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Clinical Efficacy of Dengyin Naotong Capsule for Cognitive Impairment Related to Cerebral Small Vascular Disease

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Abstract **Objective:** This study aims to investigate the clinical efficacy of Dengyin Naotong (DYNT) capsule for cognitive impairment related to cerebral small vascular disease (CSVS). **Methods:** Total of 105 patients with cognitive impairment related to CSVD hospitalized in Zibo Fifth People's Hospital from July 2021 to June 2023 were selected and randomly divided into control group (53 cases) and treatment group (52 cases). The patients in control group were treated with anti-arteriosclerosis, anti-platelet aggregation, nicergoline treatment, etc. while in treatment group combined with DYNT capsule on the basis of control group for 6 months both in the two groups. Before and after treatment, the Mini-mental State Examination (MMSE), Montreal Cognitive Assessment Scale (MoCA), Ability of Daily Living (ADL) score, Tinetti Balance and Gait Assessment Scale (POMA) score, Traditional Chinese Medicine Syndrome Scores (TCMSS), and the plasma levels of homocysteine (Hcy), C reactive protein (CRP) and D-dimer of patients were observed. **Results:** After treatment, the MMSE scores, MoCA scores ADL scores and POMA scores of patients increased significantly than those before treatment (P<0.05) both in the two groups, and which in the treatment group were significantly higher than those in the control group (P<0.05). After treatment, the TCMSS of patients decreased significantly than those before treatment (P<0.05) both in the two groups, and which in the treatment group was significantly lower than that in the control group (P<0.05). After treatment, the plasma levels of Hcy, CPR and D-dimer both in the two groups were significantly lower than before treatment (P<0.05), and which in the treatment group were significantly lower than those in the control group (P<0.05). Conclusion: DYNT capsule has some clinical efficacy in the treatment of cognitive impairment related to CSVD.

Keywords: *Dengyin Naotong capsule, cerebral small vascular disease, cognitive impairment, MMSE, MoCA, ADL, POMA, TCMSS*

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1. Introduction

In 2008, the idea of "small stroke, big trouble" was put forward internationally based on the characteristics of stroke, and early prevention and treatment were clearly discussed [1]. Modern medical imaging technology has greatly improved the detection rate of Cerebral small vascular disease (CSVD) [2]. Pathological and imaging studies have found that CSVD is asymptomatic in the early stages of its development and mainly causes vascular cognitive impairment (VCI) in the long term [3,4]. One study found that about 60% of patients with VCI have CSVD, while the percentage of patients with AD is only 30%. Modern medical research confirms that CSVD is the main factor causing VCI. Cerebral lacunar infarction (LI) and white matter lesion (WML) are the most prominent manifestations of VCI [6] and also are independent risk factors for VCI [7]. There is also a direct relationship between cerebral microbleeds (CMB) and dementia [8]. Maclullich et al. [9] found that when the CMB developed to a severe degree, the patients' cognitive function declined significantly. Previous clinical experience has shown that CSVD leads to reduced executive ability in patients with VCI [10], and the mechanisms of occurrence included the long-association fibers damage theory and the prefrontal-subcortical loop damage theory [11]. Gait is

often impaired in patients with severe damage to projection fibers in the paraventricular and bilateral frontal lobes [12,13]; and the damage of the superior frontal-occipital tract is strongly associated with dysuria [14]. Leukoaraiosis (LA) is also a factor in the development of cognitive deficits [15]. Huijts et al. [16] found that the overall cognition of patients with WML and CMB greatly affects their processing speed of information. Dengyin Naotong (DYNT) capsule is mainly a compound preparation developed from the active ingredients of *Erigeron breviscapus*, *Ginkgo biloba*, *Schisandra propinqua* and *Radix notoginseng* [17]. Wang et al. [18] showed that DYNT capsule has a therapeutic effect on sequelae of acute cerebral infarction, ischemic vertigo and depression. Li et al. [19] showed that DYNT capsule can enhance the learning and memory ability of aged mice models. Qu et al. [20] showed that DYNT capsule combined with olanzapine can help alleviate vascular dementia, however, its specific mechanism is not very clear now. For this reason, this study attempted to observe the effect of DYNT capsules in treating the cognitive impairment related to CSVD.

2. Information Data and Methods

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2.1. Patients' Information Data

Total of 105 patients with cognitive impairment related to CSVD hospitalized in Zibo Fifth People's Hospital from June 2021 to June 2022, according to the Declaration of Helsinki and approved by the Ethics Committee of our hospital (No: 2021-004-01).

2.1.1. Diagnosis and Inclusion Criteria

①Meet the relevant diagnostic criteria in the "China Guidelines for Diagnosis and Treatment of Cognitive Impairment Related to Cerebrovascular Disease (2019)" [21] formulated by the Geriatric Neurology Group of the Geriatrics Branch of the Chinese Medical Association; ② Montreal Cognitive Assessment (MOCA) scores <26; ③ Refer to Chinese Consensus on the Diagnosis and Treatment of CSVD (2021) [22], the cranial CT or MRI films showed the presence of new subcortical small infarcts, lacunae, and high signal in the white matter, etc.; ④The presence of two or more lacunar infarcts other than the brainstem; ⑤ The patient and his/her guardian voluntarily participated in the study and signed a written informed consent document for the use of the medication; ⑥It was consistent with the Chinese medicine pattern of cognitive dysfunction related to CSVD [23]: the primary symptoms included unresponsiveness, dullness and speechlessness, dullness of color, and headache, and the secondary symptoms included lopsidedness of the mouth and eyes, hemiplegia, and a fine-stringed/sinking pulse.

2.1.2. Exclusion Criteria

①The patient with cognitive impairment, which affects the independence of life; ②Those with alcohol and drug abuse; ③Those with a history of new-onset stroke in the 3 months prior to enrollment; ④Those with a history of combined epilepsy and psychiatric disorders; ⑤ Those with central nervous disorders, including brain tumors, hydrocephalus, and Alzheimer's disease, etc.; and ⑥Those who withdrew voluntarily from the study in the middle of the study or who were participating in other studies at the same time.

2.1.3. Principle of Grouping

Total of 105 patients with cognitive impairment related to CSVD were randomly divided into 2 groups according to the randomized numerical table, and there was no significant difference in the comparison of the baseline information data between the two groups (P>0.05).

Control group: 53 (male 30, female 23) cases, age 50-68 (57.24±4.36) years. Imaging manifestations: 17 cases of cerebral microbleeds, 21 cases of cerebral white matter sparing, 15 cases of cavernous cerebral infarction; education level: 13 cases in junior high school and below, 28 cases in senior high school, 12 cases in college and above.

Treatment group: 52 (male 28, female 24) cases, age 51-70 (57.48±4.29) years. Imaging manifestations: 18 cases of cerebral microbleeds, 20 cases of cerebral white matter sparing, 14 cases of cavernous cerebral infarction; education level: 11 cases in junior high school and below, 30 cases in high school, 11 cases in junior college and above.

2.2. Treatment Programs

2.2.1. Control Group

Including anti-atherosclerosis (conquering blood glucose, blood lipids and blood pressure), anti-platelet aggregation, and nicergoline treatment. Nicergoline (No. H20054470, Pfizer Pharmaceutical Co. Ltd. 30 mg each time, 3 times a day, taken orally after meals for 6 months.

2.2.2. Treatment Group

On the basis of the treatment program of the control group, add DYNT capsule (State Drug Permit Z20026228, Kunming Pharmaceutical Group Co. Ltd.), 2 capsules each time, 3 times a day, taken orally after meals for 6 months.

2.3. Treatment Programs

2.3.1. Mini-Mental State Examination (MMSE) scale

The MMSE scale has a total score of 30, and cognitive

impairment is indicated by a score of < 24 for secondary school and above, < 20 for elementary school, and < 17 for illiteracy.

2.3.2. Montreal Cognitive Assessment (MoCA) scale

The total score of MoCA is 30, and a score of < 26 indicates cognitive impairment. The higher the score, the better the patient's cognitive function; on the contrary, it indicates severe cognitive impairment.

2.3.3. Activity of Daily Living (ADL) Scale

Assessing the patient's ability to take care of himself/herself, with a total score of 0-100 on the ADL. Evaluation criteria: ① total score > 60 points suggests mild daily life dysfunction (mild dependence, a small part of the need for other people to take care of); ② 41-59 points suggests moderate daily life dysfunction (moderate dependence, a small part of the need for other people to take care of); ③ < 40 points suggests severe daily life dysfunction (severe dependence).

2.3.4. Tinetti Performance Oriented Mobility Assessment (POMA) scale

Assessing patient's mobility and balance before and after treatment, including balance (16 points) and gait (12 points), with a total score of 28 points. The higher the score, the better the patient's mobility and balance. Evaluation criteria: ① total score > 24 points suggests no risk of fall; ② 19-24 points suggests risk of fall; ③ < 19 points suggests high risk of fall.

2.3.5. Traditional Chinese Medicine Syndrome Scores (TCMSS) [23]

Primary symptoms: forgetfulness, dullness, inability to speak, slow reaction, clumsiness, or delusional thinking; headache that is difficult to be cured, dark complexion; 2 points for each symptom. Secondary symptoms: accompanied by hemiplegia, crooked mouth and eyes, hemianopsia, and unfavorable speech; purple petechiae on the tongue, and fine stringy or sluggish pulse; 1 point for each symptom. The cumulative sum is the patient's TCMSS; the higher the score, the more severe the symptoms, and vice versa, the less severe the symptoms.

2.4. Laboratory Indexes

2.4.1. Plasma Level of Homocysteine (Hcy)

Normal value 5-15 μmol/L. If Hcy > 15 μmol/L, combined with brain CT suggests that there is vascular blockage, insufficient blood supply, thrombus, which may indicate cerebral infarction. If < 5 μmol/L, it is not clinically significant.

2.4.2. Plasma level of C-reactive Protein (CRP)

Normal value < 2.5 mg/dL. for CRP level > 2.5 mg/dL, the higher the value, the greater the severity and the higher the probability of atherosclerosis and acute cerebral infarction. On the contrary, there is no clinical significance.

2.4.3. Plasma Level of D-dimer

Normal value is less than 0.2 mg/L. Normal human plasma D-dimer is negative. If the patient's plasma D-dimer level is > 0.2 mg/L, the higher the value, the higher the D-dimer positivity, which suggesting a higher possibility of hypercoagulability or thrombophilia.

2.5. Laboratory Indexes

All data were applied to SPSS26.0 software statistics, verified by the Shapiro-Wilk test, the information in this study conformed to normal distribution, and the measurement information ($\bar{x} \pm s$) was tested by *t*-test, and the difference was considered statistically significant at $P<0.05$.

3. Results

3.1. MMSE Scores

Before treatment, there was no significant difference in the MMSE scores of the patients between the two groups; after treatment, the MMSE scores of the patients in the treatment group were significantly higher than those of the control group (Table 1).

Table 1. Comparison of MMSE scores between the two groups ($\bar{x} \pm s$)

Groups	Pre-treatment	Post-treatment	*t*	*P*
Control group (n=53)	24.33±1.18	26.67±1.32	9.62	<0.01
Treatment group (n=52)	24.40±1.22	28.92±1.65	15.88	<0.01
t	0.30	7.72		
P	0.61	<0.01		

3.2. MoCA Scores

Before treatment, there was no significant difference in the MoCA scores of the patients between the two groups; after treatment, the MoCA scores of the patients in the treatment group were significantly higher than those of the control group (Table 2).

3.3. ADL Scores

Before treatment, there was no significant difference in the ADL scores of the patients between the two groups; after treatment, the ADL scores of the patients in the treatment group were significantly higher than those of the control group (Table 3).

Table 2. Comparison of MoCA scores between the two groups ($\bar{x} \pm s$)

Groups	Pre-treatment	Post-treatment	*t*	*P*
Control group (n=53)	19.33±2.47	24.69±2.06	12.13	<0.01
Treatment group (n=52)	19.31±2.50	26.78±2.15	16.34	<0.01
t	0.04	5.09		
P	0.97	<0.01		

Table 3. Comparison of ADL scores between the two groups ($\bar{X} \pm S$)

Groups	Pre-treatment	Post-treatment	*t*	*P*
Control group (n=53)	55.25±6.06	62.33±6.35	5.87	<0.01
Treatment group(n=52)	55.11±5.97	68.75±6.86	10.82	<0.01
t	0.12	4.98		
P	0.91	<0.01		

3.4. POMA Scores

Table 4. Comparison of POMA scores between the two groups ($\bar{X} \pm S$)

Groups	Equilibrium		Gait		Total scores	
	pre-treatment	post-treatment	pre-treatment	post-treatment	pre-treatment	post-treatment
Control group(n=53)	8.70±1.58	11.20±1.85	6.88±1.62	9.25±1.33	15.55±3.11	20.44±3.05
Treatment group (n=52)	8.81±1.49	12.96±1.88	6.94±1.66	10.39±1.46	15.48±3.20	23.68±2.88
t	0.37	4.84	0.18	4.18	0.11	5.59
P	0.71	<0.01	0.85	<0.01	0.91	<0.01

Before treatment, there was no significant difference in the total POMA scores of the patients between the two groups; after treatment, the total POMA scores of the patients in the treatment group were significantly higher than those of the control group (Table 4).

3.5. TCMSS

Before treatment, there was no significant difference in the TCMSS of the patients between the two groups; after treatment, the TCMSS of the patients in the treatment group was significantly lower than that of the control group (Table 5).

Table 5. Comparison of TCMSS scores between the two groups ($\bar{X} \pm S$)

Groups	Pre-treatment	Post-treatment	*t*	*P*
Control group(n=53)	18.03±1.81	13.62±1.40	14.031	<0.01
Treatment group(n=52)	17.94±1.77	9.68±1.24	27.56	0<.01
t	0.26	15.26		
P	0.25	<0.01		

3.6. Laboratory Indexes

Before treatment, there was no significant difference in the plasma levels of Hcy, CRP and D-dimer of the patients between the two groups; after treatment, the plasma levels of Hcy, CRP and D-dimer of the patients in the treatment group were significantly lower than those in the control group (Table 6).

Table 6. Comparison of experimental indexes between the two groups of patients ($\bar{X} \pm S$)

Groups	Hcy(μmol/L)		CRP(mg/dL)		D-dimer(mg/L)	
	pre-treatment	post-treatment	pre-treatment	post-treatment	pre-treatment	post-treatment
Control group(n=53)	15.07±1.96	11.62±1.22	4.92±0.79	3.86±0.51	0.38±0.15	0.19±0.09
Treatment group(n=52)	14.85±1.57	10.31±1.15	4.69±1.09	3.01±0.41	0.36±0.12	0.12±0.06
t	0.36	4.87	0.17	4.16	0.14	5.13
P	0.73	<0.01	0.81	<0.01	0.89	<0.01

4. Discussion

VCI is mainly caused by various cerebrovascular diseases [24,25], and the site of disease is located in the brain, which is a complicated disease of deficiency and excessiveness, and the basic pathogenesis of TCM is “root cause deficiency with syndrome excess”. The deficiency of kidney essence is as the root cause, while the “Qi” stagnation, blood stasis, phlegm, and heat toxicity as the syndromes. Clinically, the qi stagnation and blood stasis and deficiency of kidney essence are the most common syndromes.

4.1. DYNT Capsules Improved Cognitive Function of CSVD Patients

DYNT capsule contains a variety of blood-activating and stasis-eliminating ingredients, which can realize the therapeutic effect of promoting blood circulation and relieving pain, dispelling “wind” and dispersing “cold”. *Radix notoginseng* can inhibit platelet-activating factor (PAF) and improve red blood cell (RBC) deformability; *Erigeron breviscapus* has anticoagulant effect to promote vasodilatation and improves microcirculation; *Ginkgo biloba* can activate blood circulation and eliminate blood stasis to relieve pain and asthma by converging the lungs, so as to prevent thrombosis, improve the activity of antioxidant enzymes, enhance vascular activity, reduce effectively oxidative damage, and alleviate the condition significantly; *Schisandra propinqua* has the same properties of *Schisandra*, which can relieve tendons and activate blood circulation, reduce swelling and anti-inflammatory effect, and its effect of activating blood circulation is close to that of *Panax ginseng* [26,27]. The combination of all the drugs can inhibit oxidative damage, lower lipids, play a certain protective effect on vascular endothelial cells, reduce the symptoms of mental impairment and improve cognitive function [20]. In this study, DYNT capsule combined with nicergoline could effectively improve the cognitive function of patients, and the MMSE scores, MoCA scores and TCMSS of patients in the treatment group were significantly better than those in the control group. It suggested that DYNT capsule has a role in improving cognitive impairment related to CSVD.

4.2. DYNT Capsule Improved Self-care Ability of CSVD Patients

Modern pharmacological studies have shown that DYNT capsule can resist platelet and RBC aggregations, reduce blood viscosity, and increase the level of blood supply and blood flow. On this basis, DYNT capsule could improve blood circulation condition, inhibit protein kinase activity, reduces the secreting level of thromboxane (TX), decrease the damage of nerve cell and promote the nerve repairs. Three components in the drug (*Lampsia chinensis*, *Ginkgo biloba*, *Manzanita*) could all reduce the contents of triacylglycerol (TG) and total cholesterol (TC), promote the transportation of metabolic wastes, and reduce oxidative damage [28,29]. Hcy expression causes inflammatory cytokine overload through oxidative stress, which promotes calcium overload and impaired cellular function, and so significantly decrease the cognitive function of patients [30]. *Panax ginseng* and *Schisandra propinqua* in the DYNT capsule have anti-atherosclerotic, vasodilatory, and other circulation-promoting effects. It could also reduce the plasma levels of CRP and Hcy. The results of this study shows that after adequate intervention, the ADL scores of patients in the treatment group were significantly higher than those of the control group, which indicating that DYNT capsule could improve the patients' self-care ability.

4.3. DYNT Capsules Improved Mobility and Balance of CSVD Patients

The pathogen of gait and balance instability caused by cerebrovascular disease is not only a single conduction bundle terminal, but also closely associated with the existence of a wide range of neural networks. When the patient's attention is not focused, it will lead to problems in execution, thus affecting the movement and balance [31,32]. DYNT capsule could enhance the expression of brain-derived neurotrophic factor (BDNF) of the patients, thereby promote neuronal repair, growth and differentiation, so to restore function of the damaged neurons. At the same time, DYNT capsules stimulate neurons or nerve axon connections in the motor pathway, which is conducive to cerebral hemispheric function compensation, thus improving clinical symptoms [33]. The results of this study indicated that the POMA balance score, gait score, and total score of patients in the DYNT capsule treatment group are significantly higher than those of the control group, which indicating that DYNT capsule could improve mobility and balance of the patients.

Conclusion: DYNT capsules are clinically effective in the treatment CSVD by improving the cognitive function, self-care ability, mobility and balance of patients.

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Ethics Approval and Consent to Participate

All related experiments were approved by the Ethics Committee of Shandong Zibo Fifth People's Hospital (No: 2021-004-01).

Conflicts of Interest Statement

The authors declare that there are no conflict of interest.

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