

Research Article

Exploring the Therapeutic Effect of Early Hyperbaric Oxygen Therapy on Severe Traumatic Brain Injury and Its Cognitive and Behavioral Dysfunction

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Abstract

Objective To investigate the therapeutic effect of Hyperbaric oxygen therapy (HBO) on the secondary cerebral cognitive insufficiency and behavioral insufficiency of severe traumatic brain injury (sTBI) that is underwent to groups evaluated for with establish diagnosis of cognitive function therapy and damaging brain imaging. **Methods** A retrospective case-series study was conducted to analyze 87 patients with sTBI secondary cerebral cognitive insufficiency and behavioral insufficiency from January 2020 to January 2024, including 45 patients in the HBO treatment group and 42 patients in the control group. The baseline data of the two groups were comparable to compare the differences in GOS and FIM recovery between the two groups. **Results** The curative effect of the HBO treatment group was significantly better than that of the traditional treatment group, and there was a significant difference in medical statistics ($P < 0.05$). **Conclusion** The significant therapeutic effect of HBO in the treatment of sTBI's brain cognitive insufficiency and behavioral disorder can be attributed to the improvement of the pathological morphology and structure of specific brain injury sites.

Keywords

Cranio-cerebral Injury, HBO, Cerebral Cognitive Insufficiency, Nerve Recovery, Efficacy

1. Background

Severe traumatic cranial injury (sTBI) is relatively common in clinic that with an incidence of 59.9%-67.1% [1]. There were easy to lead to primary multiple or secondary intracranial injury, and which poses double threat to the health and life safety of patients. Surgery is the main treatment for sTBI to ensure a significant reduction in the mortality of patients. However, due to the different injury mechanisms of sTBI, different changes in consciousness or decreased consciousness level, forgetfulness, cognitive insufficiency,

behavioral insufficiency and neuropsychological abnormalities may be secondary to sTBI [2]. Among these secondary impairments, the incidence of cognitive dysfunction is the highest, followed by behavioral dysfunction. In addition, the more severe the brain injury, the higher the incidence, which has a mutual causal relationship and is the key factor affecting the recovery of sTBI. However, The mechanism of brain cognitive and behavioral dysfunction is different from that of trauma mechanisms (rapid

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acceleration or deceleration and of the head etc), and the specific anatomical parts (Front lobe, temporal lobe, cingulate gyrus, anterior part of corpus callosum, brain stem, etc). of the brain and the content of neuromolecular in blood after injury are related to systemic inflammation. Recent advances in radiology and medical imaging, in particular diffusion tensor imaging and advanced perfusion models, could potentially fill the gap and provide better understanding of the interdependence among white matter structure, cerebral blood flow and cognition. Nevertheless, HBO therapy for cognitive dysfunction after traumatic brain lesion than that cerebrovascular stroke. If the early treatment is not timely, it will seriously affect the quality of life of patients, and even cause permanent chronic traumatic encephalopathy or vegetative state. In view of the unsatisfactory curative effect at present, 45 patients treated with hyperbaric oxygen (HBO) in our hospital from January 2020 to January 2024 were retrospectively analyzed, and 42 patients were compared with traditional treatment. The following report is reported:

2. Clinical Data and Methods

2.1. General Data

From January 2020 to January 2024, 45 patients with TBI secondary cerebral cognitive insufficiency and behavioral disorder were treated with HBO (HBO treatment group); In addition, 42 patients with TBI secondary cognitive impairment treated with traditional therapy (non- HBOT group) were selected to be included from January 2020 to January 2024. There were no statistically significant differences in baseline data such as age, gender, GCS and manifestations of cognitive impairment between the two groups ($p > 0.05$, Table 1), indicating comparability.

2.2. Inclusion Criteria

- (1) All patients met the diagnostic criteria for TBI;
- (2) all patients had cognitive dysfunction and behavioral dysfunction after secondary brain injury;

(3) patients requiring surgery were operated on time and their vital signs were stable;

(4) cerebrospinal fluid leakage was stopped after;

(5) There is no absolute contraindication to enter HBO cabin.

3. HBO Treatment and Results

3.1. HBO Treatment

16/3200 mm large hyperbaric oxygen treatment chamber manufactured by Hongyuan Oxygen Factory in Yantai, Shandong Province, Oxygen was supplied by oxygen helmet or secondary oxygen mask, and 2-3-4 treatment courses were performed respectively, the duration was 2 hours, pressure Force 2ATA (0.1MPa), rest for 10 minutes in the middle, liquid oxygen concentration $\geq 95\%$, after the completion of the total course of treatment imaging review was performed. Observation indicators and follow-up: All clinical observation Indicators (see Table 1) were followed up (See Table 2). Meanwhile, imaging changes were observed before and after treatment.

3.2. Statistical Analysis

Statistical methods: SPSS 20, 0 soft ware was used for statistical analysis. Clinical baseline data were represented by $\bar{x} \pm s$, and t test was used to compare the two groups. Radix data were represented by the number of cases and percentage or composition ratio, and χ^2 test or fisher exact probability method were used for comparison between the two groups; Rank sum test was used for rank data comparison. The results were statistically significant except for sex and age.

4. Results

Table 1. Comparison of clinical baseline data between the two groups Impact factors. After statistical treatment, $P < 0.05$ was considered to be different and statistically significant. Table 2. Logistic regression analysis shows significant differences, $P < 0.05$.

Table 1. Patient characteristics.

	HBO group n =(45)	control group (n = 42)	P
Age, y	55.48 \pm 15.21	60.55 \pm 9.92	0.078
x, n (male/female)	29/16	0.701	
The time of injury d 32.19 \pm 23.32	34.34.13 \pm 37.64.13	0.741	

	HBO group	control group	P
	n =(45)	(n = 42)	
Treatment time, d	38.38 ±15.14	38.90 ±32. 71	0.558
Causeofinjury, n (%)			0.469
Traffic injuries	30 (66.6)	29 (69.1)	
Height fall injuries	8 (17.8)	6 (14.3)	
Other	7 (15.6)	7 (16.7)	
Education y, years	5.91 ±2.11	5.83 ±2.74	0.849
Head AIS, score	4 (4-5)	4 (3-5)	0.094
GCS, score	7.01 ±2.92	7.31 ±2.20	0.707
Hypertension, n (%)	10 (22.8)	10 (24.4)	0.797
Systolic blood pressure			
mmHg	123.95±16.08	1 25.90±15.52	0.495
Diabetes, n (%)	3 (6.7)	7 (16.7)	0.181
Weak pupil response, n (%) 13 (28.9)	18 (42.9)	0.141	
derwent surgery, n (%) 29 (79.3)	21 (50.0)	0.211	
Tracheotomy, n (%)	23 (51.1)	19 (45.2)	0.662
Blood glucose, mmol/L	5.92 ±1.51 6.	28 ±1.87	0.349

Comparison of clinical baseline data between the two groups Impact factors.

After statistical treatment, $P < 0.05$ was considered to be different and statistically significant.

Table 2. DRS, FIM and GOSE evaluation at follow-up after 6 months.

	HBO group	control group	t	p
	(n = 45)	(n = 42)		
DRS	7.82 ±3.71	14.83 ±7.94	-4.881	<0.001*
Open eyes 0.05 ±0.30	0.56 ±1.21	-2.476	0.018*	
Ability to communicate	0.48 ±0.66	1.67 ±1.67	-4.014	<0.001*
Motion	36 ±0.57	1.58 ±2.77	-2.596	0.013*
Cognitive ability	2.02 ±1.70	4.81 ±2.96	-4.996	<0.001*
Functional dependence	2.50 ±0.98	3.31 ±1.14	-3.348	0.001*
Coordination force	2.45 ±0.70	2.64 ±0.64	-1.21	0.226
FIM	95.27 ±20.86	80.67 ±38.39	2.048	0.046*
FIM -- Movement	69.25 ±17.00	64.81 ±28.77	1.553	0.126
FIM – Cognition	26.02 ±5.51	20.14 ±10.30	3. 231	0.002*
GOSE	4.48 ±1.42	3.67 ±1.57	2.422	0.018*

After treatment, the two groups were controlled and treated by medical statistics, * $P < 0.05$. There was significant difference.

5. Discussion

5.1. Basic Principles of Hyperbaric Oxygen Therapy

HBO, as the focus of clinical treatment and research in the 21st century [3], has become a more mature clinical treatment means, mainly applied to brain trauma in neurosurgery [4]. In this study, HBO to the medical administration of 100% oxygen at environmental pressure greater than one atmosphere absolute (ATA) that is used clinically for a wide range of medical conditions. One of HBO treatment, its main mechanisms of action is elevation of the partial pressure of oxygen in the blood and tissues as compared to simple oxygen supplementation. This allows five to ten times more oxygen to enter the blood plasma and to reach tissues suffering from low oxygen supply. HBO was actively used to treat sTBI and its secondary brain damage after the injury condition and vital signs were still stable, and good clinical results were achieved. The main symptoms of sTBI were improved, such as brain-cognitive insufficiency and behavioral insufficiency, and the primary brain damage affecting its recovery was also improved. Mainly manifested in the recovery of limb muscle dysfunction caused by injury in the motor area of the brain faster and more obvious, and for the cranial nerve damage that is difficult to cure, the olfactory nerve and optic nerve were also slowly improved. This is because HBO treatment can enhance the oxygen delivery of brain tissue injury, increase the dispersion of oxygen, thus increase the production of reactive oxygen species (ROS) and active nitrogen (RNS), and then reduce inflammatory response, improve angiogenesis, facilitate the synthesis of wound growth factors, and promote antibacterial action. At the same time, it was also found that insTBI patients treated with HBO, the pathway of brain injury caused by hypoxia was improved mainly by restoring the loss of metabolic homeostasis in neurons, which could facilitate the absorption of hematoma, alleviate brain edema, reduce intracranial pressure (ICP), prevent apoptosis and activate inactive nerve cells. It also significantly increased brain tissue pO₂, cerebral glucose utilization, vascular density and promoted synaptic remodeling. However, HBO physical dissolved oxygen can improve the survival rate of neurons by increasing the dissolved oxygen in blood without significantly changing the blood viscosity, which is conducive to the repair of the lesion and the establishment of collateral circulation, accelerate the relief of clinical symptoms, promote the recovery of primary craniocerebral injury, and have a synergistic effect on alleviating or promoting the curative effect of secondary diseases. Therefore, the clinical survival rate and quality of life were improved. In this study, timely MRI examination of the patients after HBO treatment proved that the anatomical structure of brain injury was significantly improved.

5.2. Significant Improvement of Cerebral Cognitive Dysfunction

sTBI patients are prone to cognitive dysfunction, motor dysfunction, sensory dysfunction, behavioral dysfunction, etc [5]. Among them, cognitive dysfunction is called cerebral cognitive dysfunction in modern times, and has the highest incidence in this study. Cerebral cognitive dysfunction is the key to the reduction of patients' quality of life. Currently, it is believed that the lower the GCS score after sTBI, the more serious the cognitive dysfunction, the longer the duration, and the worse the prognosis. Therefore, cerebral cognitive dysfunction after sTBI should be considered as an independent factor in clinical research. In this study, the patients with secondary cerebral cognitive insufficiency after sTBI were treated with HBO, and the contents of NSE, S100 β , dopamine and Ach in blood and cerebral blood flow were measured before entering the cabin. It was found that the higher the content and the lower the blood flow, the more obvious the degree of cognitive insufficiency was, and the patients' conscious state was also changed. At the same time, it was observed that it also had an impact on behavior disorders and emotions. It is concluded that the incidence and degree of cerebral cognitive insufficiency after sTBI are closely related to the increase of neuromolecular markers in blood and the decrease of blood flow, which is one of the important reasons for the symptoms and signs of clinical cognitive insufficiency. At the same time, it can be used as an indicator of the onset and efficacy evaluation of sTBI brain cognitive insufficiency, and it is also the target of selecting treatment. The increase or overexpression of these neuromarkers in blood and the decrease of blood flow are closely related to hypoxia. HBO therapy is preferred as an important approach that is more targeted than specific. The quantitative analysis of neuromolecular markers and the measurement of blood flow before and after HBO treatment were compared [6]. It was confirmed that the downregulation or adjustment of neuromarkers and the change of blood flow could improve brain cognitive dysfunction or behavioral disorders. However, the repair of nerve tissue and blood vessel injury can promote the rapid recovery of cognitive dysfunction. HBO treatment can induce neuroplasticity, induce cerebrovascular formation and improve the structural destruction of cerebral nerve anatomy related to cognition, and effectively promote the recovery of memory impairment, attention deficit, executive dysfunction and language function in the cognitive dysfunction. The pathological morphology of the specific parts of brain injury was significantly improved by MRI, which was caused by the strong penetrating effect of HBO on the injured brain glial cells. HBO treatment promoted neuroprotection by regulating mitochondrial permeability and reducing neuroinflammation, alleviated the secondary injury of sTBI, and promoted the recovery of brain cognitive dysfunction. Therefore, early HBO treatment can achieve a short-term effect of cognitive dysfunction in sTBI patients, and can also significantly improve the long-term. At the same time,

HBO treatment can also significantly improve the symptoms of cognitive dysfunction and behavioral and psychological defects by changing the cerebral blood supply and repair of glial cells in the anterior cingulate gyrus, posterior central gyrus, prefrontal and temporal regions after HBO treatment, and improve the quality of life is the ultimate goal of treatment [7]. This study believes that the sign of significant improvement of cognitive dysfunction is to enable patients to have the ability of self-rationality in daily life and orderly social communication, which is the key to improve the quality of life. Although it has been observed that the improvement of cerebral cognitive dysfunction in patients with continuous HBO treatment can significantly improve the quality of life. However, preventing the onset of chronic traumatic encephalopathy is very tricky [8]. Therefore, after 6 months of follow-up, the cognitive function of the HBO group was better than that of the control group according to DRS and FIM scores, indicating that HBO not only improved cognitive dysfunction in the short term, but also improved the cognitive dysfunction and prognosis of sTBI patients in the long term. And reduced the incidence of chronic traumatic encephalopathy caused by insufficient HBO treatment.

5.3. Improvement of Accompanying Behavior Disorders

The incidence of physiological, behavioral and cognitive dysfunction caused by sTBI was 79.69% [9], which was relatively high. However, in this study, cerebral cognitive dysfunction was listed as the highest incidence, and HBO treatment has achieved significant effect or cure. The secondary incidence rate is higher in patients with behavioral dysfunction, and early treatment has been paid more and more attention. At present, with the extensive and in-depth research of sTBI treatment, it is generally believed that sTBI treatment or rehabilitation intervention should be started as early as possible, and it is generally considered that early intervention therapy should be started within 1 month. In this study, HBO treatment was used within 2-3 weeks after injury and achieved good curative effect, mainly in the improvement of restlessness, emotional control, word order disorder, decision-making ability and environmental adaptation and other behavioral deficiencies, and also significantly controlled disorders such as paroxysmal hallucination, fantasy, anxiety and fear, which is also very beneficial for improving brain cognitive dysfunction. Animal experimental studies have shown that early treatment and intervention can improve the behavioral dysfunction of sTBI rats [11]. Similar to the observation of clinical HBO treatment effect in this study. However, due to the serious behavior disorder of a few patients, the combination of treatment is poor, which not only affects the curative effect, but also adversely affects the recovery of other functions. In order to obtain the treatment opportunity early, HBO treatment after appropriate medication is beneficial to promote the increase of blood vessel density in the hippocampal region and improve local blood flow. At the

same time, it can improve the regeneration of neurons and restore the normal function and remodeling of the presynaptic membrane, which plays an important role in the recovery of behavior and manic affective dysfunction.

5.4. Efficacy Evaluation for Dysfunction of Cognitive and Behavioral

In this study, when HBO treated the patients with cerebral cognitive and behavioral dysfunction after sTBI, or both achieved significant curative effect, the recovery of cerebral nerve injury was relatively obvious, and the muscle strength of the patients with limb paralysis was improved rapidly, and the limb muscle strength could completely reach normal with the increase of treatment course. But this study observed limb paralysis caused by brain nerve structure damage in clinical practice that is significant impact on the recovery or increased of cognitive dysfunction in the brain. The structural damage to the brain nerves that leads to cognitive impairment and limb paralysis is different. When HBO is used to treat cognitive and behavioral dysfunction that is pay attention to the therapeutic effect of brain specific nerve structure damage. Sometime, severe limb paralysis affects the recovery of cognitive and behavioral dysfunctions, and cognitive and behavioral functions affect the recovery of paralysis that is the importance of further strengthening rehabilitation. As a result, the hospitalization time was reduced, and the quality of daily living activities of out-of-hospital patients was significantly improved. At the same time, increasing the intensity of rehabilitation training is an important factor affecting the therapeutic effect. In this study, intensive rehabilitation training during HBO treatment of sTBI secondary damage can help patients recover function faster and improve GOS prognostic score and FIM score. According to DRS, FIM and GOSE scores after HBO treatment, the patients receiving HBO treatment had better results in cognition, behavior, communication ability and functional level than the control group ($P < 0.05$). It was confirmed that treatment can improve the secondary and primary lesions of sTBI. HBO treatment will increase the atmospheric pressure and high oxygen concentration in the physiological range as drugs, and improve the pathophysiological process of the disease through the downregulation of the expression of neurobiological markers and the inhibition of brain blood flow, so as to achieve the long-term prognosis or cure of patients. However, the therapeutic effect is determined by the dose and time of intervention after sTBI brain injury. However, this study believes that the reasonable choice of HBO treatment time window, the number of treatment courses and oxygen concentration are the key to obtain good curative effect. At the same time, intensive rehabilitation training in HBO treatment of sTBI secondary damage can help patients recover function faster, improve GOS prognostic score and FIM score. Therefore, according to DRS, FIM and GOSE scores, the HBO treatment group showed that patients receiving HBO treatment had better results in cognition, behavior, communication ability and functional level than the control group ($P < 0.05$). However,

significantly better than drug therapy [14].

6. Conclusion

sTBI's cognitive insufficiency and behavioral insufficiency belong to secondary brain damage. As the secondary brain damage is easy to lead to hypoxia, the content of neuromolecular markers in the blood of the patients increases, and the higher the secondary brain damage, the more serious the clinical symptoms and signs of cerebral cognitive insufficiency and behavioral disorders. Early treatment with HBO has achieved significant recent curative effect and improved long-term prognosis. At the same time, the nerve injury has a good recovery. In this way, the neural markers were not only used as the main indicators for the diagnosis and treatment of sTBI, such as brain recognition insufficiency and behavioral dysfunction, but also MRI showed that the damage of special intracranial neuroanatomical structures was significantly improved. However, the mechanism of HBO's treatment of sTBI brain cognitive insufficiency and behavioral insufficiency needs to be further explored.

7. Limitation Restricted

Due to the focus of this study on clinical patients efficacy that is the mechanism of HBO treatment needs further research.

Abbreviations

HBO	Hyperbaric Oxygen
FIM	Functional Independence Measure
ARS	Ability Rating Scale
sTBI	Severe Traumatic Brain Injury
MRI	Magnetic Resonance Imaging
GCS	Glasgow Coma Scale
ICP	Intracranial Pressure
GOS	Glasgow Outcome Scale
RNS	Active Nitrogen
ROS	Reactive Oxygen Species

Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] Ruan Xiaorui, Cheng Peixia, Hu Guo-qing, Incidence and prevalence trend analysis of craniocerebral trauma in China from 2000 to 2019 [J]. Chinese Journal of Neurosurgery, 37(12), 1225. (in Chinese)
- [2] Margherita Di Paola, PsyS, PhD; OwuenPhillips, MSc et al. Selective Cognitive Dysfunction Is Related to a Specific Pattern of Cerebral Damage in Persons With Severe Traumatic Brain Injury [J]. J Head Trauma Rehabil, 2015, Vol. 30, No 6 403.
- [3] Irit Gottfried, Nofar Schottlender and Uri Ashery. Hyperbaric Oxygen Treatment From Mechanisms to Cognitive Improvement [J]. Journal of Biomolecules. 11202, 1150.
- [4] Ding Jian bo. Application of hyperbaric oxygen therapy in the treatment of brain stromal tumors [J]. Chinese Journal of Neurosurgery, 2011, 27(2), 210. (in Chinese).
- [5] Han Xi, Hou Lijun, Dong Yan. Research progress of insomnia after traumatic craniocerebral injury [J], Chinese Journal of Neurosurgery, (33), 7.752.
- [6] Zhang Yan ping, Sun Haitao, Zhai Jianfeng, et al. To investigate the effect of hyperbaric oxygen on classification of cognitive insufficiency after severe traumatic brain injury [J]. Medicine and Health, 1, 2022, 94.
- [7] Amir Hadanny, Stefanie Abbott, Gil Suzin et al: Effect of hyperbaric oxygen therapy on chronic neurocognitive deficits of posttraumatic brain injury patients: retrospective Analysis [J] British Medical Journal, 2018, (8): e023387. <https://doi.org/10.1136/bmjopen-2018-023387>
- [8] Inbal Ethel, MA, CCC-SLP, Amy O, Bowles, MD et al: Rehabilitation of Cognitive Dysfunction Following Traumatic Brain Injury [J]. Phys Med Rehabil Clin N Am 30(2019) 190.
- [9] Su Liu, Guangyu Shen, Shukun Deng, et al: Hyperbaric oxygen therapy improves cognitive functioning after brain injury [J]. Neural Regeneration Research. (35), 8, 3334.
- [10] Liang Xi 'an. Incidence and manifestations of mental disorders after severe craniocerebral injury. Analysis of influencing factors [J]. Clinical and Practice. 14(13), 2015, 53.
- [11] Laura B. Tucker, Amanda H. Fu, and Joseph T. McCabe. Hippocampal-Dependent Cognitive Dysfunction following Repeated Diffuse Rotational Brain Injury in Male and Female Mice. Journal of Neurotrauma [J]. June 1, 2021. 1587.
- [12] Yin Lu, Zhou Xianshan, Cheng Jincheng. Et al. Hyperbaric oxygen therapy and early intensive rehabilitation training for functional disorders and prognosis of patients with craniocerebral injury [J]. Advances in Wound Care. (12) 10.2021.
- [13] Paul G. Harch, Susan R. Andrews, Cara J. Row 3 et al: Hyperbaric oxygen therapy for mild traumatic brain injury with persistent post concussion syndrome [J]: A randomized controlled trial. 2023 vol 10, Issue 1, 9-10.
- [14] Zhang Yan ping, Sun Haitao, Zhai Jianfeng, et al. To investigate the effect of hyperbaric oxygen on classification of cognitive insufficiency after severe traumatic brain injury [J]. Medicine and Health, 1, 2022, 93.