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Original Research Article

Efficacy of cerebroxin capsules combined with aspirin in prevention of post-ischemic stroke in patients treated with thrombolysis

Jiaqi Wang, Hong Tan*
Department of Neurology, Changsha First Hospital, Changsha, China

For correspondence:* ***Email:* *tanh68@126.com;* ***Tel:*** *860731-84667660*

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Abstract

Purpose: *To analyze the efficacy of Cerebro-Cardiac capsules combined with aspirin for secondary prevention in post-ischemic stroke patients treated with thrombolysis, and also to explore its clinical application value.*
Methods: *224 ischemic stroke patients in the outpatient clinic of Changsha First Hospital, China from June 2022 to December 2022 were randomly divided into treatment and control groups, with 112 patients per group. Both groups were given oral aspirin (100 mg/daily) but treatment group received cerebroxin capsules (four capsules, three times daily) in addition. The types of recurrent strokes, clinical efficacy, NIHSS score scale, modified Barthel index, levels of fibrinogen and plasma viscosity, total cholesterol and triacylglycerol were assessed and compared between the groups.*
Results: *During the 6-month follow-up, 10 patients in treatment group and 12 patients in control group experienced dislodgment, and 202 cases completed treatment, but the difference was not statistically significant ($p > 0.05$). Treatment group showed a higher effective rate (92 %) compared to control group (75 %), with a statistically significant difference in clinical symptom efficacy ($p < 0.05$). Hemodynamic parameters were significantly better in treatment group than in control group ($p < 0.05$). Both groups exhibited improved total cholesterol levels, triacylglycerol levels and modified Barthel index post-treatment. Treatment group had better NIHSS scores and Barthel index than control group ($p < 0.05$), while their triacylglycerol levels were lower ($p < 0.05$).*
Conclusions: *Cerebroxin capsules combined with aspirin improve the symptomatic effect of thrombolytic therapy in patients after ischemic stroke with high safety profile. Analysis of the effect of this combination in an increased sample size and a longer follow-up period will be required in the future.*

Keywords: *Ischemic stroke, Secondary prevention, Cerebroxin capsules, Aspirin*

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INTRODUCTION

Ischemic stroke (IS), also referred to as cerebral infarction, is a condition in which the brain's local blood supply is compromised by cerebro-vascular obstruction resulting from a variety of causes. This leads to brain tissue hypoxia and ischemia, as well as clinical signs of abrupt neurological deficits [1]. Cerebral infarction is the leading cause of disability and the second

leading cause of death globally [2]. As the number of persons above 65 years increases, the incidence of stroke has also been found to increase. While there are still few treatment options for ischemic stroke, advancements in revascularization therapy, with medication and mechanical thrombolysis, have helped some patients to recover. However, the risk of recurrent stroke remains statistically higher in individuals with a history of post-IS than in the general population, with recurrence rates for IS patients in China reaching 16 % within a year and up to 50 % within five years [3]. To enhance the prognosis of patients, it is crucial to prevent the recurrence of IS following thrombolysis. Anti-platelet aggregation medications, such as aspirin, are frequently used in the secondary prevention of IS. However, when used over an extended period, this medication causes gastrointestinal distress, intracranial and extracranial hemorrhage, and other side effects [4]. It also does not effectively prevent the recurrence of IS. Safflower, Astragalus, whole scorpion, Peach kernel, Dilong, salvia and frankincense are among the sixteen herbs that make up the Chinese medicinal preparation known as Brain Heart Capsule. These herbs work together to improve blood viscosity, inhibit platelet aggregation, increase the activity of fibrinogen and activate blood circulation, all of which contribute to the prevention of thrombosis [5]. In order to minimize the recurrence of IS, the effect of combination of aspirin with Cerebro-cardiac capsules has been investigated in this study.

METHODS

General conditions

A total of 224 patients who received IS thrombolytic therapy and were seen at Changsha First Hospital from August 2022 to December 2022 were included. There were 112 patients in each of the treatment and control groups. The baseline characteristics of the patients enrolled in the two groups are detailed in Table 1, and the differences between the two groups at baseline were not statistically significant ($p > 0.05$). This study was approved by the Ethics Committee of Changsha First Hospital (approval no. 2023-Ethic-NO-85). The study was performed by following the protocol in the Helsinki Declaration [6]. Signed informed consent was obtained from all participants before the study.

Inclusion criteria

Patients who complied with the following conditions participated in the investigation. These included being older than eighteen years, having experienced the infarction for at least ten days, receiving thrombolytic therapy, signing an informed consent form, and not having any serious cardiac, hepatic, renal, or related diseases. The patients also fulfilled the requirements for a diagnosis of cerebral infarction as stated in the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018 [7].

Exclusion criteria

The following medical issues prevented a patient from participating in the study: Severe stroke, coma; Neurological Impairment Score (NIHSS) > 20; Any combination of severe cardiopulmonary disease, abnormalities in platelets and coagulation, liver and renal insufficiency, malignant tumors, gastrointestinal bleeding, etc.; Patients suffering from mental illness; Women who are pregnant or nursing; Individuals participating in other pharmaceutical clinical trials; Individuals with allergies or who are allergic to known drug components; Individuals undergoing thrombolytic or anticoagulant therapy; and patients who had hypersensitivity or allergy to study drug's recognized ingredients.

Treatments

Patients in both the treatment and control groups received a single oral dose of aspirin enteric soluble tablets (Shiyang Group Ouyi Pharmaceutical Co., Ltd., State Drug quantification H13023635; 100 mg) daily. In addition, patients in the treatment group were treated with Cerebroxin Capsules (Shaanxi Buchang Pharmaceutical Co., Ltd., State Drug quantification Z20025001), four capsules per dose, three times daily. Treatment lasted for six months for patients in both groups and patients with additional conditions received symptomatic treatment, but this had no bearing on how well the tested medications worked. During the treatment period, the enrolled patients were not allowed to take other traditional Chinese medicines and proprietary Chinese medicines with preventive effects on stroke as confirmed by clinical trials.

Evaluation of parameters/indices

Primary efficacy index

The number of recurrent strokes (including cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage) and death due to recurrent stroke were compared between the two groups after 6 months of treatment [8]. The

NIHSS score scale and modified Barthel index were compared between the two groups before and after treatment.

NIHSS score scale

The NIHSS score scale included 11 items, including consciousness, the ability to answer questions, the ability to follow instructions, eye movement, visual field, facial muscle strength, upper limb motor function, lower limb motor function, limb coordination, sensory function, language, articulation, and sensory neglect. Each item is scored on a scale of 3 to 5, ranging from 0 to 42, with higher scores indicating more severe neurological impairment. A score of 0 - 1 indicates normal or approaching normal, a score of 1 - 4 indicates minor stroke, a score of 5 - 15 indicates moderate stroke, a score of 15 - 20 indicates moderate to severe stroke, a score above 20 indicates severe stroke and higher scores indicate more severe disease.

Modified Barthel Index rating scale

The modified Barthel Index rating scale was modified based on BI by Shah *et al* [9] and the content was still the original 10 items with a full score of 100. The score of MBI was divided into 5 levels, and the scores were (15, 12, 8, 3, 0; 10, 8, 5, 2, 0; 5, 4, 3, 1, 0). Different levels represent different levels of independence, ranging from level 1 to level 5, with higher levels representing higher levels of independence.

Secondary efficacy indicators

Total cholesterol and triglyceride

Before treatment and 1 month after treatment, 1.5 mL peripheral blood was collected from the two groups, and the serum was centrifuged at 3000 rpm for 10 min. The changes in total cholesterol and triglyceride were determined by SIEMENS1800 automatic biochemical analyzer.

Platelet aggregation rate

Platelet aggregation rate of the two groups was determined by optical turbidimetry. The higher the platelet aggregation rate, the higher the platelet aggregation function. The kit was purchased from Shandong Tailixin Medical Technology Co., LTD.

Fibrinogen

Fibrinogen was determined by Clauss method in the two groups. Higher values indicate increased fibrinogen in the patient. The kit was purchased from Shanghai Enzyme Linked Biotechnology Co., LTD.

Plasma viscosity

Plasma viscosity of the two groups was determined by rotational viscometer method. Higher values indicate higher plasma viscosity in patients.

Adverse events

The type of adverse events, their time of occurrence, measures taken, regression/progression and the determination of whether the adverse event was connected to the test medicine were recorded. The attending physicians in the Department of Neurology were responsible for follow-up, and case report form was completed on time. After completion of the case report form, double-record and double-checking were performed to lock the database for statistical analysis.

Statistical analysis

Statistical Packages for Social Sciences (SPSS) software (version 26.0) and GraphPad Prism 9 (La Jolla, CA, USA) were used for all data processing and statistical analyses. Measurement data are expressed as mean ± standard deviation (SD), and *t*-test was used to compare among groups. Count data are expressed as relative numbers, and χ^2 t-test was used to evaluate the differences between groups. At $p < 0.05$, differences were deemed statistically significant.

RESULTS

Baseline characteristics

All patients were followed up for 6 months. During the follow-up period, 10 cases (8.93 %) in treatment group dropped out, including 2 cases due to adverse events, 1 case taking other Chinese medicine with preventive effect on stroke, and 4 cases with poor compliance. In control group, 12 cases (10.71 %) dropped out. The baseline characteristics of the patients enrolled in the two groups are detailed in Table 1. The differences between the two groups at baseline were not statistically significant ($p > 0.05$).

Recurrent stroke

In treatment group, there were 7 cases of recurrent IS (6.86 %) while there were 13 cases (13 %) in control group. There was no statistically

significant difference ($p > 0.05$) in the incidence of cerebral infarction, cerebrovascular hemorrhage, or subarachnoid hemorrhage between the two groups, nor the risk of recurrent stroke. After six months, treatment group had fewer cerebral infarction recurrences than control group, as seen in Table 2.

Clinical efficacy

When the clinical efficacy of the two groups was compared (Table 3), treatment group's overall effective rate was higher than control group's ($\chi^2 = 8.140$, $p < 0.05$).

NIHSS scores and modified Barthel index

After six months of therapy, the NIHSS scores of both groups decreased compared to the pre-treatment values and treatment group's recovery of neurological impairments was significantly greater than that of control group ($p < 0.05$). As shown in Table 4 and Table 5, after 6 months of therapy, the modified Barthel index increased in both groups relative to the baseline index, with treatment group experiencing a more favorable increase than control group.

Hemodynamic profiles

Before treatment, the levels of fibrinogen and plasma viscosity in the two groups did not differ statistically ($p > 0.05$). However, following treatment, the values in both groups were significantly lower than pre-treatment levels ($p < 0.05$), and treatment group's improvements in these parameters were more pronounced than those in control group ($p < 0.05$).

Table 1: Comparison of baseline characteristics of patients in the two groups after thrombolytic therapy for ischemic stroke

Parameter	Treatment	Control	*P*-value
Age	65.3±10.22	64.9±9.22	0.871
BMI (kg/m^2)	25.82±3.22	25.98±2.70	0.831
Systolic Pressure (mmHg)	135.9±14.22	134.78±18.94	0.668
Diastolic pressure (mmHg)	82.32±6.22	84.01±10.22	0.796
Male (n, %)	70 (68.62)	65 (65.00)	0.584
Hypertension (n, %)	87 (85.29)	89 (89.00)	0.432
Diabetes (n, %)	32 (31.37)	33 (33.00)	0.804
Hyperlipidemia (n, %)	28 (27.45)	30 (30.00)	0.688
Familial History (n, %)	45 (44.11)	48 (48.00)	0.579
Smoking (n, %)	50 (49.02)	48 (48.00)	0.885
Drinking (n, %)	34 (33.33)	36 (36.00)	0.694
Duration of disease ≤ 1 month (n, %)	76 (74.51)	72 (72.00)	0.687
Duration of disease 1-6 months (n, %)	10 (9.80)	8 (8.00)	0.652
Duration of disease > 6 month (n, %)	16 (15.69)	20 (20.00)	0.423

Table 2: Comparison of outcomes of recurrent stroke in the two groups (cases (%))

Group	Cerebral infarction	Cerebrovascular hemorrhage	Subarachnoid hemorrhage	Total incidence
Treatment	5 (4.90)	2 (1.96)	0	7 (6.86)
Control	10 (10.00)	2 (2.00)	1 (1.00)	13 (13.00)
χ^2	1.909	0.000	1.149	2.132
P-value	0.1670	0.984	0.314	0.144

Table 3: Comparison of clinical efficacy between the two groups (n (%))

Group	Basic cure	Proven effectiveness	Effective	Invalid	Total
Treatment	24 (23.53)	30 (29.41)	38 (37.25)	10 (9.80)	92 (90.19)
Control	20 (20.00)	23 (23.00)	32 (32.00)	25 (25.00)	75 (75.00)

Table 4: Comparison of NIHSS scores between the two groups

Group	Pre-treatment	Post-treatment	*t*	*P*-value
Treatment	9.52±1.28	4.12±0.82	35.881	<0.05
Control	9.46±1.33	5.47±0.41	28.668	<0.05
T	0.327	14.754	-	-
P-value	>0.05	<0.05	-	-

Table 5: Comparison of the modified Barthel index between the two groups

Group	Pre-treatment	Post-treatment	*t*	*P*-value
Treatment	40.36±3.54	69.69±3.71	13.728	<0.05
Control	39.13±2.85	52.38±3.95	7.519	<0.05
t	0.327	14.754	-	-
P-value	>0.05	<0.05	-	-

Table 6: Comparison of fibrinogen and plasma viscosity levels before and after treatment between the groups

Group	Fibrinogen (g/L)		Plasma viscosity (mPa·s)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Treatment	4.98±1.03	3.01±0.78*#	1.92±0.68	1.43±0.58*#
Control	4.89±1.16	3.83±0.82#	1.91±0.71	1.73±0.34#

*$P < 0.05$ between the groups; #$p < 0.05$ vs. pre-treatment within the group

Table 7: Comparison of total cholesterol and triacylglycerol levels before and after treatment

Group	Total cholesterol (mmol/L)		Triacylglycerol (mmol/L)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Treatment	5.78±1.56	3.18±1.88*#	1.92±0.88	1.63±0.98#
Control	5.26±1.43	3.83±0.92#	1.95±0.57	1.73±0.74#

**P* < 0.05 vs. control; #*P* < 0.05 vs. pre-treatment

Table 8: Comparison of the occurrence of adverse reactions in the two groups

Group	Gastrointestinal reactions	Diarrhea	Headaches	Itchy skin	Total
Treatment	1 (0.98)	2 (1.96)	0	1 (0.98)	4 (3.92)
Control	7 (5.00)	1 (1.00)	1 (1.00)	1 (1.00)	10 (10.00)
χ^2	4.811	0.299	1.025	0.000	2.892
P-value	0.028	0.584	0.311	0.988	0.089

Total cholesterol and triacylglycerol levels

Both groups' triacylglycerol and total cholesterol levels decreased significantly ($p < 0.05$) following treatment. However, there was no significant difference in the pre-treatment levels of triacylglycerol and total cholesterol between the two groups. As shown in Table 7, the total cholesterol levels in treatment group were likewise lower than that in control group ($p < 0.05$), but the difference was not statistically significant ($p > 0.05$).

Adverse effects

Adverse events that were noted in both groups included headache and dizziness, rash that itched, gastrointestinal problems, leukopenia, hepatorenal toxicity and other conditions. Although the incidence of gastrointestinal reactions in treatment group was lower than that in control group ($p < 0.05$), the difference in incidence of adverse reactions in treatment group and control group was not statistically significant ($p > 0.05$; Table 8).

DISCUSSION

One of the oldest diseases to affect humans, stroke is known as IS in Chinese medicine. Its incidence and mortality rate are currently highest in China and Western developed countries, with a lifetime risk of up to 39.9 % for Chinese citizens and more than 20 % of deaths from cerebrovascular disease each year [3]. A thorough national study on stroke revealed that 7.2 % of IS patients who survived in China had a stroke recurrence after six months, compared to the 5.0 % reported in Western nations. The underutilization of proven secondary prophylaxis contributes to the elevated risk of recurrence in China [10]. Low-dose aspirin is still the most commonly prescribed drug for the secondary prevention of noncardiogenic ischemic stroke and transient ischemic attack [11]. Because of its relatively simple pharmacokinetics, which limits drug-to-drug interactions and gives it a distinct advantage over most antiplatelet agents, low-dose aspirin is recommended for use either alone or in combination with other antiplatelet agents. The logical modification of aspirin dosage as well as the combination with other drugs is a very important and popular research topic because various studies have shown side effects that are frequently induced by aspirin, such as gastrointestinal complications, hepatic and renal impairment, and salicylic acid reactions [12]. Cerebroxin capsules have been proven in recent clinical research to have neuroprotective effects on IS, improving brain function and

dependence on daily activities as well as decreasing serum inflammatory markers and stabilizing peripheral hemodynamics [13,15]. Furthermore, using a network pharmacological approach, Zhu *et al* [16] examined the comparative and synergistic effects of Cerebroxin capsules and Danhong injection on IS. They discovered that Cerebroxin Tong capsules target proteins related to the blood-brain barrier and the vasodilator system, and are involved in redox imbalance, neurotrophic factor activity and brain inflammation. As an additional benefit to antiplatelet therapy, cerebroxin capsules have been discovered to increase the antiplatelet effect and decrease major cardiovascular events. In older patients with non-valvular atrial fibrillation, cerebroxin capsules combined with aspirin have also been demonstrated to lower the incidence of serious bleeding within a year [17,18]. All these results suggest that cerebro-cardiac capsules may provide effective secondary prevention of IS without increasing the incidence of serious adverse events.

This study showed that the combination of the two drugs, aspirin and cerebro-cardiac capsule, could improve the clinical symptoms of patients with ischemic stroke without serious adverse effects. By comparing the results of patients in both groups pre- and post-treatment, it can be seen that cerebro-cardio capsules improve the proportion of patients with good prognosis after IS thrombolysis.

Limitations of this study

There were few patients included in this study, and the follow-up time was only six months. By increasing sample size and prolonging follow-up period, more comparative studies might be carried out in the future.

CONCLUSION

For patients with ischemic stroke, the combination of cerebroxin capsule with aspirin is effective, as it improves patients' blood lipid levels and influences hemodynamics, enhances therapeutic effect, and promotes early improvement of patients' conditions. Further comparative analysis with an increased sample size and a longer follow-up period will be required.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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