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Study on the Effect of Adjuvant Therapy of Shexiang Sihuang Granules on Neurological Function and Coagulation Function in Patients with Acute Cerebral Infarction

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Keywords

Shexiang Sihuang granules, Alteplase, Acute cerebral infraction, Nerve function, Coagulation function

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Abstract

Objective To explore the effect of adjuvant therapy of Shexiang Sihuang granules on neurological function and coagulation function in patients with acute cerebral infarction (ACI). **Methods** 126 ACI patients who received treatment in our hospital from March 2019 to March 2022 were randomly divided into a control group and an observation group, with 63 cases in each group. Patients in the control group was treated with alteplase, while those in the observation group were treated with Shexiang Sihuang granules based on the control group. The clinical efficacy, serum factor levels, coagulation function indicator levels and adverse reactions of the two groups were compared. **Results** The total effective rate of clinical treatment in the observation group was significantly higher than that in the control group (P<0.05); after treatment, the levels of neuron-specific enolase (NSE), central nervous system specific protein (S-100β), and D-dimer (D-D) in the two groups were significantly lower than those before treatment (P<0.05), and these levels in the observation group were significantly lower than those in the control group (P<0.05). After treatment, the levels of nerve growth factor (NGF) and prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) were obviously higher than before treatment (P<0.05), and the levels in the observation group were evidently higher than those of the control group (P<0.05). The incidence of adverse reactions in the two groups was not statistically significant (P>0.05). **Conclusion** Adjunctive treatment with Shexiang Sihuang granules can effectively relieve the clinical symptoms of patients with ACI, which is helpful for improving the body's neurological function and coagulation function, and its effect is safe and reliable.

Introduction

Acute cerebral infarction (ACI) is a common cerebrovascular disease worldwide, with a high incidence, mortality and disability, resulting in a serious impact on human health. ACI is a series of clinical syndromes that occur secondary to the ischemic hypoxic necrosis of brain tissue caused by the sudden reduction or interruption of blood supply to the brain. Therefore, the key to the treatment of ACI patients is to recanalize blood vessels and restore cerebral blood perfusion as soon as possible. Within the thrombolytic time window, thrombolytic therapy is the first choice for clinical vascular dredging, that is, fibrinolysis is facilitated by the injection of drugs, so as to dissolve the thrombus and recanalize the blood vessels. At present, the commonly used thrombolytic drugs include urokinase, alteplase (rt-PA) and so on. Although thrombolytic therapy with rt-PA can benefit ACI patients in a short time, the effective treatment time window of intravenous thrombolytic therapy is only 4.5 hours (h), and the effective rate of this therapy with rt-PA is about 30%. After thrombolytic therapy, angiogenic edema, reperfusion injury and other side effects may still occur, resulting in decreased neurological function [1]. In recent years, studies have shown that Western medicine could combine with the concept of tradition Chinese medicine (TCM) "syndrome differentiation and treatment", and administration of TCM decoction, acupuncture, and other TCM characteristic therapies can help to improve the clinical outcomes of patients with ACI [2]. Shexiang Sihuang granule is derived from "Angong Niuhuang pill", which has the effects of dredging collaterals and removing blood stasis, supplementing Qi and activating blood circulation. At present, there is a lack of research on the treatment of ACI patients with Shexiang Sihuang granule. The purpose of this study is to explore the effect of Shexiang Sihuang granule assisted thrombolytic therapy on the nervous function and coagulation function of ACI patients, so as to provide reference for clinical treatment. The research results are reported as follows.

Materials and methods

General data

A total of 126 ACI patients treated in our hospital from March 2019 to March 2022 were selected and randomly divided into observation (n = 63) and control (n = 63) groups. There were no significant differences in gender, age, infarct location, and average time from onset to admission between the two groups (P>0.05), which are shown in Table 1. This study was approved by the medical ethics committee, and patients were informed and consented.

Table 1 Comparison of general data between the two groups

Group		Observation group (n=63)	Control group (n=63)	χ^2/t	P
Gender (cases)	Male	34	32	0.127	0.721
	Female	29	31		
Age (years)		55.58±4.20	55.15±5.14	0.514	0.608
Average time from onset to admission (h)		3.01±0.51	3.08±0.51	-0.770	0.443
Infarct location (cases)	Frontal lobe	32	34	0.632	0.959
	Parietal lobe	18	17		
	Temporal lobe	8	7		
	Occipital lobe	3	4		
	Basal ganglia	2	1		

Inclusion criteria

(1) Those who meet the diagnostic criteria for ACI in the *Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2014* [3] and the *Expert consensus of Chinese and Western medicine emergency treatment for acute ischemic stroke in China* [4]; (2) Those who visited the doctor within 6 h after the onset of the disease; (3) Age ≤ 80 years old, with National Institute of Health stroke scale (NIHSS) ≤ 25 points; (4) Those with complete clinical data and no history of recent major surgery and related drug allergies.

Exclusion criteria

(1) Those with a combined history of acute intracranial hemorrhage; (2) Those combined with severe uncontrolled hypertension and hyperglycemia; (3) Those with severe head trauma, stroke, and myocardial infarction within the previous 3 months; (4) Those combined with coagulopathy and immune dysfunction; (5) Those who had received anticoagulant therapy within nearly 3 months; (6) Those combined with thrombolytic contraindications such as epilepsy, peptic ulcer, intracranial tumor, aneurysm and cerebral arteriovenous malformation.

Treatment

Patients in both groups were given routine symptomatic support such as respiratory support, blood pressure reduction, cranial pressure reduction, and blood glucose control. The control group was given thrombolytic therapy with alteplase (Boehringer Ingelheim Pharma GmbH & Co.KG, registration certificate number: S20160054, specification: 20mg). The dosage was calculated according to the multiplication of the patient's weight and 0.9mg/kg. The first 10% alteplase was injected intravenously, and the last 90% was pumped intravenously within 1 h. The head CT reexamination was performed after 24 h. Patients in the observation group took Shexiang Sihuang granules on the basis of the control group. The prescription included: 12g each of stir fried Zhizi (*Gardenia jasminoides Ellis*), Tianzhu Huang (*Bambusa textilis McClure*), Gualou (*Trichosanthes kirilowii Maxim*) and Dang Gui (*Angelica sinensis*), 10g each of Huanglian (*Coptis chinensis Franch*), Quanxie (*Buthus martensii Karsch*) and Chuanxiong (*Ligusticum chuanxiong hort*), 9g of raw Dahuang (*Crude rhubarb*), and 1g each of Shexiang (*Moschus*), Niuhuang (*Bos taurus domesticus Gmelin*) and antelope horn powder. It was prepared by the TCM granule preparation department and was taken with warm waterat 1 dose per day. It was taken separately in the morning and evening for 14 days.

Detection indicators

(1) Clinical efficacy: before and 14 days after treatment, the neurological functions of the two groups were assessed with the NIHSS [5], and the higher NIHSS score indicated the more severe neurological impairment. Meanwhile, the clinical efficacy was judged according to the reduction of NIHSS score, and the judgment criteria were: Well-healed: >90% reduction; Markedly effective: 45% reduction; Effective: 17% reduction; Ineffective: ≤ 17% reduction, total effective rate = (well-healed cases + markedly effective cases + effective cases) / total cases × 100%. (2) Serum factors: 5mL of fasting venous blood of the two groups were collected in the early morning before and 14 days after the treatment, and the levels of neuron specific enolase (NSE), central nerve specific protein (S-100β) and nerve growth factor (NGF) were detected by enzyme-linked immunosorbent assay (ELISA) kit (Shanghai Enzyme-linked Biotechnology Co., Ltd.). (3) Coagulation indicators: 5mL venous blood was taken from the two groups before and 14 days after treatment. After centrifugation, supernatant was taken, and D-Dimer (D-D), plasma prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT) were detected by automatic coagulation tester (Beijing Zhongchi automation equipment Co., Ltd, XL1000e, Beijing medical device registration certificate standard number: 20152220146); (4) Adverse reactions: during the treatment period and after 14 days of treatment, the occurrence of asymptomatic intracranial hemorrhage, gingival hemorrhage, nasal mucosal hemorrhage and

other adverse reactions in the two groups were observed.

Statistical analysis

SPSS 20.0 was used for statistical analysis, the measurement data were expressed by the mean ± standard deviation ($\bar{x}\pm s$). Independent sample t-test was used for comparison between the two groups, and paired sample t-test was used for comparison at different time points in the same group. $P<0.05$ was taken as statistically significant.

Results

Comparison of clinical efficacy between the two groups

The total effective rate in the observation group was obviously higher than that in the control group ($P<0.05$), as shown in Table 2.

Table 2 Comparison of clinical efficacy between the two groups [cases (%)]

Group	Cases	Well-healed	Markedly effective	Effective	Ineffective	Total effective rate
Observation group	63	25 (39.68)	23 (36.51)	10 (15.87)	5 (7.94)	58 (92.06)
Control group	63	21 (33.33)	19 (30.16)	9 (14.29)	14 (22.22)	49 (77.78)
χ^2						5.020
P						0.025

Comparison of NSE, S-100β and NGF levels between the two groups before and after treatment

Before treatment, there was no significant difference in NSE, S-100β and NGF levels between the two groups ($P>0.05$); After treatment, the levels of NSE and S-100β in the two groups were largely lower than those before treatment ($P<0.05$), and the levels in the observation group were significantly lower than those in the control group ($P<0.05$). After treatment, NGF level in the two groups was evidently higher than that before treatment ($P<0.05$), and NGF level in the observation group was significantly higher than that in the control group ($P<0.05$), as depicted in Table 3.

Table 3 Comparison of NSE, S-100β and NGF levels between the two groups before and after treatment ($\bar{x}\pm s$, points)

Group	Cases	NSE (μg/L)		S-100β (μg/L)		NGF (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	63	19.80±3.25	12.17±1.86*	1.98±0.34	1.24±0.15*	77.89±5.11	118.17±12.05*
Control group	63	20.38±2.60	14.04±2.63*	1.95±0.31	1.48±0.21*	77.74±4.63	105.31±10.21*
t		-1.106	-4.608	0.518	-7.381	0.173	6.463
P		0.271	0.000	0.606	0.000	0.863	0.000

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

Comparison of coagulation function indicators between the two groups before and after treatment

Before treatment, there was no significant difference in PT, APTT, TT and D-D levels between the two

groups (P>0.05). After treatment, PT, APTT and TT levels in the two groups were markedly higher than those before treatment (P<0.05), and the levels in the observation group were remarkably higher than those in the control group (P<0.05). After treatment, the D-D level of the two groups was obviously lower than that before treatment (P<0.05), and the D-D level in the observation group was lower than that in the control group (P<0.05), as illustrated in Table 4.

Table 4 Comparison of coagulation function indicators between the two groups before and after treatment ($\bar{x}$±s)

Observation indicator		Observation group (n=63)	Control group (n=63)	t	P
PT (s)	Before treatment	11.25±1.51	11.51±1.25	-1.053	0.294
	After treatment	14.27±2.11*	12.86±1.93*	3.914	0.000
APTT (s)	Before treatment	23.23±3.06	23.77±2.81	-1.032	0.304
	After treatment	29.52±4.09*	26.40±3.40*	4.656	0.000
TT (s)	Before treatment	14.55±1.70	14.68±1.70	-0.429	0.669
	After treatment	18.20±2.61*	16.47±2.06*	4.130	0.000
D-D (mg/L)	Before treatment	0.79±0.13	0.77±0.08	1.040	0.300
	After treatment	0.40±0.09*	0.56±0.09*	-9.978	0.000

Note: compared with that before treatment: *P<0.05.

Comparison of adverse reactions between the two groups

There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05), based on Table 5.

Table 5 Comparison of adverse reactions between the two groups [cases (%)]

Group	Cases	Asymptomatic intracranial hemorrhage	Gingival hemorrhage	Nasal mucosal hemorrhage	Total incidence
Observation group	63	3 (4.76)	4 (6.35)	1 (1.59)	8 (12.70)
Control group	63	2 (3.18)	5 (7.94)	2 (3.18)	9 (10.30)
χ^2					0.068
P					0.794

Discussion

The sharp decrease of cerebral blood flow in ACI patients will lead to the necrosis of some brain tissues, resulting in neurological deficit, hemiplegia,

dysphagia and even coma. There is an ischemic penumbra between the brain core necrotic area and the healthy brain tissue, which contains a large number of dormant or semi dormant brain cells that can maintain their own morphological integrity, restore cerebral blood perfusion as soon as possible, and have the opportunity to save the brain nerves in this area. Intravenous thrombolysis is the first choice for patients within the thrombolysis time window, rt-PT is one of the most commonly used thrombolytic drugs in clinic, which can dissolve local fibrin clots, dredge blood supply arteries and alleviate cerebral hypoxia [6]. In TCM, ACI is classified as “stroke”, and there are other names such as “Dajue (coma)”, “Pianku (hemiplegia)”, and “Fengfei (hemiplegia)” in ancient books. As recorded in *Suwen-Tiaojinglun* (Essential Questions-On Regulating Meridians): “If blood and Qi travel upwards together, it will lead to Dajue, while Dajue may cause the sudden death.” The mechanism of the disease is that the viscera are out of nourishment, the liver and kidney are deficient, and the blood stasis is endogenously generated, which leads to blockage of cerebral collaterals and dysfunction of the mind. It is associated with many factors, such as “Qi, blood, fire, phlegm, wind, and deficiency”. The treatment should focus on promoting blood circulation, regulating menstruation, dredging channels and removing blood stasis, supplemented by nourishing Yin and Qi and regulating the liver and kidney. This study investigated the clinical efficacy of Shexiang Sihuang granules assisted intravenous thrombolysis in patients with ACI, as well as its effect on neurological function and coagulation function. The results showed that Shexiang Sihuang granules had a good effect.

NSE is one of the important proteins in the glycolysis process of nerve tissue cells. S-100β protein is involved in the proliferation and differentiation of glial cells. During the onset of ACI, local ischemic and hypoxic necrosis of brain tissue will cause the escape of NSE, S-100β and other substances from necrotic neurons to cerebrospinal fluid, and then enter the serum through the damaged blood-brain barrier (BBB). The higher the level, the more serious the neurological damage [7]. In addition, NGF can promote the growth and development of central neurons, promote the repair and regrowth of the nervous system, inhibit the release of toxic amino acids and superoxide free radicals, and protect neurons [8]. The results showed that the total effective rate of the observation group was significantly higher than that of the control group. After treatment, the levels of NSE and S-100β in the two groups were significantly lower than those before treatment, and the levels in the observation group were significantly lower than those in the control group. After treatment, the level of NGF in the two groups was significantly higher than that before treatment, and the NGF level in the observation group was significantly higher than that in the control group. Besides, there was no significant difference in the incidence of adverse reactions between the two groups. It is suggested that Shexiang Sihuang granules can effectively alleviate the clinical symptoms of ACI patients, and help to improve the nervous function of the body, and its effect is safe and reliable. Alteplase is a plasminogen activator, which can be combined with fibrin to activate plasminogen into plasmin and promote the decomposition of fibrin so as to remove thrombus and restore cerebral blood perfusion. Shexiang Sihuang granules include stir-fried Zhizi, Tianzhu Huang, Gualou, Dang Gui, Huanglian, Quanxie, Chuanxiong, raw rhubarb, Shexiang, Niuhuang and the powder of antelope horn. Among them, Shexiang can induce resuscitation, promote blood and channel circulation. Niuhuang can clear away heat and toxic material, remove phlegm and awaken the mind. Antelope horn can calm the liver and extinguish wind, disperse blood and detoxify toxin. Tianzhu Huang can clear heat and remove phlegm, and raw rhubarb can remove blood stasis and reduce heat. In addition, Gualou, Dang Gui, Quan Xie, Chuanxiong, stir-fried Zhizi and other drugs can reduce fire and eliminate phlegm, cool the blood and dissipate blood stasis. And the whole prescription plays the effect of inducing resuscitation, removing blood stasis, dredging collaterals and activating blood circulation. Modern pharmacological studies have shown that [9-11], Shexiang Sihuang

granules can protect brain tissue and reduce neurological ischemic damage. Shexiang contains effective components such as muscone, which can regulate BBB permeability and accelerate the effect of drugs on the nervous system. In addition, muscone can stimulate olfactory ensheathing cells, increase the expression of neurotrophic factors and nerve growth factors, and reduce cerebral ischemic injury, brain edema and cerebral ischemia-reperfusion injury, thereby protecting brain tissue. Coptisine can promote the expression of brain-derived neurotrophic factor and reduce neuronal apoptosis, and berberine in Coptis chinensis can reduce cerebral ischemia-reperfusion injury by reducing the level of methyltransferase. Niuhuang can act on multiple targets, inhibit neuronal apoptosis and promote the expression of steroids, thereby reducing neurological deficit. Liu Tao [12] et al. used the combination of Shexiang Sihuang granules and alteplase to treat patients with phlegm-heat abdominal solid type ACI, and they found that the combined treatment has a good effect on improving patients' neurological function, which is consistent with the results of this study.

In patients with ACI, TT, PT, APTT and other coagulation function indicators are low, and the blood is in a hypercoagulable state, which then forms a thrombus to block the arterial lumen, leading to the onset of ACI [13]. D-D is the product of cross-linked fibrin clot degraded by plasmin, which is a specific marker of fibrinolysis process, and its high expression in serum is a sign of high-level coagulation and fibrinolysis. The results of this study showed that after treatment, PT, APTT and TT levels in the two groups were significantly higher than those before treatment, and the levels in the observation group were significantly higher than those in the control group. After treatment, the level of D-D in the two groups was significantly lower than that before treatment, and the level in the observation group was lower than that in the control group. It is suggested that Shexiang Sihuang granules can effectively improve the coagulation function of ACI patients. The reason may be as follows: firstly, alteplase can activate plasminogen, promote fibrinolysis and regulate coagulation function; Secondly, modern pharmacological research shows that [9,11] muscone, berberine and other components have the effect of inhibiting platelet aggregation, which can effectively prolong the coagulation time and improve the coagulation function of the body.

In conclusion, adjunctive treatment with Shexiang Sihuang granules can effectively relieve the clinical symptoms of patients with ACI, which is helpful for improving the body's neurological function and coagulation function, and its effect is safe and reliable.

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Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization, Writing - Original draft, Writing - review and editing, J.L.F, Data curation, and Methodology, S.J.C and Z.Q.H; All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee, and the patients were informed and consented.

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Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Material

Not applicable.

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