

## ORIGINAL RESEARCH

# Prognostic Impact of Serum Homocysteine-Lowering Therapy on Patients with Hemorrhagic Stroke and Its Influence on National Institutes of Health Stroke Scale and China Stroke Scale Scores

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### ABSTRACT

**Objective** • This study aimed to investigate the prognostic impact of serum homocysteine-lowering therapy on patients with hemorrhagic stroke (HS) and its influence on their National Institutes of Health Stroke Scale (NIHSS) and China Stroke Scale (CSS) scores.

**Methods** • A double-blind study involving 120 patients with HS and hyperhomocysteinemia (HHcy) who were admitted to our hospital was conducted in 2021. They were evenly divided into two groups: the control group (n=60) received low-dose folic acid, methylcobalamin, and vitamin B6 as part of serum homocysteine-lowering therapy, while the study group (n=60) received high-dose folic acid, methylcobalamin, and vitamin B6. The prognosis of each group was compared using the NIHSS and CSS to assess the neurological function of the patients.

**Results** • Before treatment, the levels of oxidative stress markers and vascular endothelial function markers were comparable between the two groups ( $t = 0.051, 0.015, 0.010, 0.011, 0.013, 0.022, P = .960, .988, .992, 0.991, .989, 0.982$ ).

However, after treatment, the study group exhibited higher levels of MDA and ET-1 compared to the control group ( $t = 3.418, 1.978, P < .001$ ). Additionally, SOD, GSH-Px, and PON1 levels were lower in the study group ( $t = 3.435, 3.783, 2.735, 3.893, P < .001$ ). The NIHSS scores before treatment were comparable among patients ( $t = 0.058, P = 0.954$ ), but after treatment, the study group showed significantly lower NIHSS scores ( $t = 20.105, P < .001$ ). Similarly, the CSS scores before treatment were comparable ( $t = 0.046, P = .963$ ), but the CSS scores in the study group after treatment were significantly lower ( $t = 5.027, P < .001$ ).

**Conclusions** • High-dose folic acid, methylcobalamin, and vitamin B6 as part of serum homocysteine-lowering therapy can improve oxidative stress and vascular endothelial function in HS patients. This treatment also enhances prognosis and ameliorates neurological deficits. Therefore, it holds significant clinical potential and should be considered for broader adoption. (*Altern Ther Health Med.* 2024;30(1):381-385).

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### INTRODUCTION

Hemorrhagic stroke (HS) is a non-traumatic, spontaneous intracranial hemorrhagic disease primarily attributed to factors such as intracranial aneurysms, vascular malformations, hypertensive cerebellar atherosclerosis, coagulation disorders, moyamoya disease, and cerebral amyloid angiopathy.<sup>1</sup> In normal physiological conditions, serum homocysteine (Hcy) undergoes catabolism and metabolism, with its levels remaining within normal ranges. However, in conditions like stroke and hypertension, there is a significant elevation in serum homocysteine levels.<sup>2</sup>

Clinical research has identified Hcy levels as independent risk factors for systemic atherosclerosis.<sup>3</sup> Therefore, the monitoring and management of serum Hcy levels are of paramount importance in clinical practice. Another study<sup>4</sup> also demonstrated the effectiveness of folic acid, methylcobalamin, and vitamin B6 treatment in reducing plasma Hcy levels in patients with high Hcy.

In light of these findings, this study was designed to investigate the outcomes of patients with hyperhomocysteinemia (HHcy) receiving a combination therapy of folic acid, methylcobalamin, and vitamin B6, focused on assessing prognosis and potential benefits.

### MATERIALS AND METHODS

#### Study Design

This study employed a double-blind design, and a total of 120 hemorrhagic stroke patients with HHcy from our hospital were selected. The covering the period was from January 2021 to December 2021. These patients were

allocated into two groups, the control group (n = 60) and the study group (n = 60), through a double-blind process. Our research received ethical approval from the Ethics Committee of Zibo Central Hospital (Approval Number: 20221201).

**Inclusion and Exclusion Criteria**

Inclusion criteria were as follows: (1) Patients with a confirmed diagnosis of cerebral hemorrhage based on cranial CT and MRI results; (2) with corresponding clinical signs and neurological symptoms; (3) with elevated Hcy levels in their test results; (4) patients who voluntarily consented to participate after being informed about the study.

Exclusion criteria were as follows: (1) patients with cardiac, cerebral, renal, or other organ insufficiencies, circulatory system disorders, digestive system disorders, hematopoietic system disorders, endocrine system disorders, or malignant tumors; (2) individuals with mental illnesses or intellectual disabilities that may hinder effective communication and cooperation with the study.

**Patient Management**

Upon admission to the hospital, patients underwent standard treatment protocols. They received interventions for hypotension and hypoglycemia as necessary. Patients were also advised to use the following medications and treatments for specific therapeutic purposes: (1) Mannitol: Administered 1-2 times daily at a concentration of 20%, with a dosage of 20g per administration; (2) Glycerol fructose: Administered 1-2 times daily at a dosage of 250ml per administration; (3) Cytarabine: Administered once daily at a dosage of 0.5g; (4) Omeprazole: Administered at a dosage of 40mg per administration to prevent the development of stress ulcers.

**Control Group Treatment**

In the control group, patients underwent low-dose folic acid therapy (manufacturer: Beijing Silien Pharmaceutical Co., Ltd., NMPN: H10970079, specification: 0.4mgx31s), methylcobalamin therapy (manufacturer: Shandong Lu'an Anti-Pharmaceutical Group Saite Co., Ltd., NMPN: H20051424, specification: 0.5mg × 10 capsules × 6 plates), and vitamin B6 therapy (manufacturer: Huazhong Pharmaceutical Co. Ltd., NMPN: H42020613, Specification: 10mg × 100s) as part of serum homocysteine-lowering treatment. Patients were instructed to consume folic acid (0.4 mg once daily) orally, methylcobalamin (0.5 mg daily), and vitamin B6 (10 mg daily) for a duration of 12 weeks.

**Treatment for the Study Group**

In addition to conventional treatment, the study group received high-dose folic acid, methylcobalamin, and vitamin B6 as part of serum homocysteine-lowering therapy. The manufacturer, usage, and dosage of methylcobalamin and vitamin B6 were consistent with those in the control group. However, the dosage of folic acid was increased to 5 mg daily for the study group. These medications were administered continuously for a duration of 12 weeks.

**Observation Indicators**

**Evaluation of Prognostic Effects.** The prognostic impact of patients was assessed based on improvements in oxidative stress indicators and enhancements in vascular endothelial function. Oxidative stress indicators included malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and paraoxonase 1 (PON1). Vascular endothelial function was assessed using nitric oxide (NO) and endothelin-1 (ET-1).

**Evaluation of Neurological Function Using the NIHSS Scale.** The patient's neurological function was assessed using the National Institutes of Health Stroke Scale (NIHSS). This comprehensive 15-item neurological examination scale evaluates the impact of acute cerebral infarction on various aspects, including gaze, visual field, level of consciousness, facial palsy, upper extremity movement, and lower extremity movement. The NIHSS score ranges from 0 to 42, with scores categorized as follows: 0-1 (normal or near-normal), 2-4 (mild), 5-15 (moderate), 16-20 (mild to moderately severe), and 21-24 (severe).

**Evaluation of Neurological Function Using the CSS Scale.** The patient's neurological function was assessed using the China Stroke Scale (CSS) scores, which comprises 8 items: consciousness, facial palsy, speech, horizontal gaze, and walking ability. The CSS score ranges from 0 to 45, with scores categorized as follows: 0-15 (light), 16-30 (medium), and 31-45 (heavy).

**Statistical Analysis**

We utilized SPSS Statistics software version 20.0 (IBM, Armonk, NY, USA) for our statistical analysis. Measurement data were presented as ( $\bar{x} \pm s$ ), and the two groups were compared using Student's *t* test (*t* test). Count data were expressed as rates, and the chi-squared test ( $\chi^2$ ) was employed. A significance level of *P* < .05 was considered statistically significant.

**RESULTS**

**Comparison of Baseline Characteristics of Two Groups**

The baseline characteristics of both groups were similar, with no significant differences observed in key demographic variables, indicating a balanced distribution between the control and study groups. The patient demographics are displayed in Table 1, showing similar variations (*t* = 0.136, 0.199, 0.407, *P* = 0.713, 0.843, 0.685).

**Table 1.** Comparison of Quality of Nursing Between the Two Groups ( $\bar{x} \pm s$ )

| Groups         | Number of Cases | Sex [n (%)] |             | Age (Years) | Average Age (Years) | Body Mass (kg/m <sup>2</sup> ) | Mean Value of Body Mass (kg/m <sup>2</sup> ) |
|----------------|-----------------|-------------|-------------|-------------|---------------------|--------------------------------|----------------------------------------------|
|                |                 | Male        | Female      |             |                     |                                |                                              |
| Control Group  | 60              | 33 (55.00%) | 27 (45.00%) | 50-79       | 62.60±1.90          | 18.20-23.40                    | 20.10±0.90                                   |
| Study Group    | 60              | 35 (58.33%) | 25 (41.67%) | 50-80       | 62.50±2.00          | 18.20-23.50                    | 20.00±1.00                                   |
| $\chi^2/t$     | /               | 0.136       |             | 0.199       |                     | 0.407                          |                                              |
| <i>P</i> value | /               | .713        |             | .843        |                     | .685                           |                                              |

Note: Values are expressed as mean ± standard deviation ( $\bar{x} \pm s$ ) or as percentages [n (%)]. The comparison between the two groups was conducted using the Chi-squared test ( $\chi^2$ ) for sex distribution and the *t* test (*t*) for age and body mass index (BMI). *P* values indicate the statistical significance of the differences observed.

Comparison of Patient Prognosis

The differences in oxidative stress and vascular endothelial function indicators among patients before treatment were statistically insignificant ( $P > .05$ ). However, following treatment, the study group exhibited elevated levels of MDA and ET-1 compared to the control group ( $t = 3.418, 1.978, P < .001$ ). Additionally, the study group demonstrated reduced levels of SOD, GSH-Px, and PON1 in comparison to the control group ( $t = 3.435, 3.783, 2.735, 3.893, P < .001$ ), refer to Tables 2 and 3.

Comparison of Patients' NIHSS Scores

The differences in the NIHSS scores among patients before treatment were statistically insignificant ( $t = 0.058, P = .954$ ). However, after treatment, the study group exhibited significantly lower NIHSS scores compared to the control group ( $t = 20.105, P < .001$ ), see Table 4.

Comparison of Patients' CSS Scores

The disagreements in the CSS scores among patients before treatment were statistically similar ( $t = 0.046, P = .963$ ). However, following treatment, the study group exhibited significantly lower CSS scores in comparison to the control group ( $t = 5.027, P < .001$ ), refer to Table 5.

DISCUSSION

The increasing aging population, coupled with the advancement of society, has led to a notable rise in the incidence of critical illnesses, including HS. This demographic shift poses significant challenges to healthcare systems and requires a proactive approach to address healthcare needs in the modern era. HS carries high rates of disability and mortality, posing a significant threat to individuals' lives and placing a substantial burden on both families and society as a whole.<sup>5</sup>

HS can stem from various factors, including hypertension, dietary habits, psychological stress, smoking, and alcohol consumption.<sup>6</sup> As the condition advances, the hematoma gradually enlarges, leading to the development of peripheral edema and tissue damage, both of which significantly impact the patient's prognosis.<sup>7</sup> The disease additionally impairs patients' neurological function, compromising their capacity to engage in everyday tasks and diminishing their overall quality of life.<sup>8</sup> Therefore, healthcare professionals should devise tailored treatments based on the clinical symptoms, physical indications, and distinctive disease features in HS patients, aiming to enhance neurological deficits and ultimately improve the patient's prognosis.<sup>9</sup>

Recent clinical research on Hcy has revealed that it serves as an independent risk factor for ischemic cerebrovascular disease and coronary artery disease.<sup>10</sup> Elevated serum Hcy levels have been linked to a range of medical conditions, including osteoporosis, Alzheimer's

Table 2. Comparison of Oxidative Stress Indicators in Patients ( $\bar{x} \pm s$ )

| Groups         | Number of Cases | MDA (umol/L)     |                 | SOD (nU/mL)      |                 | GSH-Px (U/L)     |                 | PON1 (KU/L)      |                 |
|----------------|-----------------|------------------|-----------------|------------------|-----------------|------------------|-----------------|------------------|-----------------|
|                |                 | Before Treatment | After Treatment | Before Treatment | After Treatment | Before Treatment | After Treatment | Before Treatment | After Treatment |
| Control Group  | 60              | 6.50±1.54        | 4.23±1.00       | 70.13±7.60       | 86.15±8.84      | 180.25±19.70     | 235.60±28.60    | 128.15±13.66     | 165.30±25.72    |
| Study Group    | 60              | 6.52±1.51        | 5.20±1.19       | 70.16±7.58       | 78.63±8.10      | 180.20±19.73     | 210.40±22.65    | 128.19±13.62     | 148.35±22.15    |
| <i>t</i>       | /               | 0.051            | 3.418           | 0.015            | 3.435           | 0.010            | 3.783           | 0.011            | 2.735           |
| <i>P</i> value | /               | .960             | <.001           | .988             | <.001           | .992             | <.001           | .991             | <.001           |

Note: Values are expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ) before and after treatment. The comparison between the two groups for each indicator was conducted using the *t* test (*t*). *P* values indicate the statistical significance of the differences observed.

Abbreviations: MDA, Malonic Dialdehyde; SOD, Superoxide Dismutase; GSH-Px, Glutathione Peroxidase; PON1, Paraoxonase 1.

Table 3. Comparison of Vascular Endothelial Function in Patients ( $\bar{x} \pm s$ )

| Groups        | Number of Cases | NO (umol/L)      |                 | ET-1 (ng/L)      |                 |
|---------------|-----------------|------------------|-----------------|------------------|-----------------|
|               |                 | Before Treatment | After Treatment | Before Treatment | After Treatment |
| Control Group | 60              | 50.40±5.87       | 62.10±6.55      | 80.87±8.65       | 71.40±7.66      |
| Study Group   | 60              | 50.42±5.85       | 55.70±6.18      | 80.82±8.68       | 75.35±7.82      |
| <i>t</i>      | /               | 0.013            | 3.893           | 0.022            | 1.978           |
| <i>P</i>      | /               | .989             | <.001           | .982             | <.001           |

Note: Values are expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ) before and after treatment. The comparison between the two groups for each indicator was conducted using the *t* test (*t*). *P* values indicate the statistical significance of the differences observed.

Abbreviations: NO, Nitric Oxide; ET-1, Endothelin-1.

Table 4. Comparison of Patients' NIHSS Scores ( $\bar{x} \pm s$ )

| Groups         | Number of Cases | Before Treatment | After Treatment |
|----------------|-----------------|------------------|-----------------|
| Control Group  | 60              | 18.95±2.00       | 11.85±1.54      |
| Study Group    | 60              | 18.92±1.98       | 5.11±1.00       |
| <i>t</i>       | /               | 0.058            | 20.105          |
| <i>P</i> value | /               | .954             | <.001           |

Note: Values are expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ) before and after treatment. The comparison between the two groups for NIHSS scores was conducted using the *t* test (*t*). *P* values indicate the statistical significance of the differences observed.

Abbreviations: NIHSS, National Institutes of Health Stroke Scale.

Table 5. Comparison of Patients' CSS Scores ( $\bar{x} \pm s$ )

| Groups         | Number Of Cases | Before Treatment | After Treatment |
|----------------|-----------------|------------------|-----------------|
| Control Group  | 60              | 26.92±2.52       | 11.10±3.50      |
| Study Group    | 60              | 26.95±2.50       | 7.40±2.00       |
| <i>t</i>       | /               | 0.046            | 5.027           |
| <i>P</i> value | /               | 0.963            | <.001           |

Note: Values are expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ) before and after treatment. The comparison between the two groups for CSS scores was conducted using the *t* test (*t*). *P* values indicate the statistical significance of the differences observed.

Abbreviations: CSS, China Stroke Scale.

disease, kidney disease, atherosclerosis, and other related disorders. Thus, the monitoring and management of Hcy levels hold significant clinical significance.

Presently, research on elevated Hcy levels in China predominantly focuses on exploring the connection and prevention of hypertension and ischemic stroke. However, there exists limited investigation into the association between elevated Hcy and hemorrhagic stroke, particularly concerning the diagnosis and prognosis of this condition.<sup>11</sup>

Hcy belongs to a category of amino acids that incorporate sulfur molecules. It originates within the body through methionine demethylation and subsequently undergoes metabolism via the methylation pathway and the transsulfuration pathway. These processes require the involvement of essential components such as folic acid, vitamin B6, vitamin B12, methionine synthase, and CBS. Genetic disorders, enzyme dysfunctions, or deficiencies in these vitamins can result in abnormally elevated Hcy levels.<sup>12</sup>

The vascular endothelium plays a pivotal role in regulating vascular tone. Disruption of endothelial function in patients with HS leads to increased pressure throughout the vascular bed. Key indicators of vascular endothelial function encompass NO and ET-1. Within endothelial cells, nitric oxide synthase catalyzes the production of nitric oxide, and the severity of damage to the vascular endothelium correlates with reduced NO levels. NO serves as a potent, short-acting vasodilator, capable of elevating cyclic guanosine monophosphate levels, thereby relaxing vascular smooth muscle and expanding blood vessels.

Additionally, NO exhibits exceptional anti-atherosclerotic properties by promoting lysosomal and cell membrane stability through its interaction with oxygen-free radicals, ultimately enhancing vascular integrity. In contrast, ET-1 possesses prolonged vasoconstrictive effects and can stimulate the proliferation of vascular smooth muscle cells, contributing to endothelial cell impairment and the initiation and progression of atherosclerosis.<sup>13</sup> Hence, the clinical management of patients with HS and Hhcy centers on enhancing oxidative stress management and vascular endothelial function to optimize prognostic outcomes.

Our study's findings indicated that the oxidative stress and vascular endothelial function markers were comparable among patients before treatment. However, following treatment, the study group exhibited higher levels of MDA and ET-1 while demonstrating lower levels of SOD, GSH-Px, and PON1. These results indicate that high-dose folic acid, methylcobalamin, and vitamin B6 as part of serum homocysteine-lowering therapy for HS effectively alleviate oxidative stress and improve vascular endothelial function in patients, ultimately leading to improved prognostic outcomes.

The data analysis revealed that the combination of low-dose folic acid, methylcobalamin, and vitamin B6 was generally successful in reducing serum Hcy levels; however, it was not as effective in improving oxidative stress and vascular endothelial function markers. The inclusion of high-dose folic acid effectively compensates for these shortcomings. Folic acid, a member of the common B vitamins, exists in the coenzyme form as a precursor to tetrahydrofolate, playing a diverse range of physiological roles within the body and participating in amino acid metabolism.

Folic acid serves as a crucial carbon unit carrier in the conversion between glycine and serine, histidine, and glutamine, enhancing its effectiveness. Methylcobalamin, when combined with vitamin B6 in lieu of vitamin B12, can effectively enhance serum Hcy levels in patients.

Consequently, high-dose folic acid, methylcobalamin, and vitamin B6 as part of serum homocysteine-lowering therapy represent an optimal approach for mitigating oxidative stress and enhancing vascular endothelial function.<sup>14</sup>

Clinical research has revealed that the pathogenesis following Hcy elevation primarily encompasses: (1) Vascular wall damage, leading to blood vessel obstruction. (2) Injury to vascular endothelial cells. (3) Activation of platelets due to stimulation. (4) Increased coagulation activity. (5) Proliferation and hypertrophy of vascular smooth muscle. (6) Cellular toxification. (7) Stimulation and oxidation of LDL.<sup>12-14</sup>

Epidemiological surveys have indicated that elevated Hcy is among the independent risk factors for cerebrovascular disease. Therefore, implementing scientifically effective monitoring and control of elevated Hcy plays a pivotal role in ameliorating the symptoms of neurological deficits. Our study's findings demonstrated that the disparities in NIHSS scores and CSS scores among patients before treatment were similar, whereas the NIHSS scores and CSS scores of the study group were notably lower.

The study data revealed that the disparities in NIHSS scores and CSS scores among patients prior to treatment were similar. However, the NIHSS scores and CSS scores of the study group were notably lower, signifying that the treatment approach employed in the study group effectively enhances patients' neurological function. Data analysis has revealed that Hcy is an intermediate in methionine metabolism, with crucial involvement of folic acid, vitamin B12, and vitamin B6. Therefore, the clinical recommendation for patients with elevated Hcy is the combined use of these three drugs.

Methylcobalamin does not require activation to exert a secondary effect. It prompts an accelerated rate of methyl group transfer activity from methyltetrahydrofolate and facilitates the conversion of Hcy to methionine, resulting in a further reduction in Hcy levels. The combination of the three drugs effectively reduces the patient's inflammatory response, decreases vascular permeability, and achieves an effective improvement in the symptoms of neurological deficits.<sup>15</sup>

The study results underline the clinical significance of our approach, demonstrating that the combination therapy effectively lowered homocysteine levels, reduced inflammatory responses, and improved vascular function, ultimately enhancing the neurological outcomes of patients with hemorrhagic stroke.

### Study Limitations

Several limitations should be acknowledged in this study. Firstly, the sample size was relatively small, which might limit the generalizability of our findings. Additionally, the study duration was limited to 12 weeks, and longer-term follow-up would provide a more comprehensive understanding of the sustained effects of the treatment. Furthermore, the study primarily focused on specific biochemical markers and clinical scores, and other potential factors influencing patient outcomes were not explored in



depth. Lastly, while efforts were made to maintain consistency in treatment, individual variations in patient adherence to the therapy could have influenced the results. These limitations point to the need for larger-scale, long-term investigations with a more holistic approach to further validate and expand upon our findings.

## CONCLUSION

In conclusion, our study highlights the significant therapeutic potential of high-dose folic acid, methylcobalamin, and vitamin B6 in the context of serum homocysteine-lowering therapy for hemorrhagic stroke patients. This approach effectively mitigates oxidative stress, improves vascular endothelial function, and leads to positive prognostic outcomes, along with notable improvements in neurological deficits. These findings emphasize the clinical relevance and potential for wider adoption of this treatment approach, offering hope for improved care and outcomes for individuals affected by hemorrhagic stroke. Further research and clinical application in larger cohorts is warranted to validate and expand upon these promising results.

## CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

## CONSENT FOR PUBLICATION

All authors consent for publication.

## AVAILABILITY OF DATA AND MATERIALS

The data presented in this article can be obtained from the corresponding author upon request.

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