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ORIGINAL RESEARCH

Effects of early hyperbaric oxygen therapy with different frequencies on the nerve injury and vascular endothelial function in patients with acute cerebral infarction

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Abstract

The therapeutic efficacy of multi-frequency hyperbaric oxygen therapy (HBOT) on neurological function and vascular endothelial function in patients with acute cerebral infarction (ACI) has not been demonstrated. In the present study, a total of 92 patients with ACI admitted to the emergency department and neurology department of the First Affiliated Hospital of Gannan Medical College were divided into a low-frequency and a high-frequency group, and HBOT was given once and twice a day, respectively, on the basis of routine drug treatment. The National Institutes of Health Stroke Scale (NIHSS) score, clinical outcomes, neurological function and vascular endothelial function before and after treatment were compared between the two groups, and the safety of treatment was evaluated. No deterioration or death was observed in both groups, and the overall effective rate of the high-frequency group was significantly higher than that of the low-frequency group (95.65% *vs.* 84.78%); NIHSS score and neuron-specific enolase (NSE) and brain-specific protein (S100-β) levels were significantly lower in the high-frequency group than those in the low-frequency group after one-month treatment; endothelin-1 (ET-1) level obviously decreased, whereas the levels of vascular endothelial growth factor (VEGF) and nitric oxide (NO) were significantly increased after 1 month of treatment in the high-frequency group, indicating better vascular endothelial function compared with that in the low-frequency group; the results of safety assessment showed that no serious adverse reactions occurred in both high-frequency and low-frequency groups. Therefore, early HBOT at a frequency of twice a day can not only effectively improve neurological function, but also have a restorative effect on vascular endothelial function in ACI, which is a safe and effective therapy.

Keywords

ACI; HBOT; Neurological function; Vascular endothelial function; Safety

1. Introduction

Cerebral infarction, also known as ischemic stroke, is the most commonly diagnosed disease in China in secondary and higher hospitals, with acute cerebral infarction (ACI) being the most common and its mortality rate in the top three of all causes of death (Edwards and Hughes [4] 2021). The serious life-threatening disease is mostly acute and can develop rapidly within a few hours. In addition to neurological damage, it also causes clinical symptoms such as hemiplegia and aphasia (Xu, *et al*. [22] 2021). Traditional pharmacological treatment, for example, thrombolytic therapy, is currently a popular treatment regimen at home and abroad, but the clinical outcome of ACI is not satisfactory due to many reasons including contraindications and drug-related safety risks (Wang, *et al*. [20] 2021). Hyperbaric oxygen therapy (HBOT) is an effective therapeutic regimen that has been developed clinically more rapidly in recent years, and is characterized by a painless treatment process and good patient compliance. Besides, it has an important impact on sequelae and clinical outcomes (Moghadam, *et al*. [12] 2020; Resanović, *et al*. [14] 2020). Currently, there is no worldwide standard for optimal HBOT frequency, which is used once a day in conventional treatment. The therapeutic efficacy of multi-frequency HBOT has been demonstrated in the treatment of other conditions such as sudden deafness, but there are few reports involving the clinical treatment of ACI. This therefore prompted us to undertake the present study.

2. Materials and methods

2.1 Basic information

A total of 92 patients with ACI admitted to the emergency department and neurology department of the First Affiliated Hospital of Gannan Medical College We were selected from October 2020 to March 2021, as the study subjects. The basic information of all study subjects met the patient inclusion criteria of this study (see 1.2 for details), and the 92 cases were divided into a low-frequency group and a high-frequency group according to the frequency of HBOT received. The average age of the two groups was 64.13 $\pm$ 7.81 *vs.* 62.99 $\pm$ 10.34 years and the male-female ratio was 30/16 *vs.* 27/19, respectively. There were no significant differences in terms of the basic information above.

2.2 Screening criteria

Inclusion criteria: (1) Acute onset, first presentation and within one week; (2) In accordance with the ACI diagnostic criteria (Wang, *et al*. [21] 2012); (3) NIHSS score between 5–20 (excluding boundary values); (4) Patients who were sober and able to complete the questionnaire independently; (5) Patients with complete study data and willing to sign the informed consent forms.

Exclusion criteria: (1) Massive hemorrhage happened before admission, or failure of important organs, or excessive area of infarction, or unstable vital signs; (2) Patients with thrombolytic therapy history or mechanical thrombectomy before enrollment; (3) Contraindications to hyperbaric oxygen therapy (such as acute syndrome of respiratory distress, pregnancy, *etc.*) or intolerance; (4) Patients with poor compliance and incomplete statistical data who failed to complete the treatment.

2.3 Research methods

For low-frequency group, HBOT was administered once a day to the patients based on conventional drug therapy for acute cerebral infarction; for high-frequency group, HOBT was administered twice a day plus daily routine therapy. Routine medications include: Aspirin Enteric-coated Tablets (100 mg once a day after breakfast, produced by Bayer Healthcare Co.Ltd., HI20160685, Beijing, China), Atorvastatin Calcium Tablets (20 mg once a day at bedtime, produced by Pfizer Pharmaceuticals Co., Ltd., H20051407, Dalian, China), Xingnaojing Injection (intravenous infusion, once daily, 20 mL, Z41020664, Produced by Henan Tiandi Pharmaceutical Co., Ltd, Kaifeng, China), and Edaravone Injection (intravenous infusion, twice daily, 30 mg, H20050280, Produced by Nanjing Xiansheng Dongyuan Pharmaceutical Co., Ltd, Nanjing, China). The hyperbaric oxygen equipment is a medical large-scale multi-person air-pressurized chamber (version YC-3200, produced by Shandong Yantai Hongyuan Oxygen Industry Co., Ltd., Yantai, China). Details of HBOT were as follows: After the initial entry of the patient into the pressurized chamber, the air was pressurized at a uniform speed, when the air pressure in the pressurized chamber is twice the usual atmospheric pressure (0.22 MPa), intermittent oxygen inspiration is adopted in the manner of oxygen inhalation for 20 min, followed by a 5 min break for a total of three cycles. After a total oxygen inhalation time of 60 min, decompression was initiated at a constant speed, with the total duration of each hyperbaric chamber treatment being approximately 110 min. Patients in the low-frequency group received session once per day, whereas those in the high-frequency group received two sessions per day. The time interval between two treatments is approximately 5 to 6 hours, and 10 days was considered as one course of treatment, with both groups undergoing three courses of treatment.

2.4 Study contents

Efficacy evaluation was based on the reduction rate of National Institutes of Health Stroke Scale (NIHSS) scores after treatment, referring to the "Clinical Efficacy Evaluation Criteria for Stroke Patients". Patients were considered largely cured when the value was between 91% and 100%; effective when the value was between 46% and 90%; effective was between 18% and 45%; ineffective when the value was less than 18% or the increase was less than 18%; when the increase was more than 18%, the treatment was defined as worsening of the treatment effect or death (Zhang, *et al*. [24] 2020). The summation of the first three was considered as the total effective rate.

Neurological function indicators, including levels of neuron-specific enolase (NSE) and brain-specific protein (S100-β), were measured by enzyme-linked immunoassay, and indicators reflecting vascular endothelial function such as vascular endothelial growth factor (VEGF), endothelin-1 (ET-1) and nitric oxide (NO) were measured using radioimmunoassay before and one month after treatment. All biochemical indicators were provided by the Department of Laboratory, First Affiliated Hospital of Gannan Medical College.

Patients' vital signs were closely monitored during treatment, and adverse effects such as oxygen toxicity, decompression sickness, mental disorder, and syncope were counted.

2.5 Statistics

The raw data were summarized and analyzed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA) statistical software. The quantitative data such as the NIHSS score and levels of each indicator were represented as mean $\pm$ standard deviation (Mean $\pm$ SD), and independent sample t-test was used; the enumeration data was described by percentage, and χ^2 test was applied. A p value less than 0.05 was considered statistically significant.

3. Results

3.1 Comparisons on the therapeutic effects between low-frequency and high-frequency groups

There were no cases of deterioration or death in either the low-frequency or high-frequency groups during the treatment period. Only 2 cases of treatment were categorized as ineffectiveness and the overall effective rate was 95.65% in high-frequency group, which was significantly higher than the 84.78% of the low-frequency group, with a statistically

TABLE 1. Comparisons on the therapeutic effects between low-frequency and high-frequency groups (n, %).

Group	Number of Cases	Almost Healed	Effective	Valid	Ineffective	Deterioration or Death	Total Efficacy
Low-frequency	46	0	26 (56.52)	13 (28.26)	7 (15.22)	0	84.78
High-frequency	46	4 (8.69)	35 (76.09)	5 (10.87)	2 (4.35)	0	95.65
χ^2 value							11.661
p value							0.009

TABLE 2. Comparisons on the indicators of nerve damage between low-frequency and high-frequency groups ($\overline{X} \pm$ s).

Group	Number of Cases		NIHSS (points)	NSE (μg/L)	S100-β (μg/L)
Low-frequency	46	Prior treatment	12.93 ± 3.82	12.37 ± 1.60	1.04 ± 0.19
		1 month after treatment	6.17 ± 2.94	9.82 ± 1.39	0.65 ± 0.10
High-frequency	46	Prior treatment	13.38 ± 3.55	11.94 ± 2.02	1.04 ± 0.14
		1 month after treatment	4.72 ± 2.42	7.36 ± 1.42	0.35 ± 0.12
t value			2.579	8.417	13.086
p value			0.012	0.000	0.000

NIHSS: National Institutes of Health Stroke Scale; NSE: neuron-specific enolase; S100-β: brain-specific protein.

TABLE 3. Comparisons on the indicators of vascular endothelial function between low-frequency and high-frequency groups ($\overline{X} \pm$ s).

Group	Number of Cases		VEGF (ng/L)	ET-1 (μg/L)	NO (μmoL/L)
Low-frequency	46	Prior treatment	236.75 ± 27.09	108.93 ± 13.44	36.65 ± 5.85
		1 month after treatment	324.64 ± 47.17	71.13 ± 6.96	51.38 ± 7.72
High-frequency	46	Prior treatment	246.03 ± 30.42	109.55 ± 14.34	35.84 ± 5.32
		1 month after treatment	447.99 ± 51.02	43.99 ± 5.72	79.35 ± 9.77
t value			12.041	20.435	15.233
p value			0.000	0.000	0.000

VEGF: vascular endothelial growth factor; ET-1: endothelin-1; NO: nitric oxide.

significant difference ($p < 0.05$). See details in Table 1.

3.2 Comparisons on the indicators of nerve damage between low-frequency and high-frequency groups

The differences in NIHSS scores and levels of NSE and S100-β were not significant between low-frequency and high-frequency groups before treatment, which were significantly decreased to different degrees after one month of treatment. These indicators showed a greater decrease in the high-frequency group than the low-frequency group after treatment, and the difference was statistically significant ($p < 0.05$). See details in Table 2.

3.3 Comparisons on the indicators of vascular endothelial function between low-frequency and high-frequency groups

The levels of vascular endothelial function-related indicators between high-frequency and low-frequency groups were relatively similar before treatment, and the difference was not significant. After one month of treatment, the levels of VEGF, ET-1 and NO were ameliorated to certain extent in the two groups. In detail, the level of ET-1 was decreased, while the the levels of VEGF and NO were increased. Additionally, the levels of VEGF and NO increased more, and ET-1 level decreased more in the high-frequency group compared to that in the low-frequency group. The difference were statistically significant ($p < 0.05$), as shown in Table 3.

3.4 Comparisons on the undesirable outcomes between low-frequency and high-frequency groups

Statistically, there were no adverse effects in the low-frequency group during the treatment period. In the high-frequency group, one female patient presented with mild nasal obstruction due to a mild cold prior to hyperbaric oxygen therapy, and the symptoms were mild. The hyperbaric oxygen therapy was continued after relevant treatment targeting nasal obstruction and symptomatic relief, and no adverse reactions occurred thereafter. As for the other patients in the high-frequency group, only oxygen toxicity and decompression sickness were observed. Therefore, the rate of adverse reaction was 2.17%.

4. Discussion

According to incomplete statistics, cerebral infarction accounts for approximately 70%–80% of the 7 million patients with cerebrovascular diseases in China (Bao, *et al*. [1] 2020). The quality of life of the Chinese population has been severely affected by the disease suffering and economic burden associated with this disease. Since the outbreak of the noval coronavirus epidemic in 2019, the epidemic situation in China has been more severe. The occurrence of diseases has not only led to the inconvenience in daily life, but also increased the difficulty of medical treatment, which in turn has affected the screening and treatment of ACI to a certain extent. Besides, relevant studies have also shown that the risk of stroke, heart disease and other cardiovascular and cerebrovascular diseases could be increased by the infection with 2019 Coronavirus disease (COVID-19) (Katsanos, *et al*. [9] 2021; Nannoni, *et al*. [13] 2021; Syahrul, *et al*. [18] 2021; Tan, *et al*. [19] 2020). As the first cause of death in China, the early diagnosis and treatment intervention for this disease are of great significance to the prognosis of patients. There are diverse means of treating ACI, and pharmacological treatment is a key one, which is not effective due to the different tolerances of patients. HBOT is a clinically proven treatment option that has shown significant results in the treatment of ischemic-hypoxic diseases, especially in the treatment of ACI (Fernández, *et al*. [6] 2021; Somaa [17] 2021). Previous studies have confirmed that HBOT therapy can effectively improve angiogenesis and memory dysfunction in rats, with important significance for prognosis and brain protection (Ishihara [7] 2019; Zhao, *et al*. [25] 2020). Currently, once-a-day treatment regimens are broadly used in clinical studies, and it is still controversial in domestic and overseas studies whether the efficacy for ACI could be enhanced by increasing the frequency of treatment. The objective of this study was to explore the effects of twice-daily treatment on neurological function and levels of vascular endothelial factors in patients with ACI compared with conventional once-daily treatment.

The NIHSS is one of the most commonly used scales in clinical trials to assess the degree of neurologic impairment in stroke patients. Previous studies have shown that the scale can achieve internal consistency of 0.93 and inter-assessor agreement of 0.95, making it suitable for healthcare professionals and rehabilitation of stroke (Chalos, *et al*. [2] 2020; Mistry, *et al*. [11] 2022; Yamal and Grotta [23] 2021). The results of this study showed significantly better overall efficacy and NIHSS scores with twice-daily HBOT treatment compared with once-daily treatment, indicating that the high-frequency treatment twice a day has a better effect on neurological repair, which may be explained by the improvement of anoxia in the lesion area, promotion of the penetration and absorption of drugs, and protection of neurological function, *etc*. The results of this study are consistent with the conclusions of published articles. It has been shown that the twice-daily regimen is more effective in restoring patients' condition and protecting neurological function (Chen, *et al*. [3] 2021; Jiang, *et al*. [8] 2021; Lin, *et al*. [10] 2019; Shwe, *et al*. [16] 2021). The results of NSE and S100-β levels in this study also confirmed these conclusions. Vascular endothelial function is an important biological parameter in the clinical management of cardiovascular disease, such as VEGF, which not only represents neuronal cell repair but also stimulates angiogenesis (Engel, *et al*. [5] 2020). A comparison of three serological parameters in patients treated with HBOT at different frequencies showed that the improvement in vascular endothelial function in patients treated twice-daily at a high-frequency was significantly better than that of once-daily treatment, indicating that twice-daily HBOT treatment exerts certain encouraging function in nerve repair and vessel regeneration. The improvement in anoxic conditions in the body could effectively promote angiogenesis, thereby improving the status of blood flow perfusion in the patient's brain tissue.

The benefits of HBOT therapy for ACI are that it promotes the hyperoxia in lesion tissue, thereby reducing cranial nerve and tissue damage due to hypoxia (Sen [15] 2021; Zhu, *et al*. [26] 2022). The above experimental results have confirmed the important impacts of HBOT therapy in neurological function repair and angiogenesis, and its clinical effect has been fully confirmed by the study; however, some adverse effects inevitably occur during the treatment process, and therefore a final statistical analysis of adverse effects was performed in both groups. This study also showed that under the circumstances of strict grasp of the indications and contraindications of HBOT, standard operation, close surveillance of therapeutic state of patient, and early risk plan, the risk of undesirable reactions is very low. Only 1 case showed minor sinus pneumatic injury due to a mild cold prior to treatment was treated symptomatically and the nasal congestion improved with no subsequent adverse effects, further confirming that HBOT twice a day is safe and effective.

5. Conclusions

In summary, HBOT with different frequencies demonstrates different clinical efficacies in the treatment of ACI. Early implementation of twice-daily HBOT can improve neurological impairment in ACI patients, improve overall outcome and actively promote angiogenesis to some extent, making it an effective and safe treatment method. In this study, twice-daily HBOT treatment was classified as a high-frequency treatment, but whether the overall treatment effect can be improved by increasing the frequency of HBOT remains unclear and needs to be further investigated with a larger study sample.

AUTHOR CONTRIBUTIONS

HJL and XFL—designed the research study. KY, JYL and QFH—performed the research. JYL and HL—analyzed the data. HJL and XFL—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Gannan Medical University (Approval no. LLSC-2022080801). Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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