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Therapeutic effects of Buyang Huanwu Tang combined with RT-PA intravenous thrombolysis on stroke of Qi deficiency and blood stasis type and its impact on Keap1-Nrf2/ARE pathway antioxidant stress

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ABSTRACT

This study investigated the impact of combining traditional Chinese medicine, Buyang Huanwu Tang, with intravenous thrombolysis using alteplase (rt-PA) in treating ischemic stroke patients with qi deficiency and blood stasis. A single-center clinical randomized trial involved 117 ischemic stroke patients treated with rt-PA in the neurology department from January 2019 to December 2021. Patients were randomly divided into two groups: the control group (58 patients) received rt-PA alone, while the combined group (59 patients) received rt-PA along with Buyang Huanwu Tang. Neurological deficit scores (NIHSS) were assessed before and after treatment, along with hemorheological indicators, vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9), and Keap1-Nrf2/ARE pathway oxidative stress indicators (Keap1, Nrf2, ARE, and NQO1 proteins). Before treatment, there were no significant differences between the groups. After treatment, the combination group exhibited lower NIHSS scores at 4, 8, and 12 weeks, indicating significant improvement compared to the control group. Additionally, the combination group demonstrated reduced plasma viscosity, low and high shear viscosity, and improved red blood cell aggregation compared to the control group after 8 weeks of treatment. Furthermore, the combination group showed elevated MMP-9 levels and reduced VEGF levels, suggesting favorable outcomes. Regarding the Keap1-Nrf2/ARE pathway, Nrf2 and NQO1 protein expression levels were higher in the combination group after 8 weeks of treatment. Clinical efficacy assessment revealed that the combined treatment group had a significantly better overall treatment response. In conclusion, combining Buyang Huanwu Tang with rt-PA intravenous thrombolysis effectively mitigated oxidative stress damage in the Keap1-Nrf2/ARE pathway among ischemic stroke patients with qi deficiency and blood stasis. This approach promoted neurological function recovery and improved overall treatment outcomes.

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Introduction

Ischemic stroke, often referred to as acute cerebral infarction, represents a prevalent cerebrovascular disorder in clinical practice. This condition is characterized by cerebral atherosclerosis, resulting in the narrowing of vascular lumens, and thrombosis, leading to the occlusion of these lumens. Such occurrences interrupt the essential blood supply to brain tissues, causing local ischemia and hypoxia. Ischemic strokes are notorious for their high rates of disability and mortality, imposing a substantial burden on both society and healthcare resources (1). In Western medicine, standard treatments for ischemic stroke typically involve intravenous thrombolysis, anticoagulation, and strategies to enhance cerebral circulation. Alteplase (rt-PA) is a widely used intravenous thrombolytic drug in clinical practice. It effectively dissolves existing thrombi and prevents the formation of new ones, thereby facilitating the restoration of cerebral tissue blood perfusion. However, the effectiveness of rt-PA intravenous thrombolytic therapy is limited by a therapeutic time window, and outcomes tend to be less favorable when this window is exceeded (2).

Traditional Chinese medicine (TCM) categorizes ischemic stroke as a type of "stroke" and frequently attributes it to evidence of qi deficiency and blood stasis. Qi deficiency, in this context, signifies an inability to promote proper blood circulation. When blood circulation becomes compromised, blood stasis can form within the brain. This impedes the nourishment of the brain's clear orifices by qi and blood, ultimately leading to the development of the disease. The TCM approach to treatment involves reinforcing qi, stimulating blood circulation, eliminating blood stasis, and clearing the channels (3). Buyang Huanwu Tang is a renowned Chinese herbal formula employed to address blood stasis-related conditions, and its clinical efficacy is well-recognized (4). Nonetheless, there remains a need for more in-depth research on its mechanisms of action.

In light of these considerations, this study aims to investigate the therapeutic effect and underlying mechanisms of Buyang Huanwu Tang in combination with rt-PA intravenous thrombolysis for the treatment of ischemic stroke patients presenting with both qi deficiency and

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blood stasis. Our research seeks to shed light on how this TCM approach, designed to invigorate yang and restore balance, complements the conventional rt-PA treatment in enhancing outcomes for individuals with ischemic stroke in the context of qi deficiency and blood stasis. By elucidating the mechanisms at play, we aspire to contribute to a better understanding of the synergistic potential of TCM and Western medicine in the management of ischemic stroke, ultimately offering more effective therapeutic strategies for patients with this challenging condition.

Materials and Methods

Basic information on research subjects

Using a single-centre clinical randomized trial, 117 ischemic stroke patients who implemented thrombolytic therapy in the Department of Neurology of our hospital from January 2019 to December 2021 were randomly grouped, of which 58 patients were treated with rt-PA intravenous thrombolysis (control group), the other 59 patients were treated with rt-PA intravenous thrombolysis+Chinese medicine tonic yang and five soups (combined group), and the basic data of patients in the combined group and the control group were compared, and the two groups were comparable and balanced (P>0.05), as shown in Table 1.

Inclusion criteria: (i) The diagnostic criteria of ischemic stroke patients referred to the criteria in the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018 (5), and the diagnostic criteria of traditional Chinese medicine referred to the Guidelines for Clinical Research of New Traditional Chinese Medicines (Trial) (6), which belonged to the type of qi deficiency and blood stasis; (ii) The patients were admitted to the hospital to receive examinations and treatments within 4.5 h after onset of the disease; (iii) The patients' age ranges were 19 -79 years old; (iv) Acute ischaemic stroke was diagnosed by cranial CT and MRI; (v) All patients were willing to accept the interventions related to this study; (vi) The study protocol was approved by the Medical Ethics Committee.

Exclusion criteria: (i) patients with advanced cancer pain; (ii) cerebral haemorrhage, ruptured cerebral aneurysm, cerebral infarction, etc.; (iii) HIV-infected patients; (iv) acute myocardial infarction; (v) history of drug abuse, patients with long-term use of analgesic drugs, history of psychiatric disorders, and history of Alzheimer's disease.

Methods

Patients in the control group were treated with intravenous thrombolysis with rt-PA (Boehringer Ingelheim, Germany: specification: 50 mg). The dose of rt-PA was 0.9mg /kg. First, 10% of the drug was injected intravenously, and the remaining 90% of the drug was injected intravenously within 1 h. After that, the patients' vital signs were closely observed, and if any adverse reaction occurred, the drug was stopped immediately, and the cranial CT was reviewed. After intravenous thrombolysis, patients' vital signs were closely observed, and if adverse reactions occurred, the drug was immediately stopped, and cranial CT was repeated. 24 h later, anticoagulation, neuroprotection, improvement of circulation and other treatments were given.

Patients in the combined group were treated with rt-PA intravenous thrombolysis+Chinese medicine tonifying yang and restoring wu tang, after the patients' vital signs were stabilised, they were given tonifying yang and restoring wu-tang: 120 g of Astragalus membranaceus, 6 g of Angelica sinensis, 6 g of Paeoniae lactiflora, 3 g of Dilong, Rhizoma ligustici chuanxiong, safflower, peach kernel, the above medicines were administered once a day in the form of a decoction of water to extract 200 ml of juice, which was warmed up in the morning and evening and taken in the morning to take 100 ml of juice, and the patients with impaired consciousness could be given nasal feeding. Continuous treatment for 8 weeks.

Indicators collected in this study and their evaluation measures

Compare the neurological deficit score (NIHSS), blood rheological indexes (plasma viscosity, whole blood low-cut viscosity, whole blood high-cut viscosity, erythrocyte aggregation index), vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9), Keap1, Nrf2, ARE, and NQO1 protein expression levels, and differences in clinical efficacy of the patients in the two groups before and after treatment.

The clinical efficacy of the patients was evaluated at 4 weeks, 8 weeks and 12 weeks of treatment, and the evaluation was graded according to the changes in NIHSS

Table 1. Comparison of the basic information of the two groups of patients.

Group	n	Age (years)	BMI (kg/m^2)	Gender (%)		Smoking (%)	Drinking alcohol (%)
				Male	Female		
Combined	59	68.3±5.9	22.66±1.90	35(59.32)	24(40.68)	21(35.59)	25(42.37)
Control	58	66.8±7.8	22.60±1.93	30(51.72)	28(48.28)	24(41.38)	19(32.76)
t/x^2		1.174	0.169	0.684		0.414	1.152
P		0.243	0.866	0.408		0.520	0.283

Group	n	Thrombolysis time window (h)	Infarct area (cm^2)	Comorbidities (%)			
				High blood pressure	Diabetes	Coronary heart disease	Hyperlipidaemia
Combined	59	2.96±0.77	24.56±6.30	29(49.15)	15(25.42)	8(13.56)	35(59.32)
Control	58	3.15±0.64	26.00±5.48	34(58.62)	21(36.21)	5(8.62)	39(67.24)
t/x^2		-1.450	-1.318	1.055	1.597	0.722	0.789
P		0.150	0.190	0.304	0.206	0.395	0.374

scores (7). Ineffective: no change or even aggravation of NIHSS scores, or a reduction of less than 18% after treatment; effective: patients' NIHSS scores were reduced by 18% to 45% after the treatment; obvious effect: patients' NIHSS scores were reduced by 46% to 90% after the treatment; basically cured: patients' NIHSS scores were reduced by 91% to 100%.

Fasting venous blood specimens of 10 ml were drawn from patients in both groups before treatment and after 8 weeks of treatment and were divided into three vacuum blood collection tubes. One blood specimen was tested for plasma viscosity, whole blood low-cut viscosity, whole blood high-cut viscosity, and red blood cell aggregation index by using a South990JS3 blood rheometer. One blood specimen was left at room temperature for half an hour, centrifuged at 3500 r/min for 10 min, and the serum was taken to detect vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) by enzyme-linked immunosorbent assay (ELISA) using a kit from Shanghai Zhenke Biotech Co, Ltd. (Shanghai, Cina), and the instrument was a Thermo Fisher (Waltham, MA, USA) MK3 enzyme marker. One blood specimen was anticoagulated with heparin, and peripheral blood lymphocytes were isolated within 2 h. Peripheral blood single nucleated cells were extracted, washed and resuspended in 1640 culture medium, and then lysed by adding cell lysate and then centrifuged and the supernatant was taken to obtain the total protein. Total protein was obtained by centrifugation of the supernatant. SDS-PAGE electrophoresis was carried out using a concentration gel at 80 V and a separator gel at 120 V. The cells were closed at room temperature with 5% skimmed milk sealing solution for 2 h. The specific primary antibody was added and incubated overnight at 4°C. The cells were washed and incubated with fluorescently labelled sheep's blood lymphocytes. Incubate the fluorescently labelled sheep anti-rabbit secondary antibody for 1h, wash the membrane, wash, and develop by ECL luminescence. QuantityOne software was used to calculate the ratio of the grey value of the target protein bands to the grey value of the inner bands to indicate the protein expression levels of Keap1, Nrf2, ARE and NQO1.

Statistical analysis

Data were analysed using the statistical software Statistic Package for Social Science (SPSS) 21.0 (IBM, Armonk, NY, USA), Keap1, Nrf2, ARE and NQO1 proteins belonged to the category of measurement data in this study, and the statistical description was described using the mean ± standard deviation ($\bar{x}$±s), and the statistical inference method used was the independent samples *t*-test; comorbidities, clinical efficacy, etc. belonged to the category of count data, and the statistical description was described by rate (%), and the statistical inference method of the above count data was adopted by the x^2 test or Mann-WhitneyU test; the difference was considered to be statistically significant at $P<0.05$.

Results

Comparative analysis of patients' neurological function recovery

Before treatment, there was no significant difference in the degree of neurological deficit (NIHSS score) between the patients in the combined group and the control group ($P>0.05$), and after active treatment, the NIHSS scores of the combined group were lower than those of the control group at 4, 8, and 12 weeks of treatment, and the neurological recovery of the patients in the combined group was better ($P<0.05$); Table 2, Figure 1.

Analysis of the improvement of blood rheology

The blood rheological indexes of patients before and after treatment were tested and analysed, and the baseline results of plasma viscosity, whole blood low-cut viscosity, whole blood high-cut viscosity and erythrocyte aggregation index determination of the patients in the combined group and the control group were not significantly different ($P>0.05$), and the study group was lower than the control group. The plasma viscosity, whole blood low-cut viscosity, and whole blood high-cut viscosity levels of the two groups of patients were measured again after 8 weeks of treatment, and the study group was lower than the control group, and the improvement of blood rheology of the patients in the study group was more significant ($P<0.05$); Table 3, Figure 2.

Analysis of changes in serum MMP-9, VEGF before and after treatment

Comparison of serum MMP-9 and VEGF levels between patients in the combined group and the control group before treatment showed no significant difference ($P>0.05$), and after 8 weeks of treatment, the above in-

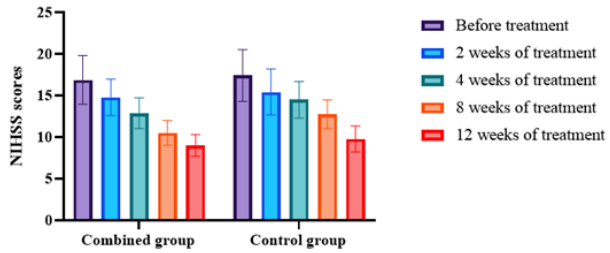

Figure 1. Comparison of changes in NIHSS scores of patients in the two groups.

Table 2. Comparison of changes in NIHSS scores of patients in the two groups ($\bar{x}$±s, points).

Group	n	Before treatment	2 weeks of treatment	4 weeks of treatment	8 weeks of treatment	12 weeks of treatment
Combined	59	16.86±2.94	14.77±2.20*	12.86±1.85*	10.50±1.48*	8.98±1.30*
Control	58	17.40±3.11	15.41±2.76*	14.48±2.20*	12.71±1.73*	9.78±1.56*
t		-0.965	-1.388	-4.314	-7.429	-3.015
P		0.336	0.168	0.000	0.000	0.003

Note: Comparison with this group before treatment *$P<0.05$.

Table 3. Comparison of blood rheological indexes between the two groups of patients ($\bar{x}$±s).

Group	n	Plasma viscosity (mPa·s)		*t*	*P*	Whole blood low-cut viscosity (mPa·s)		*t*	*P*
		Before treatment	8 weeks of treatment			Before treatment	8 weeks of treatment		
Combined	59	1.83±0.48	1.40±0.33	5.637	0.000	16.49±2.33	12.15±1.86	11.123	0.000
Control	58	1.95±0.40	1.55±0.36	5.682	0.000	16.00±1.97	13.41±2.34	6.481	0.000
t		-1.468	-2.350			1.227	-3.227		
P		0.145	0.020			0.222	0.002		

Group	n	Whole blood high cut viscosity (mPa·s)		*t*	*P*	Erythrocyte aggregation index (EAI)		*t*	*P*
		Before treatment	8 weeks of treatment			Before treatment	8 weeks of treatment		
Combined	59	6.90±1.65	4.40±1.10	9.626	0.000	2.85±0.75	2.30±0.61	4.347	0.000
Control	58	6.54±1.70	4.94±1.43	5.505	0.000	2.72±0.78	2.46±0.65	1.957	0.053
t		1.162	-2.292			0.919	-1.373		
P		0.247	0.024			0.360	0.172		

Table 4. Comparison of serum MMP-9 and VEGF levels between the two groups of patients ($\bar{x}$±s).

Group	n	VEGF (ng/L)		*t*	*P*	MMP-9 (ng/mL)		*t*	*P*
		Before treatment	8 weeks of treatment			Before treatment	8 weeks of treatment		
Combined	59	248.1±28.7	346.9±39.5	-15.497	0.000	45.30±8.56	26.92±6.61	12.984	0.000
Control	58	241.0±30.5	318.5±34.7	-12.837	0.000	43.01±8.80	30.35±7.26	8.480	0.000
t		1.297	4.129			1.427	-2.673		
P		0.197	0.000			0.156	0.009		

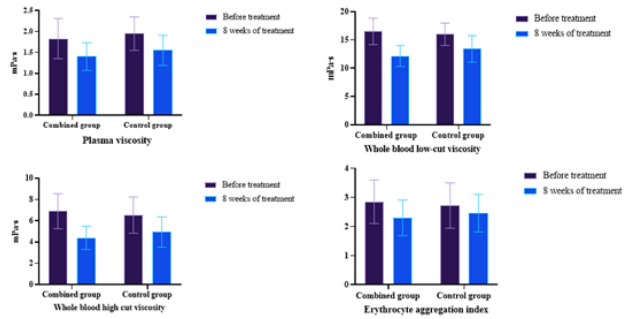

Figure 2. Comparison of blood rheological indexes between the two groups of patients.

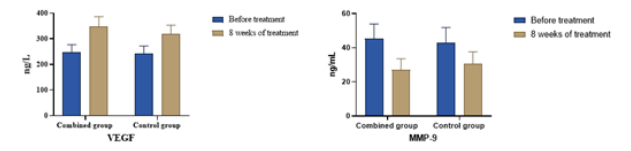

Figure 3. Comparison of serum MMP-9 and VEGF levels between the two groups of patients.

dexes of the two groups were reviewed again, and the combined group had a higher value of serum MMP-9 measurement than the control group, and the level of VEGF was lower than that of the control group, and the intergroup differences of the indexes were statistically significant (P<0.05); Table 4, Figure 3.

Comparison of Keap1-Nrf2/ARE pathway oxidative stress indicators between the two groups of patients

Before treatment, there was no statistically significant difference in the protein expression levels of Keap1, Nrf2, ARE and NQO1 between the patients in the combined group and the control group (P>0.05), and when re-examined after 8 weeks of treatment, the combined group showed a higher expression of serum Nrf2 and NQO1 proteins than that of the control group, and the difference between the groups of the above indicators was significant (P<0.05); Table 5, Figure 4.

Comparison of the clinical efficacy of the two groups of patients

After the clinical efficacy evaluation of the two groups of patients after treatment, the overall efficacy distribution of the patients in the combined group was better than that of the control group, and the difference was statistically significant (P<0.05); Table 6, Figure 5.

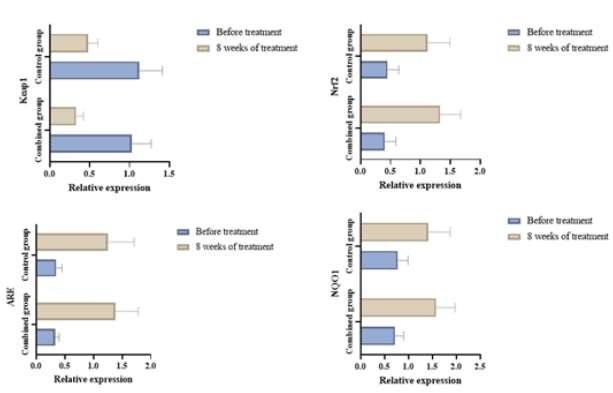

Figure 4. Comparison of Keap1-Nrf2/ARE pathway oxidative stress indexes between the two groups.

Table 5. Comparison of Keap1-Nrf2/ARE pathway oxidative stress indexes between the two groups ($\bar{x}$±s, relative expression).

Group	n	Keap1				Nrf2			
		Before treatment	8 weeks of treatment	*t*	*P*	Before treatment	8 weeks of treatment	*t*	*P*
Combined	59	1.03±0.24	0.33±0.09	20.819	0.000	0.41±0.18	1.33±0.34	-18.335	0.000
Control	58	1.12±0.29	0.48±0.12	15.549	0.000	0.45±0.19	1.12±0.37	-12.351	0.000
t		-1.830	-7.658			-1.169	3.197		
P		0.070	0.000			0.245	0.002		

Group	n	ARE				NQO1			
		Before treatment	8 weeks of treatment	*t*	*P*	Before treatment	8 weeks of treatment	*t*	*P*
Combined	59	0.33±0.07	1.38±0.40	-19.857	0.000	0.72±0.18	1.58±0.39	-15.356	0.000
Control	58	0.35±0.10	1.25±0.46	-14.681	0.000	0.78±0.21	1.41±0.46	-9.556	0.000
t		-1.255	1.632			-1.660	2.157		
P		0.212	0.105			0.100	0.033		

Table 6. Comparison of the clinical efficacy of patients in the two groups (n (%)).

Group	n	Basically cured	Significantly cured	Effective	Ineffective
Combined	59	24(40.68)	22(37.29)	11(18.64)	2(3.39)
Control	58	14(24.14)	19(32.76)	20(34.48)	5(8.62)
Z		-2.534			
P		0.011			

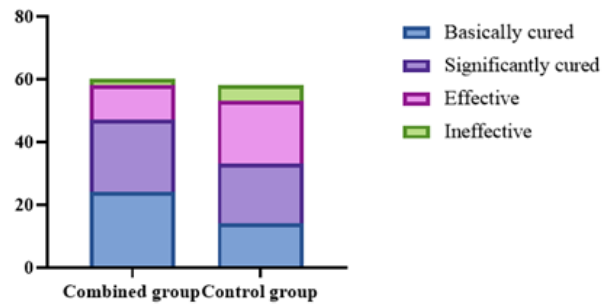

Figure 5. Comparison of the clinical efficacy of patients in the two groups.

Discussion

Ischemic stroke is the leading cause of disability among Chinese residents, and the Report on Nutrition and Chronic Disease Status of Chinese Residents (2020) (8) pointed out that the number of deaths due to cerebrovascular diseases accounted for 80.7% of the total number of deaths in China in 2019, with the incidence rate of ischemic stroke being about 276.75/10,000, with males being higher than females. Western medical treatment of ischaemic stroke is based on thrombolysis, anticoagulation, improvement of circulation, and nutrition of nerves. Intravenous thrombolytic therapy can rapidly promote vascular recanalisation, but its overall efficacy is unsatisfactory due to the deficiencies of narrowed time windows, haemorrhagic transformation, and ischemia-reperfusion injury (9).

According to the theory of Chinese medicine, vegetative weakness, old age and disease or prolonged illness can lead to the decline of visceral functions, the dark depletion of qi and blood, resulting in qi and blood deficiency, the inability to transport blood, and the lack of smooth blood flow, resulting in blood stasis and blood stasis within the body. Zhang's medical passages - the blood of the door" in the cloud: "cover the gas and blood, two-dimensional attachment, the gas is not the blood, then scattered and no system, the blood is not the gas, then congealed and do not flow" (10). The use of Astragalus as the principal drug in tonifying the Yang and returning the five soups is good at tonifying the vital energy, so that when the Qi is strong, the blood will flow, and the blood stasis will be removed and the complexes will be cleared. Angelica sinensis tail as the subject drug, good at activating blood circulation, nourishing blood and camp. Adjuvant red peony activates Blood and disperses Blood stasis, nourishes Blood and astringes Yin; chuanxiong moves Qi and activates Blood, resolves Blood stasis and relieves pain; peach kernel and safflower activates Blood and removes Blood stasis, promotes menstruation and relieves pain, which can activate Blood without injuring the body; and dilong promotes menstruation and activates collaterals, to carry out the strength of the medicine. All the drugs together play the efficacy of benefiting qi and activating blood, resolving blood stasis and opening the channels (11).

In this study, we found that the overall distribution of efficacy of patients in the combined group was better than that of the control group, and the NIHSS scores of the combined group were lower than those of the control group at 4, 8, and 12 weeks of treatment. This result suggests that Chinese medicine tonifying yang and returning five soups combined with rt-PA intravenous thrombolysis for the treatment of patients with ischaemic stroke with qi deficiency and blood stasis can promote the recovery of patients' neurological function and have better efficacy. This is due to the fact that the saponin-like components

contained in Astragalus in tonifying yang and returning five soups can improve the activity of superoxide dismutase and scavenge oxygen free radicals. Reduce secondary oxidative stress (12). The volatile oil components and ferulic acid monomer contained in Angelica sinensis can inhibit platelet aggregation, reduce erythrocyte adhesion activity, and reduce the release of thromboxane to dilate blood vessels and improve local microcirculation (13). Chuanxiong xiongzine contained in Rhizoma Ligustici Chuanxiong has pharmacological effects such as reducing calcium overload, scavenging oxygen free radicals, and antiplatelet aggregation (14). The earthworm hormone contained in Dillon can inhibit platelet aggregation and thrombosis, and dissolve formed thrombus, and have pharmacological effects such as anti-inflammatory, lipid regulation, and enhancement of immunity (15).

Blood flow retardation is an important risk factor for thrombus formation, which is conducive to platelet adhesion and aggregation, causing local microcirculation obstacles and aggravating ischemic and hypoxic injury of brain tissue (16). In this study, it was found that when reexamined after 8 weeks of treatment, the plasma viscosity, whole blood low-cut viscosity and whole blood high-cut viscosity of the combined group were lower than those of the control group. This result suggests that Chinese medicine tonifying yang and returning five soups combined with rt-PA intravenous thrombolysis can better improve blood rheology in the treatment of patients with ischaemic stroke with qi deficiency and blood stasis. This is related to the pharmacological effects of blood-stasis-activating herbs such as Angelica sinensis tail, radix peony, Rhizoma ligustici chuanxiong, peach kernel, safflower, and dirong, which diaphragm blood stasis, diaphragm blood stasis-activating herbs, diaphragm blood stasis-activating herbs, diaphragm blood stasis-activating herbs, diaphragm blood stasis-activating herbs, etc.

VEGF can promote vascular neovascularisation, and after the occurrence of ischemic stroke, local brain tissue undergoes ischemic and hypoxic injury, which stimulates the high expression of VEGF, which promotes vascular neovascularisation and rescues ischemic hemidiaphragm cells after binding specifically to the receptor (17).MMP-9 degrades matrix proteins, which leads to the destabilisation, rupture, and dislodgement of atherosclerotic plaques, which aggravates cerebral tissue ischemia (18). Cerebral ischemia-reperfusion injury is a multi-linked and multi-response pathological process, which is associated with free radical damage, oxidative stress, calcium overload, apoptosis, etc. (19). The Keap1-Nrf2/ARE signalling pathway can exert anti-oxidative stress damage, anti-apoptosis and anti-inflammatory effects by activating the expression of downstream factors, which has an important role in the pathological course of ischemic stroke (20). Nrf2 can synergistically induce the expression of phase II detoxification enzymes, encoding antioxidant proteins, with antioxidant response element ARE, to protect cellular defences. NQO1 regulates antioxidant enzyme activity and attenuates oxidative stress damage (21). In this study, we found that the serum MMP-9 assay, Nrf2, and NQO1 protein expression in the combined group was higher than that in the control group after treatment, and the VEGF level was lower than that in the control group. This result suggests that Chinese medicine tonifying yang and restoring five soups combined with rt-PA intravenous thrombolysis in the treatment of patients with ischaemic stroke with qi deficiency and blood stasis can effectively regulate the degree of brain damage induced by oxidative stress in the Keap1-Nrf2/ARE pathway. This is an important mechanism for its improvement of neurological function, which is related to the antioxidant effects of astragalus polysaccharide and saponin components.

In conclusion, the treatment of qi deficiency and blood stasis type ischemic stroke patients with intravenous thrombolysis of rt-PA combined with tonifying yang and restoring five soups of traditional Chinese medicine can effectively regulate the degree of cerebral damage caused by oxidative stress reaction of the Keap1-Nrf2/ARE pathway, promote the recovery of patients' neurological function, and enhance the therapeutic effect.

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Conflict of interests

The authors declared no conflict of interest.

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