ORIGINAL RESEARCH

Value Analysis of Shenma Yizhi Recipe in Auxiliary Treatment of Acute Cerebral Infarction Patients with Cognitive Impairment

Zhen Liu[1, *], Chunhua Gu[2], Zhiyong Peng[3], Liandeng Xu[3] and Weihua Zhou[4]

[1]Shenzhen Bao'an District Chinese Medicine Hospital Internal Medicine Clinic,518000 Shenzhen, Guangdong, China

[2]Shenzhen Bao'an District People's Hospital Emergency Department,518000 Shenzhen, Guangdong, China

[3]Shenzhen Bao'an District Hospital of Traditional Chinese Medicine Emergency Department, 518000 Shenzhen, Guangdong, China

[4]Shenzhen Bao'an District Hospital of Traditional Chinese Medicine, Department of Brain Diseases,518000 Shenzhen, Guangdong, China

Abstract

Objective To analyze the value of Shenma Yizhi Recipe in auxiliary treatment of acute cerebral infarction patients with cognitive impairment. **Methods** From May 2018 to September 2020, 128 patients with acutecerebral infarction and cognitive dysfunction were selected and randomly divided into control group and observation group, with 64 cases in each group. Patients in the control group were given routine symptomatic treatment and citalopram treatment, and those in the observation group were given Shenma Yizhi Recipe on the basis of the control group. Before and after treatment, the neurological function, cognitive function, cerebral blood perfusion parameters, oxidative stress indexes and adverse reactions were compared between the two groups. **Results** Lower national institutes of health stroke scale (NIHSS) scores, mean transit time (MTT), malondialdehyde (MDA), advanced oxidation protein products (AOPP) and superoxide dismutase (SOD) levels in the two groups after treatment were observed compared to those before treatment ($P<0.05$), and a lower tendency was shown in the observation group compared to the control group ($P<0.05$). After treatment, higher scores of montreal cognitive assessment scale (MoCA), mini-mental state examination Scale (MMSE), cerebral blood flow (CBF) and cerebral blood volume (CBV) in the two groups were observed relative to those before treatment ($P<0.05$), and a lower tendency was shown in observation group compared to the control group ($P<0.05$). **Conclusion** Shenma Yizhi Recipe shows high safety in auxiliary treatment of acute cerebral infarction patients with cognitive impairment.

Introduction

Acute Cerebral Infarction (ACI) refers to cerebral artery atherosclerosis or thrombosis, which makes the lumen narrow or even blocked, resulting in brain tissue softening and necrosis due to insufficient blood supply to the brain. It usually occurs at night. If thrombolysis is not timely performed after ACI, cognitive impairment often occurs [1]. In order to improve the neurological and cognitive functions of ACI patients with cognitive impairment and improve the life quality of patients, it is necessary to find a treatment method suitable for ACI patients with cognitive impairment. Currently, citalopram is often used clinically to treat ACI patients with cognitive impairment, but patients will have adverse reactions such as nausea, vomiting, insomnia and constipation [2]. Shenma Yizhi Recipe consists of *ginseng*, *rhizoma gastrodiae*, *ramulus euonymi* and *ligusticum wallichii*, with the main effects of clearing and activating the channels and collaterals, removing phlegm and removing blood stasis [3]. Clinically, it is mainly used to improve patients' mental decline, irritability, cyanosis of lips and other symptoms [4].

At present, there are relatively few clinical studies on the use of Shenma Yizhi Recipe to assist citalopram in the treatment of ACI patients with cognitive impairment. Therefore, this study aims to analyze the clinical effect of Shenma Yizhi Recipe to assist citalopram in the treatment of ACI patients with cognitive impairment, and discusses the reliable methods for the treatment of ACI patients with cognitive impairment. The results of the research are reported as follows.

Materials and methods

General information

From May 2018 to September 2020, 128 patients with ACI and cognitive dysfunction were selected and randomly divided into control group and observation group, with 64 cases in each group. This study was approved by the ethics committee of our hospital, and all patients signed the written informed consent. There was no statistically significant difference in the general information between the two groups ($P > 0.05$), which was comparable, as referred in Table 1.

Table 1 Comparison of general information between two groups

Groups	Number of cases	Gender (cases)		Age (years old)	Underlying diseases (cases)			Course of CI (d)
		Male	Female		Hyperlipidemia	Diabetes	Hypertension	
Observation group	64	37	27	68.08±4.57	33	36	34	5.09±1.17
Control group	64	35	29	67.59±3.22	35	38	31	5.15±1.08
χ^2/t		0.127		0.701		0.247		-0.301
P		0.722		0.484		0.884		0.764

Diagnostic criteria

Western Medicine diagnostic criteria were referred to the diagnostic criteria of ACI with cognitive impairment from Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018 [5]. Traditional Chinese Medicine diagnostic criteria were referred to the diagnostic criteria of dementia from The Standard for TCM Diseases and Syndromes therapeutic results [6].

Inclusion criteria

① Meet the diagnostic criteria of Chinese and Western Medicine; ② No cognitive impairment before ACI; ③ Cooperate with medical workers to complete the study.

Exclusion criteria

① Associated with severe primary diseases of heart,

lung, kidney, etc.; ② Those who are allergic to citalopram tablets and components of Shenma Yizhi Recipe; ③ Patients with malignant tumors; ④ People with severe mental illness.

Treatment methods

Both groups of patients were given conventional treatments of ACI with cognitive dysfunction: For the general treatments, the researchers are required to do the following: ① pay attention to the patient's blood pressure; ② Provide patients with airway support and auxiliary ventilation; ③ Reduce intracranial pressure; ④ Provide patients with anti-infection treatment. Special treatments: ① antiplatelet therapy, anticoagulation therapy, etc.; ② Rehabilitation training: a. passive training: professionals helped patients with massage and acupuncture or used intermediate-frequency therapy apparatus to help patients with functional rehabilitation of limbs; b. Active training: encourage the patient to first perform facial exercise, handshake movement and sit-up training, and then slowly carry out transition to standing training. In the control group, citalopram tablets (packing specification: 10 mg*7 tablets; SFDA Approval No.: H20080788; manufacturer: Sichuan Kelun Pharmaceutical Co., Ltd.) were taken orally once a day based on routine treatment. On the basis of the control group, patients in the observation group were treated with Shenma Yizhi Recipe (prescriptions: 10 g each *ginseng*, *rhizoma gastrodiae* and *ramulus euonymi* and 15 g *ligusticum wallichii*) decoction, twice a day. The course of treatment for both groups was 8 weeks.

Observation indexes

① Neurological function [7]: the national institutes of health stroke scale (NIHSS) was used to evaluate the neurological function of the two groups before and after treatment. The NIHSS score includes 8 items with scores ranging from 0 to 45 points. The higher the NIHSS score, the more serious the patient's nerve injury.

② Cognitive function: the montreal cognitive assessment scale (MoCA) and mini-mental state examination Scale (MMSE) [3] were applied to assess the cognitive functions of the two groups before and after treatment. The full score of both scales is 30 points. The higher the score, the better the cognitive function of patients.

③ Cerebral blood perfusion parameters: Brain CT was performed before and after treatment to compare cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) of the two groups.

④ Oxidative stress indexes: level change of malondialdehyde (MDA), advanced oxidation protein products (AOPP) and superoxide dismutase (SOD) of the two groups was compared before and after treatment. Method: 5 ml of patients' venous blood was collected. After centrifugation (3000 r/min, centrifugal radius: 10 cm, time: 10 min), the blood was stored in a refrigerator. The levels of MDA, AOPP and SOD were measured by radioimmunoassay.

Statistical methods

SPSS 20.0 was used for statistical analysis, and the statistical data were compared using χ^2 test. The measurement data were expressed by mean ± standard deviation ($\bar{x}\pm s$). The independent sample t-test was used for the comparison between two groups, and the paired sample t-test was used for the comparison before and after treatment. $P<0.05$ was considered to be statistically significant.

Results

Comparison of neurological function and cognitive function between two groups

Before treatment, there was no significant difference in NIHSS, MoCA and MMSE scores between the two groups ($P>0.05$). Compared with before treatment, the NIHSS scores of the two groups decreased evidently after treatment ($P<0.05$), and the scores of MoCA and MMSE increased markedly ($P<0.05$). The NIHSS score of the observation group were obviously lower than that of the control group ($P<0.05$), and the scores of MoCA and MMSE were significantly higher compared with the control group ($P<0.05$). The details were listed in Table 2.

Table 2 Comparison of neurological function and cognitive function between two groups ($\bar{x}\pm s$, points)

Groups	Number of cases	NIHSS scores		MoCA scores		MMSE scores	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	64	26.43±5.16	18.51±3.93*	14.48±3.35	22.39±4.51*	20.06±4.27	27.89±4.65*
Control group	64	27.62±4.85	20.48±4.20*	14.62±3.11	19.43±3.72*	20.38±3.88	23.62±4.41*
t		-1.344	-2.740	-0.245	4.050	-0.444	5.330
P		0.181	0.007	0.807	0.000	0.658	0.000

Note: compared with before treatment: *$P<0.05$

Comparison of cerebral blood perfusion parameters between two groups

Prior to the treatment, difference in CBV, CBF and MTT levels between the two groups was not significant ($P>0.05$). Compared with those before treatment, the levels of CBV and CBF in the two groups increased obviously after treatment ($P<0.05$), while the MTT level decreased significantly ($P<0.05$). CBV and CBF levels in the observation group were significantly higher yet that of MTT was markedly lower than those in the control group ($P<0.05$). The details were listed in Table 3.

Table 3 Comparison of cerebral blood perfusion parameters between two groups ($\bar{x}\pm s$)

Groups	Number of cases	CBV ($\times 10^{-2}$mL/g)		CBF[$\times 10^{-2}$mL/(g·min)]		MTT (s)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	64	1.16±0.41	1.45±0.42*	0.72±0.15	0.98±0.26*	1.34±0.16	1.03±0.14*
Control group	64	1.19±0.44	1.28±0.40*	0.70±0.17	0.79±0.21*	1.32±0.19	1.11±0.22*
t		-0.399	2.345	0.706	4.548	0.644	-2.454
P		0.691	0.021	0.482	0.000	0.521	0.015

Note: compared with before treatment: *$P<0.05$

Comparison of oxidative stress indexes between two groups

Before treatment, there was no significant difference in MDA, AOPP and SOD levels between the two groups ($P>0.05$). Compared with those before treatment, the levels of MDA, AOPP and SOD in the two groups were down-regulated obviously after treatment ($P<0.05$), and MDA, AOPP and SOD levels in the observation group were markedly lower than those in the control group ($P<0.05$). The details were listed in Table 4.

Table 4 Comparison of oxidative stress indexes between two groups ($\bar{x}\pm s$)

Groups	Number	MDA (μmol/L)	AOPP (μmol/L)	SOD (U/L)

	of cases	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	64	9.07±1.18	5.45±0.75*	110.86±20.38	72.68±9.34*	180.52±30.61	123.53±17.65*
Control group	64	9.11±1.27	7.32±0.81*	112.33±18.19	89.08±10.26*	181.14±28.36	152.58±18.49*
t		-0.185	-13.552	-0.431	-9.456	-0.119	-9.092
P		0.854	0.000	0.668	0.000	0.906	0.000

Note: compared with before treatment: *$P<0.05$

Comparison of adverse reactions between two groups

In the observation group, 3 cases had adverse reactions, including 1 case of anorexia and 2 cases of nausea, while 7 cases in the control group had adverse reactions, including 3 cases of nausea, 2 cases of dry mouth and 2 cases of headache. There was no significant difference in adverse reactions between the two groups ($P>0.05$).

Discussion

ACI with cognitive dysfunction is mainly manifested in nausea, vomiting, headache and even coma. Most patients after treatment have different degrees of sequelae, such as hemiplegic paralysis, incoordination and language and sensory disorders, characterized by sudden onset, rapid progress and high mortality, which seriously threaten the quality of life and life safety of patients [9]. In traditional Chinese medicine, ACI with cognitive dysfunction is classified as "dementia". Although the focus is in the brain, ACI with cognitive dysfunction involves all visceral organs of the body, and its pathogenesis is deficiency of liver and kidney, resulting in insufficiency of vital energy and blood, hyperactive energy flow with syndrome of upward disturbance, phlegm obstructing, blockage of brain vessels by blood stasis, and loss of nourishment of the brain [3]. According to Western medicine, hypoxia and ischemia occur in the brain tissue of the arterial control area of patients with ACI, which

results in severe blood supply deficiency in the brain tissue of the patients, leading to anoxic and irreversible necrosis, neurological function injury, and further cognitive dysfunction [10].

The pathological mechanism of cognitive dysfunction after ACI is complex, which may be related to low cerebral blood perfusion and hypoxia, resulting in damage to hippocampal tissue and neurological function. Therefore, in order to improve cognitive and neurological dysfunction in patients with ACI, the priority is to improve the blood circulation of brain tissue in patients and restore the blood supply of local brain tissue [11]. CBV, CBF and MTT are common blood perfusion parameters. Among them, the lower the level of CBV, the more serious the damage to cerebral hemodynamics. The lower the level of CBF, the less blood supply of brain tissue. The increase of MTT level indicates lower blood flow velocity [12]. This study showed that after treatment, the NIHSS score and MTT of the two groups were significantly lower than those before treatment, and those in the observation group was obviously lower compared with the control group. However, MoCA score, MMSE score, CBV and CBF of the two groups were evidently higher than those before treatment, and those in the observation group was significantly higher compared with the control group. It therefore suggested that the neurological function, cognitive function and blood perfusion of brain tissue can be improved after the treatment of ACI patients with

cognitive dysfunction with citalopram auxiliary with Shenma Yizhi Recipe. Citalopram tablets can promote the secretion of positive neurotrophic factors and angiogenic factors, thus repairing nerves and promoting the formation of brain neovascularization, increasing the blood supply of patients' brain tissue, which is conducive to the improvement of patients' neurological function and cognitive ability [13]. Shenma Yizhi Recipe consists of *ginseng*, *rhizoma gastrodiae*, *ramulus euonymi* and *ligusticum wallichii*. Among them, *ginseng* can produce saliva and slake thirst, nourish nature and calm nerves, and replenish spleen and Qi. *Rhizoma gastrodiae* has the effects of calming endogenous wind and relieving spasm, removing dampness and pain, and dispelling wind and dredging collaterals. *Ramulus euonymi* has the effects of cooling blood, hemostasis, detoxification and detumescence, and removing wind and insects. *Ligusticum wallichii* can activate blood circulation and remove blood stasis, promote Qi and relieve depression. The combination of these medicines can dispel wind and dredge collaterals, activate blood circulation and remove blood stasis, tonify deficiency and benefit intelligence [1]. Modern pharmacological studies [14] show that *rhizoma gastrodiae* can not only protect brain cells, but also alleviate cerebral ischemia and inhibit thrombosis by increasing CBF, reducing MTT level, diminishing vascular resistance and inhibiting platelet aggregation, which is conducive to improving patients' cognitive function. Ligustrazine in *ligusticum wallichii* can protect nerve cells by reducing the protein expression of Bax and increasing the expression of Bcl-2, which can also inhibit vasospasm, alleviate cerebral ischemia and improve cognitive function.

One of the pathogeneses of ACI is an oxidative stress response in the body which refers to a state of imbalance between oxidation and antioxidation after the body is adversely stimulated. It is a side effect produced by free radicals in the body, which will not only aggravate the damage of brain cells and lead to ischemia and hypoxia in brain tissues, but also inhibit the formation of collateral circulation in damaged brain tissues [15]. Therefore, it is of great significance to treat ACI patients with cognitive impairment by reducing the body's oxidative stress response. MDA, AOPP and SOD are common indicators of oxidative stress. SOD is an antioxidant enzyme with anti-oxidative effect. AOPP is not only the product of oxidative stress, but also aggravates oxidative stress. MDA will destroy the cell structure and cause the loss of cell function. The higher its content, the more serious the body damage [16]. This study showed that the levels of MDA, AOPP and SOD in the two groups were evidently lower than those before treatment, and the levels of MDA, AOPP and SOD in the observation group were markedly lower than those in the control group. It shows that the combination of Shenma Yizhi Recipe and citalopram in the treatment of ACI patients with cognitive impairment can reduce the oxidative stress response of patients. Citalopram can improve the activity of antioxidant enzymes in the body and the ability to scavenge oxygen free radicals, reduce cell damage, alleviate oxidative stress, and regulate the levels of MDA, AOPP and SOD [13]. The components of Shenma Yizhi Recipe includes *ginseng*, *rhizoma gastrodiae*, *ramulus euonymi* and *ligusticum wallichii*. Among them, ginsenoside Rg1 in *ginseng* can reduce MDA level by up-regulating the expression levels of nuclear factor E2 related factor 2 and heme oxygenase 1 [3], and improve the oxidative stress of patients. Kaempferol in *ramulus euonymi* reduces the production of reactive oxygen species and promotes their clearance, playing the role of anti-oxidative stress and anti-apoptosis [17]. In addition, after treatment, there was no significant difference in adverse reactions between the two groups, indicating that citalopram assisted by Shenma Yizhi Recipe is safe in the treatment of ACI patients with cognitive impairment.

In conclusion, citalopram auxiliary with Shenma Yizhi Recipe in the treatment of ACI patients with cognitive impairment can effectively improve the patients' neurological function, cognitive function and cerebral blood perfusion level, reduce oxidative stress of patients' body, and has high safety.

Not applicable.

References

[1] Li W,Yuan Y.Relationship between peripheral serum cystatin C level and cognitive dysfunction in elderly patients with acute cerebral infarction[J].Chinese Journal of Practical Internal Medicine,2019,39(8):705-707.

[2] Ruan J,Wei X.Clinical Observation of Dispelling Melancholy and Soothing the Nerves Pill in the Treatment of Pathogenic Fire Derived from Stagnation of Liver-qi Insomnia[J].Chinese Remedies & Clinics,2022,22(3):272-275.

[3] Liu S,Pu G,Li Y,et al.Efficacy of Shenma Yizhi Prescription Combined with Citalopram in the Treatment of Cerebral Infarction Complicated with Cognitive Dysfunction and Its Effect on Inflammatory Factors and Oxidative Stress[J].Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease,2021,29(6):77-81.

[4] Sun C.Study on the Mechanism of Shenma Yizhi Prescription in Rats with Vascular Cognitive Impairment Based on Mitochondrial Protein Pathways[D].China Academy of Chinese Medical Sciences,2021.

[5] Peng B,Wu B.Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018[J].Chinese Journal of Neurology|Chin J Neurol,2018,51(9):666-682.

[6] Yu Y,Wang W,Yuan W,et al.Effect of Comprehensive Rehabilitation Management of Traditional Chinese Medicine in 172 Convalescent Patients with Cerebral Infarction[J].Beijing Medical Journal,2019,41(4):326-328.

[7] Wu R,Liu H,Chen Y.Clinical study on Yiqi Tongluo Granules combined with clopidogrel in treatment of convalescent stage of acute cerebral infarction[J].Drugs & Clinic,2021,36(5):1008-1012.

[8] Ding H,Zhao X,Chen X,et al.Kidney and medullary acupuncture combined with compound musk injection for the treatment of cognitive impairment after stroke[J].Chinese Journal of General Practice,2019,17(3):416-418.

[9] Meng X,Geng D.Clinical Effect of Ozagrel Combined with Puerarin on Acute Cerebral Infarction and the Impact on Collateral Circulation around Nidus[J].Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease,2019,27(10):104-108.

[10] Xu L,Li H.Relationship of HbAlc rate and serum fibrinogen level with cognitive impairment in acute ischemic stroke patients[J].Chinese Journal of Hypertension,2019,27(1):100.

[11] Guo Z.Effect of Ganglioside Combined with Vinpocetine Therapy on Cerebral Blood Flow Perfusion and Neural Functional Reconstruction in Patients with Acute Cerebral Infarction[J].Chinese Journal of Integrative Medicine on Cardio/Cerebrovascular Disease, 2020, 18(21): 3679 - 3682.

[12] Xu J,Zheng S,Wu Z,et al.Diagnostic Value of Multi-Modal and One-Stop Head and Neck Energy Spectrum CT Angiography in Acute Posterior Circulation Cerebral Ischemia[J].Journal of Clinical Radiology,2021,40(8):1480-1486.

[13] Huang W,Liu H.Application of Escitalopram Tablets Combined with Piracetam Tabletsin in Patients with Post-stroke Cognitive Impairment[J].Prevention and Treatment of Cardio-Cerebral-Vascular Disease,2021,21(4):393-395.

[14] Zhao X,Yuan H,Song C,et al.Clinical Effect of Banxia Baizhu Tianma Decoction on Acute Ischemic Stroke and the Impact on Coagulation Function and Cerebral Hemodynamics[J].Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease,2019,27(4):59-63.

[15] Zheng M, Wang X, Yang J, at el. Changes of complement and oxidative stress parameters in patients with acute cerebral infarction or cerebral hemorrhage and the clinical significance[J]. Exp Ther Med,2020, 19(1):703-709.

[16] Shen X,Wei W.The correlation between cognitive impairment in patients with obstructive sleep apnea syndrome (OSAHS) and serum MCP-1,HSP70,AOPP levels[J].Stroke and Nervous Diseases,2020,27(2):209-211.

[17] Zhou L,Li N,Liu J,et al.Influence of Shen Ma Yizhi Decoction on Learning Memory, Inflammatory Factors and Antioxidant Effects in Vascular Cognitive Impaired Rats Induced by Multiple Cerebral Infarction[J].Traditional Chinese Drug Research and Clinical Pharmacology,2020,31(3):294-299.