Am J Transl Res 2023;15(3):1897-1904
www.ajtr.org /ISSN:1943-8141/AJTR0146985

Original Article

Effect of hyperbaric oxygen combined with folic acid on clinical efficacy and cognitive function in patients with cerebral small vessel disease

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Received October 13, 2021; Accepted November 23, 2022; Epub March 15, 2023; Published March 30, 2023

Abstract: Objective: To identify the effect of hyperbaric oxygen combined with folic acid on clinical efficacy and cognitive function in patients with cerebral small vessel disease (CSVD), and to analyze the risk factors affecting efficacy. Methods: Data from 108 elderly patients with CSVD (homocysteine (Hcy) > 10 μmol/L) treated in The First Hospital of Yulin from February 2019 to February 2022 were retrospectively analyzed. Among them, 50 patients treated with folic acid were set as the control group (CG), and the remaining 58 patients treated with additional hyperbaric oxygen therapy were in the study group (SG). Clinical efficacy was compared between the two groups after treatment, and changes in Hcy level before and after treatment were observed. Montreal Cognitive Assessment (MoCA) was used to compare the improvement of cognitive function between two groups. According to the efficacy after treatment, patients with markedly effective and effective responses were set as the improved group, and patients with ineffective response as the unimproved group. Risk factors affecting the efficacy of the patients were analyzed by logistic regression. Also, changes in quality of life (assessed by activities of daily living (ADL) scale) before and after treatment as well as the incidence of adverse reactions after treatment were and compared between groups. Results: Before treatment, there was no significant difference identified in MoCA scores, plasma Hcy levels, or ADL scores between the two groups ($P > 0.05$). After treatment, scores of MoCA and ADL increased and plasma Hcy level decreased in both groups, and the changes in the SG were more significant than those in the CG ($P < 0.05$). Additionally, no notable difference was observed in the incidence of adverse reactions between the two groups ($P > 0.05$). Logistic regression analysis revealed that hypertension, hyperlipidemia, and diabetes were risk factors affecting the efficacy. Conclusion: Hyperbaric oxygen combined with folic acid can effectively improve cognitive function and quality of life, and reduce Hcy level in patients with CSVD. In addition, hypertension, hyperlipidemia, and diabetes are risk factors affecting efficacy.

Keywords: Hyperbaric oxygen, folic acid, cerebral small vessel disease (CSVD), clinical efficacy, cognitive function

Introduction

Cerebrovascular disease is increasing in incidence with the aging population as well as lifestyle pressures. It is one of the most common human diseases [1, 2]. Cerebral small vessel disease (CSVD) broadly refers to a clinical, cognitive, imaging and pathologic syndrome resulting from various lesions of intracranial small vessels [3]. Cerebral small vessels mainly include arterioles, capillaries and venules, which are the basic units of blood supply to the brain tissue and play an essential role in maintaining brain function [4]. A recent study [5] revealed that CSVD was a critical factor leading to major stroke, vascular events, and dementia. However, the mechanism of cognitive impairment in CSVD remains unclear, and causes controversy due to a lack of direct animal models. Hypoperfusion injury, blood-brain barrier disruption, and genetic factors are currently considered to be factors that induce the occurrence of CSVD [6].

Currently, no special and effective treatment is identified for CSVD in clinical practice, and the

existing treatments are mainly based on drug therapy, such as calcium antagonists, statins, antiplatelet therapy, cholinesterase inhibitors, and excitatory amino acid receptor inhibitors [7, 8]. A study has confirmed [9] that hyperhomocysteinemia is an independent risk factor for inducing CSVD and a major risk factor for cognitive dysfunction in CSVD patients. Folic acid is an essential coenzyme for homocysteine (Hcy) metabolism, and the deficiency of it can lead to up-regulated levels of plasma Hcy [10]. Therefore, folic acid supplementation is considered to improve plasma Hcy level and hyperhomocysteinemia in CSVD patients. Hyperbaric oxygen therapy can effectively up-regulate the level of oxygen partial pressure in the patient's blood, tissue fluid, and intracellular fluid, greatly increase the diffusion distance between oxygen molecules as well as oxygen saturation, and relieve cerebral hypoxic-ischemic symptoms. It also has a reparative effect on nerve and can accelerate the recovery of the cranial neurocognitive function [11, 12]. However, there is currently a paucity of research on hyperbaric oxygen therapy combined with folic acid for CSVD, and whether combination of the two can improve the clinical efficacy and cognitive function of patients remains unclear.

In this study, we aimed to analyze the effect of hyperbaric oxygen combined with folic acid on clinical efficacy and cognitive function in patients with CSVD, and the risk factors affecting the efficacy, so as to provide a reference for clinical treatments.

Methods and materials

Clinical data

A total of 108 elderly patients with CSVD treated in The First Hospital of Yulin from February 2019 to February 2022 were retrospectively included as study subjects. Among them, 50 patients treated with folic acid were assigned as a control group (CG), and 58 patients treated with additional hyperbaric oxygen therapy were the study group (SG). This study was approved by the Medical Ethics Committee of The First Hospital of Yulin (Ethical No.: 2019 (033)).

Inclusion and exclusion criteria

Inclusion criteria: Patients with Hcy > 10 μmol/L; patients who met the neuroimaging criteria of CSVD according to magnetic resonance imaging or brain CT [13]; patients with no history of severe stenosis of the internal or external cerebral arteries; patients with complete clinical data.

Exclusion criteria: Patients with malignant tumor; patients with severe heart, liver, lung or kidney dysfunction; patients with massive cerebral infarction or cerebral hemorrhage; patients with other diseases that may lead to cognitive dysfunction, such as depression, anxiety and psychosis; patients with a history of traumatic brain injury and intracranial infection; patients with vascular dementia; patients with cognitive impairment from other causes (e.g., intracranial infection, Parkinson's disease).

Drug manufacturers

Vitamin B6 Tablets were from Shanghai Huayuan Anhui Jinhui Pharmaceutical Co., Ltd., GYZZ H34021643; Vitamin B12 was from Shijiazhuang Huaxin Pharmaceutical Co., Ltd., GYZZ H13023422; Folic Acid Tablets were from Liaoning Green Biology Pharmaceutical Group Co., Ltd., GYZZ H21020966.

Treatment regimens

All patients underwent neurological examination, head MRI, Hcy and other routine tests before treatment. All patients were given 4 continuous weeks of conventional treatment, including antihypertensive and hypoglycemic drugs, oral basic treatment with vitamin B6 (10 mg/time, 3 times/d) and vitamin B12 (0.5 mg/time, 2 times/d), as well as folic acid tablets (5 mg/time, 1 time/d).

Patients in the SG received additional hyperbaric oxygen therapy, which was performed in a large medical hyperbaric oxygen air pressurized chamber (GY3400, produced by Shandong Yantai Hongyuan Oxygen Industry Co., Ltd.) with a therapeutic pressure of 0.22 MPa (2.2 ATM). After pressurization for 20 min, patients were given stable mask oxygen inhalation for 60 min, intermediate rest for 10 min, decompression for 25 min, once a day. A course of treatment included 10 repetitions, and our treatment included two courses.

Outcome measures

Main outcome measures: The clinical efficacy after treatment, changes of Hcy level and cog-

Table 1. Comparative analysis of baseline data

Variable	Control Group (n = 50)	Study Group (n = 58)	χ^2 value	*P* value
Age			1.277	0.258
≥ 65 years	27	25		
< 65 years	23	33		
Sex			0.152	0.696
Male	32	35		
Female	18	23		
Course of Disease			1.019	0.312
≥ 5 years	21	30		
< 5 years	29	28		
History of Diabetes			0.106	0.744
Yes	20	25		
No	30	33		
History of Hypertension			0.565	0.452
Yes	18	25		
No	32	33		
Hyperlipidemia			0.049	0.823
Yes	12	15		
No	38	43		
Smoking history			0.152	0.696
Yes	32	35		
No	18	23		

nitive function were compared between the two groups. Then, the risk factors affecting the efficacy were analyzed by logistics regression. The improvement of cognitive function were assessed by Montreal Cognitive Assessment (MoCA) [14] with a total score of 30 points. A score of 26 points or higher were regarded as normal cognitive function. According to the treatment efficacy, patients with markedly effective and effective response were divided into an improved group, and patients with ineffective response in an unimproved group.

Secondary outcome measures: The changes in quality of life before and after treatment were compared between the two groups. The quality of life was assessed using the activity of daily living (ADL) Scale, with a total score of 100 points. Higher score indicates stronger independence. Besides, the incidence of adverse reactions after treatment was compared between the two groups.

Assessment of efficacy

Clinical efficacy was evaluated after 4 weeks of treatment in both groups. It was seen as markedly effective if patients' Hcy level decreased by 70% or more, and their diastolic/systolic blood pressure as well as cognitive impairment were significantly improved. It was regarded as effective if patients' Hcy level decreased by 40%-69%, and their diastolic/systolic blood pressure and cognitive impairment were improved. Ineffective was indicated if patients' Hcy level decreased by less than 40% or increased, and their diastolic/systolic blood pressure and cognitive impairment were not improved or deteriorated. Overall response rate = (case of markedly effective + case of effective)/total number of cases × 100%.

Statistical analysis

In this study, SPSS 20.0 software was used for statistical analysis of the collected data, and GraphPad 7 software was for plotting the figures. Measurement data were expressed as mean ± standard deviation (mean ± SD). Inter-group and intra-group comparisons were conducted with independent sample t-test and paired t-test, respectively. Enumeration data were expressed as rate (%) and processed using Chi-square test, denoted as χ^2. Logistics regression was used to analyze the independent risk factors affecting the clinical efficacy, and receiver operating curve (ROC) was to assess the value of independent risk factors in predicting the clinical efficacy. Differences were significant when $P < 0.05$.

Results

Clinical information

The two groups of patients had no significant differences in terms of sex, age, body mass index, course of disease, history of diabetes and history of hypertension ($P > 0.05$), so the participants were comparable (**Table 1**).

Changes in Hcy level

There was no significant difference in the pre-treatment Hcy level between the two groups (P

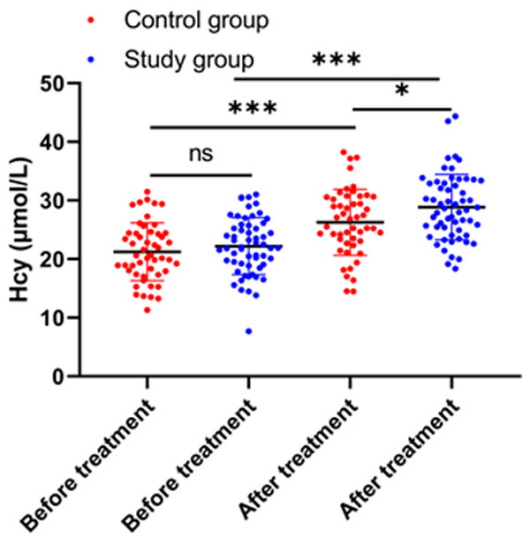

Figure 1. Changes in Hcy levels before and after treatment. Note: Homocysteine (Hcy), $^{ns}P > 0.05$, $^{*}P < 0.05$, $^{***}P < 0.001$.

> 0.05), while the Hcy levels after treatment were significantly lower in both groups ($P < 0.001$, **Figure 1**), and the posttreatment level in the SG was markedly lower than that in the CG ($P < 0.01$, **Figure 1**).

Cognitive function and quality of life after treatment

There was no significant difference in pretreatment MoCA and ADL scores between the two groups ($P > 0.05$). After treatment, the MoCA and ADL scores increased in both groups ($P < 0.001$, **Figure 2A**, **2B**), and the posttreatment scores in the SG were markedly higher than those in the CG ($P < 0.01$, **Figure 2A**, **2B**).

Comparison of clinical efficacy

The evaluation of the clinical efficacy revealed a much higher overall response rate in the SG than in the CG ($P < 0.05$, **Table 2**).

Comparison of adverse reactions

No significant difference was found in the incidence of adverse reactions between the two groups ($P < 0.05$, **Table 3**).

Analysis of risk factors affecting efficacy

In this study, patients with markedly effective and effective response were considered as the improved group, and patients with ineffective response werebthe non-improved group. Values were then assigned to the collected data (**Table 4**). By univariate logistic regression analysis, we found that age, hypertension, hyperlipidemia, diabetes, and treatment regimen were risk factors affecting the efficacy (**Figure 3A**, $P < 0.05$). However, multivariate logistic regression analysis revealed that hypertension, hyperlipidemia, and diabetes were independent risk factors affecting the efficacy (**Figure 3B**, $P < 0.05$). In addition, it was shown that the area under the curve of the combined prediction was 0.855, suggesting that this can be used for efficacy prediction (**Figure 4**).

Discussion

With the aging of the population, the prevalence of cerebral small vessel disease (CSVD) is growing, and stroke-like symptoms and cognitive impairment due to CSVD seriously affect the life quality of the elderly [15, 16]. However, the pathogenesis of CSVD is not yet clear and may be related to increased permeability of the blood-brain barrier, enlargement of the perivascular space, and sequelae such as lacunar infarcts, white matter lesions, and microbleeds [17]. At present, the treatments for CSVD are mainly based on its clinical manifestations, including thrombolytic therapy, antiplatelet therapy, risk factor therapy and targeted therapy [18].

Hcy is a degradation product from protein metabolism [19]. Normally, circulating Hcy is involved in the process of transsulfuration and transmethylation throughout the body in the presence of enzymes vitamin B6 and folic acid, and is degraded into cysteine which is converted into proteins. When metabolism is impaired, Hcy accumulates in the body due to inability to degrade it, resulting in hyperhomocysteinemia [20]. High concentration of Hcy can cause damage to the inner wall of blood vessels, such as thickening, roughness, plaque formation, luminal narrowing, and even luminal obstruction of the vascular intima and arterial insufficiency, resulting in atherosclerosis [21]. Therefore, folic acid supplementation to reduce Hcy concentration is useful in alleviating CSVD. Hyperbaric oxygen therapy is a treatment of patients in a high-pressure environment with an increased amount of dissolved oxygen, since

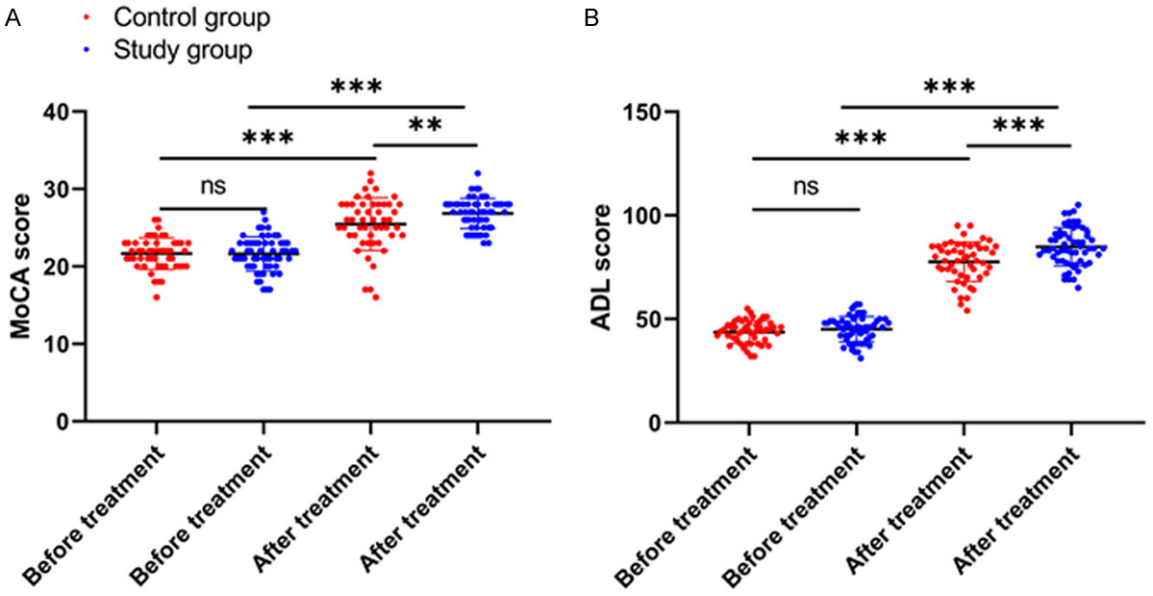

Figure 2. Changes in cognitive function and quality of life. A. Cognitive function before and after treatment. B. Quality of life before and after treatment. Note: Montreal Cognitive Assessment (MoCA), Activity of Daily Living (ADL), $^{ns}P > 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Table 2. Clinical efficacy

Group	Markedly Effective	Effective	Ineffective	Total response rate
Control Group (n = 50)	25 (50.00%)	15 (30.00%)	10 (20.00%)	40 (80.00%)
Study Group (n = 58)	30 (51.72%)	24 (41.38%)	4 (6.89%)	54 (93.10%)
χ^2 value				4.086
P value				0.043

Table 3. Comparison of adverse reactions

Group	Decreased blood pressure	Facial flushing	Bradycardia	Nausea and vomiting	Dizziness	Total Incidence
Control Group (n = 50)	2	2	1	2	3	10 (20.00%)
Study Group (n = 58)	2	3	2	1	1	9 (15.51%)
χ^2 value						0.372
P value						0.542

Table 4. Value assignment table

Variable	Assignment
Age	≥ 65 years old = 1, < 65 years old = 0
Sex	Male = 1, Female = 0
Course of disease	≥ 5 years = 1, < 5 years = 0
History of hypertension	Yes = 1, No = 0
History of diabetes	Yes = 1, No = 0
Hyperlipidemia	Yes = 1, No = 0
Smoking history	Yes = 1, No = 0
Treatment regimen	Control Group = 1, Study Group = 0
Efficacy	Improved Group = 0, Non-improved Group = 1

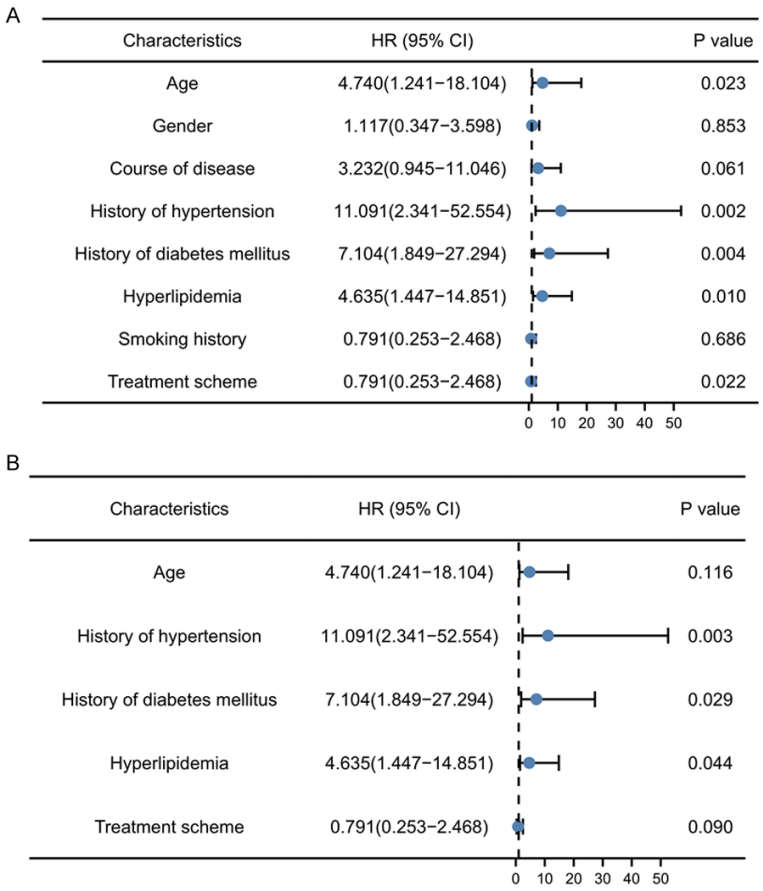

Figure 3. Analysis of risk factors affecting efficacy. A. Univariate analysis of factors affecting patient outcome. B. Multivariate logistic regression analysis of factors affecting the efficacy. Note: HR: Hazard Ratio.

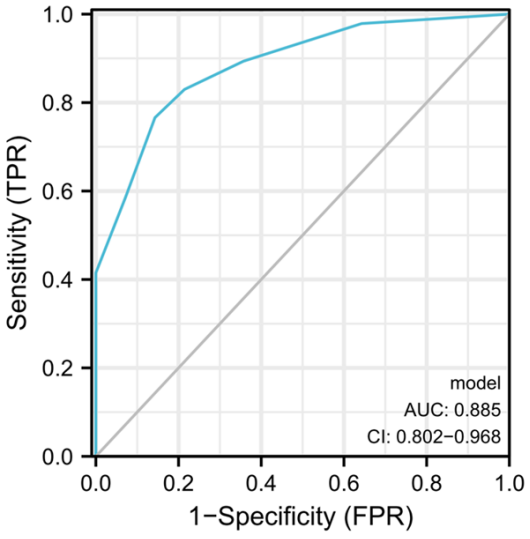

Figure 4. ROC curve for predicting efficacy. Note: ROC: Receiver Operating Curve.

oxygen molecules can enter the brain region and blood oxygen tissue, thereby alleviating the hypoxic state of cells [22]. A study found that [23] hyperbaric oxygen therapy could increase the partial pressure of oxygen in intracranial arteries and the oxygen tension of brain tissue to a certain extent, improve brain tissue hypoperfusion, and reduce brain parenchymal damage. In this study, we found that, after treatment, patients in the SG showed better serum Hcy level, quality of life, cognitive function, and clinical outcome compared to those in the CG, and there was no difference in the incidence of adverse reactions between two groups. This indicates that hyperbaric oxygen combined with folic acid can improve the clinical efficacy, life quality, and cognitive function of patients with CSVD. Previously, Hadanny et al. found that hyperbaric oxygen therapy improved neurocognitive function of patients after stroke [24]. Another meta-analysis study [25] concluded that hyperbaric oxygen is an effective and safe treatment for cognitive dysfunction in stroke through analyzing 27 randomized clinical trials. Moreover, Huo et al. [26] revealed that the combination of enalapril and folic acid significantly reduced the risk of first stroke compared to enalapril alone. On the whole, the studies mentioned above suggest that folic acid and hyperbaric oxygen have good efficacy in the treatment of stroke and cognitive dysfunction, which agrees with the results of our study. This is possibly because hyperbaric oxygen can increase the systemic blood oxygen content of the human body and up-regulate the oxygen content of the brain tissue, thereby promoting the rapid recovery of energy metabolism in brain neurons and inhibiting the apoptotic cascade induced by mitochondrial damage, which eventually reduces

the damage to brain tissue and improves the therapeutic efficacy.

By analyzing the factors affecting the treatment efficacy, we found that patients with hypertension, hyperlipidemia, and diabetes had poor clinical outcomes. Recent studies agreed that hypertension was an important risk factor for CSVD [27]. Long-term hypertension weakens the effect of intracranial vascular autoregulation of pressure, increases vascular fragility, and easily causes ischemic changes in small vessel distribution areas, which is bound to affect the therapeutic efficacy [28, 29]. High blood glucose levels lead to insulin resistance in the body, and the body promotes pancreatic β-cells to secrete more insulin, resulting in hyperinsulinemia, which can cause stroke. Hence, controlling blood glucose in patients can effectively prevent stroke [30]. Lipids are deposited in vascular endothelial cells in patients with hyperlipidemia, promote atherosclerosis and can cause cerebrovascular lesions, thereby resulting in an increased incidence of stroke [30, 31]. It is suggested that patient complications and targeted treatment should be focused on the clinical treatment of CSVD. At the end of the study, we plotted a combined ROC curve and found that the area under the curve was 0.855, indicating that the combined methods can be used as an indicator to predict the treatment outcome.

In this study, we determined that hyperbaric oxygen combined with folic acid can improve the therapeutic effect on CSVD, and analyzed the risk factors affecting the efficacy. However, this study still has some limitations. First, we failed to follow up the patients, and the incidence of adverse events after treatment could not be statistically analyzed for particular reason. Second, the sample size of this study was small, and retrospective analysis may have biased the results. So, we hope to carry out further experiments in the future to refine our conclusions.

In summary, hyperbaric oxygen combined with folic acid can effectively improve the cognitive function and quality of life, and reduce the Hcy level of patients with CSVD. In addition, hypertension, hyperlipidemia, and diabetes are risk factors affecting the treatment efficacy.

Disclosure of conflict of interest

None.

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