A higher NIHSS\textsuperscript{12} score indicated a more severe absence of neurological function and more severe neurological deficit. At 3 months after brain oxygen treatment, patients were scored using the Glasgow Outcome Scale (GOS).\textsuperscript{13} A GOS value of 5 points indicated that the patient had recovered well and returned to a normal state, despite mild defects; 4 points indicated that the patient had mild disability but could to live independently and work with precautions; 3 points indicated that the patient was conscious and had severe disability, requiring care in daily life; 2 points indicated that the patient was in a vegetative state with minimal reaction (e.g., eye opening with the sleep/wakefulness cycle); and 1 point indicated death.

Statistical analysis

The statistical analysis was performed using SPSS 22.0 (SPSS IBM Corp., Armonk, NY, USA). Enumerated data are expressed in terms of n (%)%. Comparisons of enumerated data between groups were analyzed using the $\chi^2$ test. Measurement data are expressed as means ± standard deviation. Data with a normal distribution were analyzed using an independent-samples t test, whereas those without a normal distribution were analyzed using the Mann–Whitney U test. Comparisons within groups of values before and after treatment were assessed using a paired t test. A logistic regression test was used for multivariate analysis. A value of $P < 0.05$ indicated statistical significance.

Results

General characteristics of the control and experimental groups

The control and experimental groups did not significantly differ in terms of general characteristics, including sex, age, height, weight, tracheotomy status, cerebral hernia status at admission, GCS score at admission and before hyperbaric oxygen therapy (GCS1), injury cause, and postoperative diagnosis (Table 1).

Comparison of prognoses between the control and experimental groups

In the control group, the analysis revealed a good prognosis, mild disability, severe disability, vegetative state, and death in 6 (14%), 6 (14%), 11 (25%), 8 (18%), and 13 (29%) patients, respectively. In the experimental group, the analysis revealed a good prognosis, mild disability, severe disability, vegetative state, and death in 15 (34%), 9 (20%), 9 (20%), 5 (11%), and 6 (14%) patients, respectively. Patients in the experimental group showed a significantly better prognosis than those in the control group ($P < 0.05$) (Table 2).

Comparison of cerebral metabolism and cerebral blood flow indices before and after treatment in the control and experimental groups

Before treatment, the control and experimental groups did not exhibit significant differences in the Vs, Vm, PI, intracranial pressure, and brain oxygen uptake rate. After treatment, both groups exhibited significant increases in the Vs, Vm, and brain oxygen uptake rate (all $P < 0.05$) and significant decreases in the PI and intracranial pressure (both $P < 0.05$). However, an intergroup comparison after treatment revealed a significantly higher Vs, Vm, and brain oxygen uptake rate and a significantly lower PI and intracranial pressure in the experimental group compared with those in the control group (all $P < 0.05$). (Table 3 and Figure 1).
Comparison of GCS and NIHSS scores before and after treatment in the control and experimental groups

Before treatment, the control and experimental groups did not significantly differ in terms of GCS and NIHSS scores. After treatment, both groups exhibited significant increases in GCS scores (P < 0.05) and significant decreases in NIHSS scores (P < 0.05). However, after treatment, an intergroup comparison revealed...
significantly higher GCS scores (P < 0.05) and significantly lower NIHSS scores in the experimental group relative to the control group (P < 0.05) (Table 4 and Figure 2).

Univariate analysis of factors affecting the prognosis of patients

Patients were categorized according to the GOS on day 28 after the traumatic injury. If a patient was hospitalized for fewer than 28 days, the patient was scored at the time of discharge. In the experimental group, patients with GOS values of 4 to 5 points were classified as the good prognosis group (n = 24), whereas those with GOS values of 1 to 3 points were classified as the poor prognosis group (n = 20). Upon subjecting the clinical data collected from both groups to a univariate analysis, no significant intergroup differences were observed in sex, age, and injury cause. However, significant intergroup differences were observed in the GCS score at admission, tracheotomy status, first hyperbaric oxygen therapy duration, and number of hyperbaric oxygen therapy courses (all P < 0.05). (Table 5).

Multivariate analysis of factors affecting the prognosis of patients

Indices with significant differences in the univariate analysis were included in the multivariate analysis (Table 6). The multivariate analysis revealed that although the number of hyperbaric oxygen therapy courses was not a prognostic factor, GCS score at admission (OR: 3.017, 95% CI: 0.000–0.461), tracheotomy status (OR: 2.008, 95% CI: 0.000–0.711), and first hyperbaric oxygen therapy duration (OR: 1.873, 95% CI: 0.000–0.732) were identified as prognostic factors in patients. (Tables 6 and 7).
Discussion

Severe brain injury, a common form of clinical traumatic disease, is a critical condition. Brain injury has high disability and mortality rates and may cause respiratory tract obstruction, central apnea, pulmonary infection, epilepsy, hydrocephalus, post-traumatic syndrome, cognition and language disorders, and other sequelae that decrease the quality of life of patients. Therefore, it is crucial to select effective and suitable treatment methods to improve the quality of life and survival prognosis of patients with severe brain injury.
Several recent studies have explored the efficacy of hyperbaric oxygen therapy. For example, Mozayeni et al.\textsuperscript{18} examined the safety and practicability of hyperbaric oxygen therapy for the treatment of patients with concussion following a chronic mild traumatic brain injury and reported that this therapy is clinically feasible, considering its safety and cost-effectiveness. Benincasa et al.\textsuperscript{19} found that hyperbaric oxygen therapy could reduce the tumor necrosis factor-\(\alpha\)-mediated inflammatory responses of endothelial cells, thereby promoting vascular recovery following injury. Our study revealed that the experimental group showed a better prognosis than the control group; moreover, the experimental group showed a higher GCS score and lower NIHSS score after treatment than before treatment and performed better in both aspects relative to the control group. In addition, some studies have reported

**Table 4.** Comparison in GCS and NIHSS scores before and after treatment between the control and experimental groups (means ± standard deviation).

| Group           | n  | GCS score Before treatment | GCS score After treatment | NIHSS score Before treatment | NIHSS score After treatment |
|-----------------|----|-----------------------------|---------------------------|------------------------------|----------------------------|
| Control group   | 44 | 6.49 ± 1.15                 | 9.16 ± 2.84*              | 19.46 ± 2.64                 | 14.61 ± 2.33*              |
| Experimental group | 44 | 6.18 ± 1.44                 | 12.06 ± 2.76*             | 19.61 ± 2.19                 | 8.46 ± 2.37*               |
| t               |    | 1.116                       | 4.857                     | 0.290                        | 12.270                     |
| P               |    | 0.268                       | < 0.001                   | 0.773                        | < 0.001                    |

GCS, Glasgow Coma Scale; NIHSS, U.S. National Institutes of Health Stroke Scale.

**Figure 2.** Comparison of Glasgow Coma Scale (GCS) and U.S. National Institutes of Health Stroke Scale (NIHSS) scores before and after treatment between the control and experimental groups (a) Comparisons of GCS scores before and after treatment revealed no significant intergroup difference before treatment, significant increases in both groups after treatment (\(P < 0.05\)), and a significantly higher GCS score in the experimental group than in the control group after treatment (\(P < 0.05\)). (b) Comparisons of the NIHSS scores before and after treatment revealed no significant intergroup difference before treatment, significant increases in both groups after treatment (\(P < 0.05\)), and a significantly higher NIHSS score in the experimental group than in the control group after treatment (\(P < 0.05\)). Note: * indicates a comparison with the before treatment condition, \(P < 0.05\); # indicates a comparison with the control group after treatment, \(P < 0.05\).
Table 5. Univariate analysis of factors affecting the prognosis of patients [n (%) or means ± standard deviation].

| Factors                        | Poor prognosis group (n = 20) | Good prognosis group (n = 24) | t/\(t^2\) | P     |
|--------------------------------|------------------------------|------------------------------|-----------|-------|
| Sex                            |                              |                              |           |       |
| Male                           | 12 (60.00)                   | 13 (54.17)                   | 0.151     | 0.697 |
| Female                         | 8 (40.00)                    | 11 (45.83)                   |           |       |
| Age (years)                    |                              |                              |           |       |
| ≤50                            | 7 (35.00)                    | 8 (33.33)                    | 0.013     | 0.908 |
| >50                            | 13 (65.00)                   | 16 (66.67)                   |           |       |
| Injury cause                   |                              |                              |           |       |
| Falling injury                 | 4 (20.00)                    | 3 (12.50)                    | 0.588     | 0.745 |
| Vehicle accident injury        | 15 (75.00)                   | 19 (79.17)                   |           |       |
| Blunt injury                   | 1 (5.00)                     | 2 (8.33)                     |           |       |
| Glasgow Coma Scale score at admission | 5.16 ± 1.45                        | 7.62 ± 1.68                        | 5.142     | <0.001 |
| Tracheotomy status             |                              |                              | 5.442     | 0.020 |
| Yes                            | 14 (70.00)                   | 23 (95.83)                   |           |       |
| No                             | 6 (30.00)                    | 1 (4.17)                     |           |       |
| First hyperbaric oxygen therapy duration (d) | 8.16 ± 1.78                                     | 4.15 ± 1.12                                     | 9.096     | <0.001 |
| Number of hyperbaric oxygen therapy courses | 3.14 ± 0.49                                      | 5.65 ± 1.91                                     | 7.988     | <0.001 |

Table 6. Assignment.

| Factors                        | Assignment                                                                 |
|--------------------------------|-----------------------------------------------------------------------------|
| GCS score at admission         | Raw data of continuous variables were used for the analysis                 |
| Tracheotomy status             | Yes = 1, No = 0                                                             |
| First hyperbaric oxygen therapy duration (d) | Raw data of continuous variables were used for the analysis |
| Number of hyperbaric oxygen therapy courses | Raw data of continuous variables were used for the analysis |
| Efficacy of hyperbaric oxygen therapy | Good prognosis = 1, poor prognosis = 0                                      |

GCS, Glasgow Coma Scale.

Table 7. Multivariate analysis of factors affecting the prognosis of patients.

| Factors                        | B    | SE   | Wald  | Sig. | Exp(B) | 95% CI of EXP(B) |
|--------------------------------|------|------|-------|------|--------|------------------|
| GCS score at admission         | 7.955| 3.848| 4.282 | 0.038| 2.571  | 0.182 - 8.598    |
| Tracheotomy status             | 13.769| 5.838| 5.63  | 0.017| 0.021  | 0.005 - 0.681    |
| First hyperbaric oxygen therapy duration (d) | -4.273 | 2.14 | 3.986 | 0.04 | 0.016  | 0.002 - 2.278    |

CI, confidence interval; GCS, Glasgow Coma Scale.
that hyperbaric oxygen therapy could improve the oxygen supply to injured brain tissues by promoting vasoconstriction and vascular regeneration and preventing secondary brain injury, demonstrating a good ability to promote the recovery of bodily and cognitive functions of patients.\textsuperscript{20–22} Patients with severe brain injury often present with different degrees of hypoxia and ischemia as well as increases in intracranial pressure, which damage the brain microcirculation and induce a vicious circle. Therefore, the additional resolution of these features using hyperbaric oxygen therapy can significantly improve treatment efficacy.\textsuperscript{8} The present study revealed that after treatment, both the control and experimental groups had an increased Vs, Vm, and brain oxygen uptake rate and a decreased PI and intracranial pressure, although the experimental group exhibited more significant improvements in these aspects (all \( P < 0.05 \)). Using a constructed rat model, Yang et al.\textsuperscript{23} demonstrated that hyperbaric oxygen therapy could promote the proliferation of neural stem cells by activating vascular endothelial growth factor. One study by Lim et al.\textsuperscript{24} revealed that hyperbaric oxygen therapy could improve traumatic brain injury-induced depression-like behavior in rats by reducing neural inflammation. In addition, a study by Harch et al.\textsuperscript{25} revealed that hyperbaric oxygen therapy is significantly effective for the treatment of patients with mild and moderate traumatic brain injury. Hadanny et al.\textsuperscript{26} showed that hyperbaric oxygen therapy is safe and beneficial for patients with mild to moderate traumatic brain injury. Hyperbaric oxygen can induce neuroplasticity and improve cognitive function of patients with hypoxic brain damage. These findings suggest that hyperbaric oxygen can effectively promote the recovery of neurological function and is a feasible and effective solution for the treatment of severe brain injury. Regarding the underlying mechanism, we suspect that hyperbaric oxygen can promote brain cell metabolism, accelerate the decomposition and absorption of damaged brain tissue, promote the establishment of collateral circulation, and restore the oxygen supply to neurons. Furthermore, the oxygen supply is associated with neuronal regeneration, improved local microcirculation, and reduced free radical levels.

In the present study, the univariate analysis of the good and poor prognosis groups revealed significant intergroup differences in the GCS score at admission, tracheotomy status, first hyperbaric oxygen therapy duration, and number of hyperbaric oxygen therapy courses, whereas the multivariate analysis confirmed that all of these factors, except the number of hyperbaric oxygen therapy courses, were independent prognostic factors. Therefore, hyperbaric oxygen therapy may play an important role in improving the prognosis of patients with severe brain injury. A study by Xu et al.\textsuperscript{27} compared hyperbaric oxygen therapy with routine therapy for the treatment of severe brain injury and found that brain contusion, coronary heart disease, hydrocephalus, and tracheotomy affected the prognosis of patients with severe brain injury. In addition, that study reported that hyperbaric oxygen therapy could improve the indices of patients with severe brain injury, thereby significantly improving their prognosis. These findings are consistent with those of our study and indicate that hyperbaric oxygen therapy can effectively improve the prognosis of patients with severe brain injury.

The present study confirmed that hyperbaric oxygen therapy was an effective treatment for patients with severe brain injury; however, the underlying mechanism was not further explored. The optimal hyperbaric oxygen therapy duration in a clinical setting remains unknown. This study did not conduct a long-term follow-up examination of patients with severe brain injury, and therefore, the
long-term performance remains unclear. Furthermore, this study was not blinded or sham controlled. These shortcomings of our study should be addressed in future studies to further verify our conclusions.

In conclusion, hyperbaric oxygen therapy can effectively promote the recovery of neurological function as well as improve the cognitive function and prognosis of patients with severe traumatic brain injury.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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