Hyperbaric oxygen on rehabilitation of brain tumors after surgery and effects on TNF-α and IL-6 levels

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Received May 17, 2018; Accepted January 21, 2019

DOI: 10.3892/ol.2019.10000

Abstract. Hyperbaric oxygenation (HBO) on postoperative rehabilitation of brain tumors and effects on tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels were explored. A retrospective analysis of 132 patients with brain tumors treated in the People's Hospital of Rizhao from October 2014 to October 2017 was performed. There were 62 patients in the observation group and 70 patients in the control group. Patients in the control group were treated with conventional drugs, and patients in the observation group were treated with HBO on the basis of conventional drug therapy. Levels of serum TNF-α and IL-6 were measured by ELISA before and after treatment. Cerebral arterial flow velocity and spasticity were measured by cranial color Doppler ultrasonography. Neurological function deficit (NFD) and activities of daily living (ADL) were used to evaluate the clinical recovery of the patients. Clinical efficacy was compared and analyzed. There were no significant differences between the two groups before treatment (P>0.05). After treatment, serum TNF-α and IL-6 levels were significantly lower than pretreatment levels (P<0.05), and serum TNF-α and IL-6 levels in the observation group were lower than those in the control group (P<0.05). Cerebral arterial flow velocity in observation group after treatment was significantly lower than that in the control group. The number of patients with cerebral arterial spasm after treatment in the observation group was significantly smaller than that in the control group. NFD scores in the observation group were lower than those in the control group after treatment. After treatment, ADL scores in the observation group were significantly higher than those in the control group (P<0.05). The comprehensive treatment effect of HBO is significant. It can inhibit the expression of inflammatory factors in serum and reduce cerebral arterial flow velocity and effectively reduce the number of patients with cerebral arterial spasm. It can reduce NFD and improve the quality of life of patients. Therefore, it is worthy of clinical popularization.

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Key words: brain tumor, HBO, TNF-α, IL-6, rehabilitation effect

Introduction

Brain tumors are generally divided into two major categories, primary tumors originating from intracranial tissue and metastatic tumors originating from other parts (1). Prevalence of metastatic brain tumors is 10-fold that of primary brain tumors, and brain metastases occur in 20-40% of tumor patients (2,3). Brain tumors seriously endanger human life and health. Brain tumors mostly occur in young adults and gliomas is the most common type (4). Genetic factors, radiation exposure, intracranial injury, and viral factors are correlated with the etiology of brain tumors (5). Due to the high metabolic state of tumors and the abnormal disorder of blood vessels, oxygen level required by tumor cells is significantly higher than oxygen supply, which in turn causes hypoxia of the tumor tissues. It has been reported that the existence of the hypoxic microenvironment may cause the recurrence of tumors and increase the degree of malignancy (6,7).

Hyperbaric oxygen (HBO) is an adjuvant therapy that plays an important role in the treatment of malignant tumors (8). HBO is pure oxygen with a higher pressure than normal atmospheric pressure, and its mechanism of action mainly depends on increasing the oxygen capacity in cytoplasm and further increasing oxygen content in cells, resulting in a decrease in cerebrovascular blood flow due to cerebral vasoconstriction, and a corresponding decrease in intracranial pressure (9). Inflammatory factors can cause tissue damage after brain injury by causing excessive release of inflammatory mediators, and HBO can improve brain metabolism and restore brain function (10). In the development of brain tumors, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are polypeptide cytokines involved in inflammation and have a wide range of biological activities (11). Elevated levels of IL-6 and TNF-α in serum can cause the body to undergo a stress reaction after brain injury in order to destroy the blood-brain barrier, and cause monocytes and neutrophils to enter the brain (12).

The current study aimed to investigate the effect of HBO on postoperative rehabilitation of brain tumors and the effects on TNF-α and IL-6 in patients, so as to provide references for the treatment of brain tumors.

Patients and methods

General information. This is a retrospective study. A total of 132 brain tumor patients who were admitted to the People's Hospital of Rizhao (Rizhao, China) from October 2014 to October 2017 were selected. Those patients included 64 males and 68 females, with an age range of 13-72 years. There were 62 patients in the observation group and 70 patients in the control group. Patients in the control group were treated with conventional drugs, and patients in the observation group were treated with HBO on the basis of conventional drug therapy. There was no statistically significant difference in general data between the groups (P>0.05). All the cases were diagnosed by imaging and postoperative pathological examinations. The patients were excluded from pregnancy, lactation, bleeding after brain surgery and contraindications, tumors in other parts of the body, cerebral thrombosis, liver and kidney dysfunction, and other diseases. The study was approved by the Ethics Committee of People's Hospital of Rizhao. All patients or their family members signed informed consent. General information is shown in Table I.

Table I. General information.

Indexes	Observation (n=62)	Control (n=70)	χ^2/t	P-value
Age (years)				
≥43	29 (46.77)	35 (50.00)	0.137	0.730
<43	33 (53.23)	35 (50.00)		
Sex				
Male	35 (56.45)	29 (41.43)	2.971	0.116
Female	27 (43.55)	41 (58.57)		
Course of disease (years)				
≥2	16 (25.81)	20 (28.57)	0.127	0.845
<2	46 (74.19)	50 (71.43)		
Blood glucose (mmol/l)	5.64±2.13	5.82±2.09	0.489	0.625
Hemoglobin (g/l)	12.24±1.25	12.32±1.07	0.396	0.693
Blood calcium (mmol/l)	2.33±0.25	2.28±0.31	1.012	0.314
Hematocrit (%)	37.25±5.24	37.92±5.13	0.741	0.460
Albumin (g/l)	39.86±3.56	40.18±4.21	0.468	0.640
Insulin-like growth factor-I (ng/ml)	232.53 ±19.28	235.46±18.86	0.882	0.380
Sialic acid (mg/l)	252.26±46.84	254.31±45.67	0.254	0.800

Reagents and equipment. TNF-α and IL-6 ELISA kits were purchased from Wuhan Boster Biological Technology, Ltd., Wuhan, China. The Anthus PHOMO automatic microplate reader was purchased from Shanghai Zhongsheng Science Development Co., Ltd. (Beijing, China). The KJ-2V4M Ultrasonic Transcranial Doppler Blood Flow Analyzer was purchased from Nanjing Kejin Industrial Co., Ltd. (Nanjing, China). Medical air pressurized cabin was purchased from Guizhou Fenglei Oxygen Capsules Co., Ltd. Vitamin C was purchased from Guangdong Hengjian Pharmaceutical Co., Ltd., Jiangmen, China (state approval no. H44021171).

Two treatment methods. In the control group, routine treatment methods such as brain neurotrophic drugs, dehydration drugs, hemostatic drugs, and awakening agents were used, and the observation group was supplemented with HBO treatment. Medical air pressurized cabin was used with treatment pressure 0.18 Mpa. Pressure was increased for 25 min and patients were asked to wear mask to absorb pure oxygen for 60 min, rest for 10 min and decompression for 25 min, once a day. Routine use of vitamin C (0.1 g/time, 3 times per day) was performed during BO treatment. Treatment efficacy was reviewed after 10 HBO treatments.

Detection of serum TNF-α and IL-6. Peripheral venous blood (3 ml) was extracted from each patient at 1 day before treatment and 1 day after treatment. Blood was centrifuged at 2,300 x g for 8 min to collect serum. Serum TNF-α and IL-6 levels were measured by ELISA according to the instructions of the kit.

Observation indicators. Cerebral arterial flow velocity and spasticity were measured by cranial color Doppler ultrasonography. Neurological function deficit (NFD) and activities of daily living (ADL) were used to evaluate the clinical recovery of the patients. Clinical efficacy was compared and analyzed.

Statistical analysis. SPSS 17.0 statistical software was used for analysis (Shanghai Cabit Information Technology Co., Ltd., Shanghai, China). Chi-square test was used for the comparisons of countable data, Student's t-test was used for comparison of measurement data, and paired t-test was used for comparison before and after treatment in the same group. P<0.05 was considered to indicate a statistically significant difference.

Result

Serum TNF-α and IL-6 levels in the two groups before and after treatment. Levels of TNF-α and IL-6 in the observation group were not significantly different from those in the control group before treatment (P>0.05). Levels of TNF-α and IL-6 in both groups were significantly reduced after treatment (P<0.001). After treatment, levels of TNF-α and IL-6 were significantly lower in the observation group than in the control group (P<0.001) (Fig. 1; Table II).

Comparison of flow velocity of middle cerebral artery by transcranial Doppler before and after treatment in two groups of patients. There was no significant difference in the flow rate of cerebral arteries between the observation and the control groups before treatment (P>0.05). Flow rate of cerebral arteries in both groups were significantly reduced after treatment (P<0.001). Cerebral arterial flow velocity in the observation group after treatment of 96.74±20.86 cm/sec was significantly lower than that in the control group 119.52±18.27 cm/sec (P<0.001) (Fig. 2; Table III).

Comparison of cerebral arterial spasm between the two groups before and after treatment. Before treatment, there was no significant difference in the incidence of arterial spasm between the observation and the control groups (P>0.05).

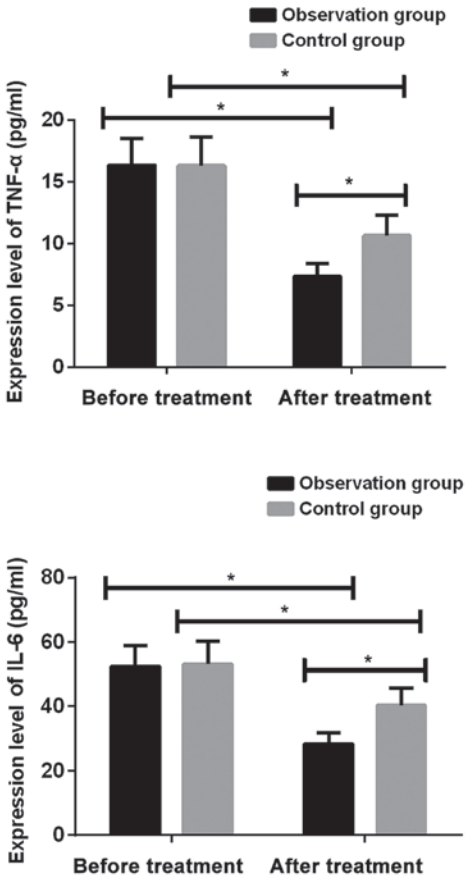

Figure 1. Levels of serum TNF-α and IL-6 before and after treatment in both groups. ELISA results showed that levels of TNF-α and IL-6 in the observation group were not significantly different than those in the control group before treatment (P>0.05). Levels of TNF-α and IL-6 in both groups were significantly reduced after treatment (P<0.001). After treatment, levels of TNF-α and IL-6 were significantly lower in the observation group than in the control group (*P<0.001). TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

Table II. Serum TNF-α and IL-6 levels in the groups before and after treatment.

Groups	Cases	Treatment time	TNF-α (pg/ml)	IL-6 (pg/ml)
Observation	62	Before	16.35±2.15	52.35±6.58
		After	7.35±1.04[a]	28.35±3.42[a]
		t value	29.67	25.48
		P-value	<0.001	<0.001
Control	70	Before	16.32±2.28	53.08±7.12
		After	10.65±1.64	40.27±5.46
		t value	16.89	11.94
		P-value	<0.001	<0.001

[a]P<0.001, compared with post-treatment level in the control group. TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

Incidence of arterial spasm was significantly decreased after treatment in both groups (P<0.001). After treatment, there were 9 patients with cerebral arterial spasm in the observation group and 27 patients with cerebral arterial spasm in the control group. Significant differences were found between the two groups (P<0.05) (Fig. 3; Table IV).

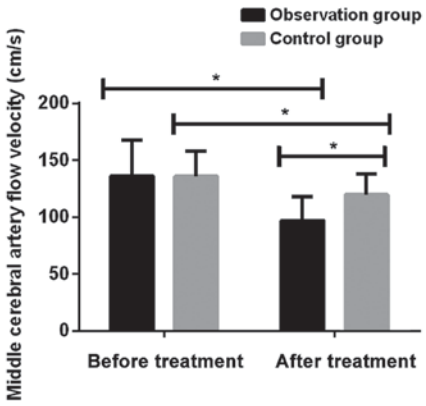

Figure 2. Comparison of cerebral arterial flow velocity before and after treatment in the two groups of patients. There was no significant difference in cerebral arterial flow velocity between the observation group and the control group before treatment (P>0.05). Cerebral arterial flow velocity in both groups were significantly reduced after treatment (P<0.001). Cerebral arterial flow velocity in the observation group after treatment was significantly lower than that in the control group (*P<0.001).

Table III. Comparison of cerebral arterial flow velocity in the two groups before and after treatment.

Groups	Cases	Treatment time	Cerebral arterial flow velocity (cm/sec)	t value	P-value
Observation	62	Before	135.89±31.42	8.174	<0.001
		After	96.74±20.86[a]		
Control	70	Before	135.78±21.84	4.778	<0.001
		After	119.52±18.27		

[a]P<0.001, compared with post-treatment level in the control group.

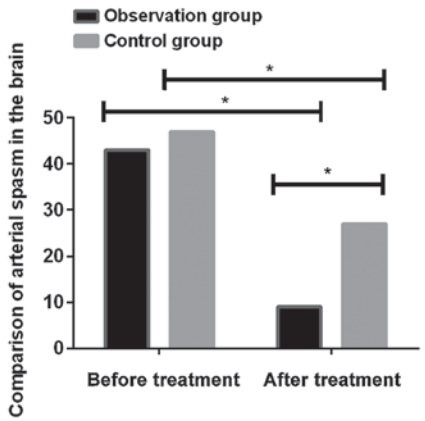

Figure 3. Comparison of cerebral arterial spasm between the two groups before and after treatment. Before treatment, there was no significant difference in incidence of arterial spasm between the observation group and the control group (P>0.05). Incidence of arterial spasm was significantly decreased after treatment in both groups (P<0.001). After treatment, number of patients with cerebral arterial spasm was significantly smaller in the observation group than in the control group (*P<0.001).

Table IV. Comparison of cerebral arterial spasm between the two groups before and after treatment.

Groups	Cases	Treatment time	Cerebral arterial spasm, n (%)	χ^2	P-value
Observation	62	Before	43 (69.35)	38.29	<0.001
		After	9 (14.52)[a]		
Control	70	Before	47 (67.14)	11.47	<0.001
		After	27 (38.57)		

[a]P<0.001, compared with post-treatment level in the control group.

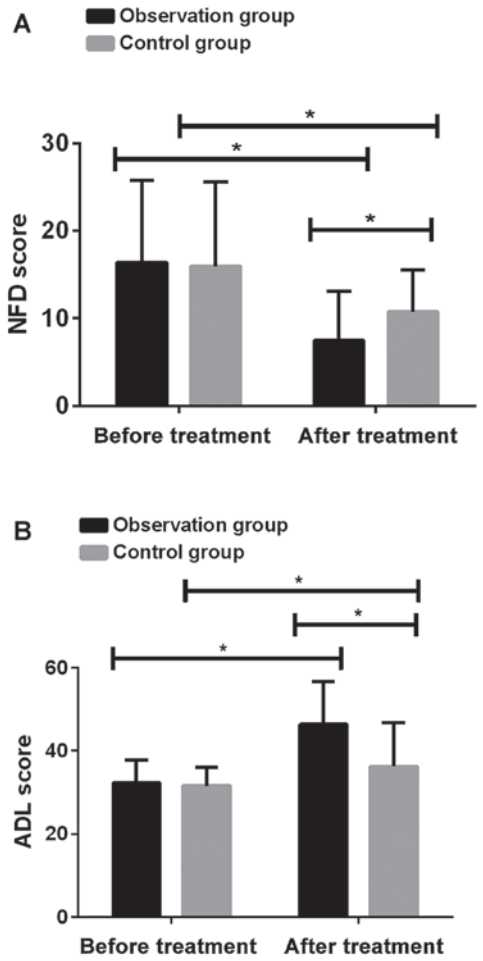

Figure 4. Comparison of NFD and ADL scores before and after treatment in two groups of patients. (A) Results showed that there was no significant difference in NFD scores between two groups before treatment (P>0.05). NFD scores were significantly reduced after treatment (P<0.0001). After treatment, NFD score was lower in the observation group than in the control group (P<0.001). (B) Results showed that there was no significant difference in ADL scores between two groups before treatment (P>0.05). ADL scores were significantly increased after treatment (P<0.0001). After treatment, ADL score was higher in the observation group than in the control group (*P<0.001). NFD, neurological function deficit; ADL, activities of daily living.

Comparison of NFD and ADL scores before and after treatment in two groups of patients. Before treatment, there was no significant difference in NFD and ADL scores between two groups (P>0.05). After treatment, NFD scores were significantly reduced and ADL scores were significantly increased (P<0.001). NFD score in the observation group after treatment (7.52±5.57) was significantly lower than that in the control group (10.74±4.75; P<0.001) and ADL score in the observation group (46.38±10.27) was significantly higher than that in the control group (36.28±10.51; P<0.001) (Fig. 4; Table V).

Table V. Comparison of NFD and ADL scores before and after treatment in two groups of patients.

Groups	Cases	Treatment time	NFD score	ADL score
Observation	62	Before	16.35±9.38	32.25±5.46
		After	7.52±5.57[a]	46.38±10.27[a]
		t value	6.373	9.566
		P-value	<0.001	<0.001
Control	70	Before	15.93±9.64	31.56±4.39
		After	10.74±4.75	36.28±10.51
		t value	4.041	3.467
		P-value	<0.001	<0.001

[a]P<0.001, compared with post-treatment level in the control group. NFD, neurological function deficit; ADL, activities of daily living.

Discussion

Brain tumor is a common neurosurgical malignancy in clinical practice. Continuous growth of intracranial tumors will compress surrounding tissues, resulting in nerve compression and cerebral edema (13). Studies have shown that most patients with brain tumors have symptoms of intracranial hypertension (14). Surgical treatment is currently the preferred treatment for brain tumors in clinical practice, but it cause some trauma to nerve tissue while removing tumors (15). Brain function recovery is a long process (16). HBO has a significant effect on decompression sickness, hypoxic-ischemic encephalopathy, and anaerobic infections (17-19). HBO has the following characteristics: it is beneficial to improve tissue hypoxia; it has significant curative effect on decompression sickness and thrombosis; it can reduce tissue edema, and brain edema can be controlled; and it can inhibit the growth of some aerobic and anaerobic bacteria (20,21).

Results of this study showed that levels of TNF-α and IL-6 in the observation group were significantly lower than those in the control group after treatment (P<0.001). Findings reported by Chen *et al* (22) are basically consistent with our results, suggesting that HBO therapy can improve the inflammatory response in patients with brain tumors. It has been reported that the course of brain tumors is related to the efficacy of HBO therapy. Early use of HBO has important implications for the reduction of inflammatory factors, improvement of hypoxic symptoms, recovery of nerve function and brain function (23). In this study, cerebral arterial flow velocity in the observation group after treatment (96.74±20.86 cm/sec) was significantly lower than that in the control group (119.52±18.27 cm/sec; P<0.001). After treatment, there were 9 patients with arterial spasm in the observation group and 27 patients with arterial spasm in the control group. The difference was statistically significant (P<0.05).

After treatment, NFD score in the observation group after treatment (7.52±5.57) was significantly lower than that in the control group (10.74±4.75; P<0.001) and ADL score in the observation group (46.38±10.27) was significantly higher than that in the control group (36.28±10.51; P<0.001). Similar results were reported by Xu (24) and Lim *et al* (25). Control group was treated with conventional drugs, and combined use of HBO was performed in the treatment group and better efficacy was achieved. HBO is an ideal treatment for postoperative rehabilitation of brain tumor patients. HBO reduces flow of cerebral arteries in patients with brain tumors, so symptoms of hypoxia were improved. At the same time, HBO can also improve the ability of the body to sterilize and engulf necrotic cells, so as to achieve the elimination of lesions (26). Without timely treatment, brain cells around the tumor 'ischemic penumbra area' will die and patients' life and health will be endangered.

In conclusion, conventional therapy plus HBO is more effective than conventional therapy alone in postoperative rehabilitation of brain tumors. It can improve the inflammatory response of brain tumor patients, reduce the flow rate of cerebral arteries, and effectively reduce the number of patients with cerebral arterial spasm. At the same time, it lowers NFD and improves ADL. Therefore, it should be popularized in clinical practices.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

SH drafted the manuscript. SH and GW were mainly devoted to collecting and interpreting the general data. JL and HC performed ELISA. SH and CC interpreted cranial color Doppler ultrasonography result. All authors read and approved the final study.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of People's Hospital of Rizhao (Rizhao, China). Signed informed consents were obtained from the patients or the guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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