Research Paper

# Clinical Efficacy of Salvia Polyphenolic Acid in the Recovery of Ischemic Stroke

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**To assess the clinical efficacy of salvia polyphenolic acid in the recovery of ischemic stroke. This randomized controlled trial recruited 80 patients with ischemic stroke treated in our hospital from September 2021 to June 2022 and assigned them to receive either aspirin enteric tablets and atorvastatin calcium tablets (control group) or aspirin enteric tablets and simvastatin tablets plus salvia polyphenolic acid (observation group), with 40 cases in each group. The primary endpoint was clinical efficacy and the secondary endpoints included neurological function, disease recovery, limb and cognitive function and quality of life. Patients with salvia polyphenolic acid had significantly higher clinical efficacy than those without ($p<0.05$). Salvia polyphenolic acid resulted in significantly lower national institutes of health stroke scale scores and higher ability of daily living scores in patients *vs.* routine management ($p<0.05$). Patients in the observation group showed significantly higher Fugl-Meyer and Montreal cognitive assessment scores and World Health Organization quality of life brief version scores than those in the control group ($p<0.05$). Salvia polyphenolic acid significantly ameliorates the stroke status of ischemic stroke patients, promotes the recovery of neurological functions, significantly enhances the patient's living ability and therapeutic effects, and optimizes the patient's limb and cognitive functions, thus effectively improving the quality of life and promoting the patient's recovery.**

**Key words: Salvia polyphenolic acid, ischemic stroke, recovery, clinical efficacy**

Ischemic stroke is highly prevalent in the elderly[1,2]. With factors such as changes in people's lifestyles, the prevalence of ischemic strokes is on a marked rise. Most patients suffer a poor prognosis, a high mortality and disability rate and long treatment duration, resulting in different magnitudes of limb dysfunction and cognitive impairment and serious sequelae such as hemiplegia can also be observed[3]. In Traditional Chinese Medicine (TCM), stroke can be divided into meridian and visceral categories according to the changes in the patient's consciousness. Ischemic and hemorrhagic strokes were proposed on the basis of further understanding of stroke by modern TCM experts and the combination of Chinese and Western medicine[4,5]. According to the length of the disease, the first identification period and the fourth identification period in the identification highlights are divided into three periods; the acute phase within 2 w after the onset of the disease, the recovery phase when the disease develops within 2 w to 6 mo and the sequelae phase when the disease develops for >6 mo. Clinical management of ischemic stroke is to improve cerebral blood flow through medication. The role of Chinese medicine in improving the symptoms and sequelae of ischemic stroke is gaining growing attention from clinicians.

Salvia polyphenolic acid is the active ingredient extracted from Radix *Salivae miltiorrhiza* (*S. miltiorrhiza*), which promotes blood circulation, activates blood vessels, reduces blood viscosity, resists platelet aggregation and improves microcirculation. Salvia polyphenolic acid injection is composed of salvia polyphenolic acid as the active ingredient, which mediates neuroprotective and ischemic activity and protects against cerebral ischemic injury[6,7]. The current study was undertaken to assess the clinical efficacy of salvia polyphenolic acid in the recovery of ischemic stroke.

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## MATERIALS AND METHODS

**General information:**

This randomized controlled trial recruited 80 patients with ischemic stroke treated in our hospital from September 2021 to June 2022 and assigned them to receive either aspirin enteric tablets and atorvastatin calcium tablets (control group) or aspirin enteric tablets and atorvastatin calcium tablets plus salvia polyphenolic acid (observation group), with 40 cases in each group. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of our hospital and all patients have signed written informed consent.

**Inclusion and exclusion criteria:**

**Inclusion criteria:** All patients were diagnosed with ischemic stroke by cranial Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) and met the diagnostic criteria for recovery from ischemic stroke; they were conscious and had stable vital signs and complete clinical data; no allergic reactions to the drugs used in the study.

**Exclusion criteria:** Malignant tumors or serious diseases of the heart, liver and kidney. Other serious diseases of the circulatory system, hematological system, digestive system and endocrine system. Physical dysfunction that prevents completion of the cognitive examination.

**Treatment methods:**

**Control group:** The patient was given symptomatic treatment for other diseases such as hypotension, regulation of blood sugar, lowering of cranial pressure and anti-infection. The patient received 100 mg of aspirin enteric-coated tablets (GuoPharm Zhizhi J20130078, Bayer Healthcare Ltd.) once daily, 20 mg of simvastatin tablets (GuoPharm Zhizhi H20010053, Jiangsu Lianhuan Pharmaceutical Co., Ltd.) once every night, followed by the administration of 30 mg of edaravone (GuoPharm QuanZi H44025125, Guangzhou Zhujiang Pharmaceutical Factory) diluted in 100 ml of 0.9 % sodium chloride solution (GuoPharm QuanZi H20080495, Kunming Jieda Pharmaceutical Co., Ltd.) and 250 ml of 0.9 % sodium chloride solution three times daily. The duration of treatment was 14 d.

**Observation group:** The basic documentation was consistent with the control group. Patients receive 200 mg of salvia polyphenolic acid hydrochloride (Guodian Z20050249, Shanghai Lvgu Pharmaceutical Co., Ltd.) diluted in 100 ml of 0.9 % sodium chloride solution (Guodian H44025125, Guangzhou Zhujiang Pharmaceutical Factory) once daily. The infusion rate is controlled to not more than 40 drops per minute, with a recommended rate of 20-30 drops per minute for the first infusion. The duration of treatment was 14 d.

**Outcome measures:**

**Clinical efficacy:** According to the scoring of the degree of neurological damage and living status criteria established by the Fourth National Cerebrovascular Disease Conference in 1995, the efficacy was divided into cured (reduction of National Institutes of Health Stroke Scale (NIHSS) score 91 %-100 %), markedly effective (reduction of NIHSS score 46 %-90 %), effective (reduction of NIHSS score 18 %-45 %) and ineffective (reduction of NIHSS score <18 % or increase >18 %).

Excellent rate=(cured+markedly effective)/total number of cases×100 %

Total efficacy=(cured+markedly effective+effective)/ total number of cases×100 %

**Disease recovery:** The NIHSS was used to assess the patient's disease recovery after treatment, with a score of 42 and the lower the score, the better the neurological function. The Ability of Daily Living (ADL) was evaluated by the modified Barthel index with a score of 100 and the higher the score, the better the self-care ability.

**Limb and cognitive function:**

The physical function of the patients was assessed by the Fugl-Meyer Motor Function Scale with a score of 100, including 66 for the upper extremity and 34 for the lower extremity and the higher the score, the better the physical function. Patient's cognitive function was assessed by the Montreal Cognitive Assessment (MoCA) and a higher score was associated with better cognitive function.

**Quality of life:**

The quality of life of patients before and after treatment was assessed by the World Health Organization Quality of Life Brief Version (WHOQOL-BREF) and a higher score resulted in a better quality of life.

**Statistical analysis:**

The data in this study were organized and analyzed

using Statistical Package for the Social Sciences (SPSS) 26.0 and GraphPad Prism 8 was used for graphics plotting. Measurement data were expressed as mean±standard deviation (x±s) and examined using the t-test. Count data were expressed as the number of cases (rate) and tested using Chi-square ($\chi^2$) test. Statistical significance of the difference was indicated by $p<0.05$.

## RESULTS AND DISCUSSION

In the control group, there were 19 males and 21 females with a Body Mass Index (BMI) of 21.5-26.5 (23.41±0.88) kg/m$^2$, aged 38-69 (45.08±6.99) y, with an onset time of 2-15 (6.18±2.14) w, 18 cases of hypertension, 14 cases of diabetes mellitus and 8 cases of hyperlipidemia. In the observation group, there were 18 males and 22 females with a BMI of 21.4-26.3 (23.18±0.91) kg/m$^2$, aged 35-67 (45.32±6.84) y, with an onset time of 2-16 (6.07±2.32) w, 22 cases of hypertension, 12 cases of diabetes mellitus and 6 cases of hyperlipidemia. The two groups did not differ in terms of patient characteristics ($p>0.05$) as shown in Table 1.

In the control group, 2 cases were cured, 13 cases were markedly effective, 17 cases were effective and 8 cases were ineffective, with an excellent rate of 37.50 % and a total efficacy of 80.00 %. In the observation group, 6 cases were cured, 21 cases were markedly effective, 12 cases were effective and 1 case was ineffective, with an excellent rate of 67.50 % and a total efficacy of 97.50 %. Patients with salvia polyphenolic acid had significantly higher clinical efficacy than those without ($p<0.05$) as shown in Table 2.

In the control group, the pre-treatment NIHSS score was (21.13±8.41) and ADL score was (27.89±6.41) and the post-treatment NIHSS score was (10.41±5.12) and ADL score was (44.48±7.74). In the observation group, the pre-treatment NIHSS score was (21.25±8.38) and ADL score was (27.59±7.11) and the post-treatment NIHSS score was (6.47±3.81) and ADL score was (68.98±5.77). Salvia polyphenolic acid resulted in significantly lower NIHSS scores and higher ADL) scores in patients *vs.* routine management ($p<0.05$) as shown in fig. 1.

The pre-treatment Fugl-Meyer score was (50.74±5.89) and MoCA score was (16.88±4.94) in the control group and the post-treatment Fugl-Meyer score was (65.41±6.78) and MoCA score was (21.48±5.17). In the observation group, the pre-treatment Fugl-Meyer score was (50.82±6.14) and MoCA score was (16.97±4.73) and the post-treatment Fugl-Meyer score was (76.14±3.88) and MoCA score was (27.01±3.17). Patients in the observation group showed significantly higher Fugl-Meyer and MoCA scores than those in the control group ($p<0.05$) as shown in fig. 2.

The WHOQOL-100 score of patients in the control group was (54.89±8.45) before treatment and (78.86±8.68) after treatment. The WHOQOL-100 was scoring (54.98±7.38) before treatment and WHOQOL-100 score was (89.87±6.17) after treatment in the observation group patients. Patients in the observation group showed significantly higher WHOQOL-100 scores *vs.* those in the reference group ($p<0.05$) as shown in Table 3.

**TABLE 1: PATIENT CHARACTERISTICS (x̄±s)**

| | | Control group | Observation group | t | p |
|---|---|---|---|---|---|
| n | - | 40 | 40 | - | - |
| Sex | Male | 19 | 18 | - | - |
| | Female | 21 | 22 | - | - |
| BMI (kg/m$^2$) | - | 21.5-26.5 | 21.4-26.3 | - | - |
| | Mean | 23.41±0.88 | 23.18±0.91 | 1.573 | 0.118 |
| Age (year) | - | 38-69 | 35-67 | - | - |
| | Mean | 45.08±6.99 | 45.32±6.84 | 0.213 | 0.832 |
| Onset time (week) | - | 42036 | 42401 | - | - |
| | Mean | 6.18±2.14 | 6.07±2.32 | 0.302 | 0.763 |
| Previous medical history | Hypertension | 18 | 22 | - | - |
| | Diabetes | 14 | 12 | - | - |
| | Hyperlipidemia | 8 | 6 | - | - |
| Education level | Middle school | 11 | 8 | - | - |
| | Junior college | 16 | 17 | - | - |
| | Undergraduate | 13 | 15 | - | - |

**TABLE 2: CLINICAL EFFICACY (%)**

| | Control group | Observation group | $\chi^2$ | p |
|---|---|---|---|---|
| n | 40 | 40 | - | - |
| Cured | 2 | 6 | - | - |
| Markedly effective | 13 | 21 | - | - |
| Effective | 17 | 12 | - | - |
| Ineffective | 8 | 1 | - | - |
| Excellent rate | 37.50 | 67.50 | 11.794 | 0.001 |
| Total efficacy | 80.00 | 97.50 | 13.713 | <0.001 |

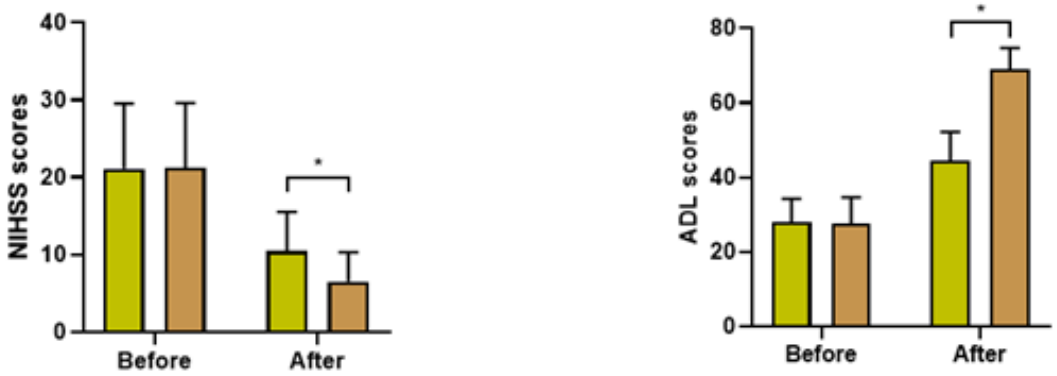


**Fig. 1: Disease recovery**
**Note: *p<0.05, ( ): Control group and ( ): Observation group**

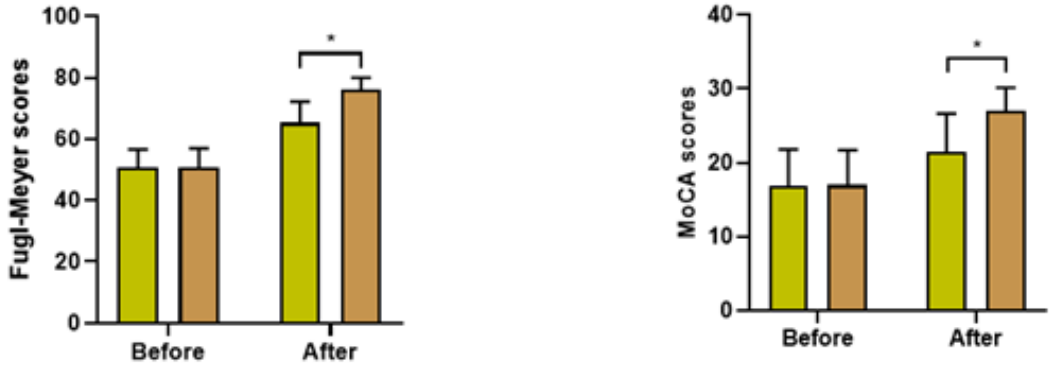


**Fig. 2: Limb and cognitive function**
**Note: *p<0.05, ( ): Control group and ( ): Observation group**

**TABLE 3: QUALITY OF LIFE ($\bar{x}$±s)**

| | Control group | Observation group | t | p |
|---|---|---|---|---|
| n | 40 | 40 | - | - |
| Before treatment | 54.89±8.45 | 54.98±7.38 | 0.069 | 0.945 |
| After treatment | 78.86±8.68 | 89.87±6.17 | 8.953 | <0.001 |

The pathogenesis of ischemic stroke is attributable to acute dysfunction of blood supply to brain tissue, which leads to local ischemia, hypoxic necrosis, and softening of brain tissue, resulting in excessive production of free radicals and brain cell damage[8,9]. With the change in people's diet structure and dietary habits, the incidence of ischemic stroke is on the rise. Previous research suggests that patients with ischemic stroke frequently experience varying degrees of sequelae during recovery, which critically compromises their quality of life[10]. Early and potent management may reduce the incidence of acute ischemic stroke and improve the prognosis of acute ischemic stroke[11]. Previously, lipid-lowering, antihypertensive, anticoagulation and antiplatelet treatments were poorly effective with

a somber prognosis. Clinical treatment is mainly anticoagulation, thrombolysis and herbal medicine to enhance blood circulation in brain tissue. Radix *S. miltiorrhiza* and its extract tannic acid have achieved good efficacy and safety in the clinical application of cardiovascular and cerebrovascular ischemic diseases. It activates blood circulation, relieves pain, dispels irritation, cools the blood and calms the mind. Thus, the clinical efficacy of salvia polyphenolic acid, the extraction of Radix *S. miltiorrhiza*, in the patient recovery after ischemic stroke was investigated.

The results of the present study showed that patients with salvia polyphenolic acid had significantly higher clinical efficacy than those without and salvia polyphenolic acid resulted in significantly lower NIHSS scores and higher ADL scores, Fugl-Meyer scores, MoCA scores and WHOQOL-BREF scores *vs.* routine management. Western medicine recognizes ischemic stroke as brain tissue necrosis caused by narrowing or occlusion of the cerebral blood supply arteries (carotid and vertebral arteries) and insufficient cerebral blood supply[12], which is mostly managed by aspirin plus atorvastatin in clinical treatment[13]. Aspirin is a cyclooxygenase I inhibitor[14] that reduces the inhibition of cyclooxygenase activity, blocks the synthesis of thrombospondin-2, blocks the platelet activation pathway and prevents thrombus formation. It also dilates blood vessels, promotes blood flow and alleviates cerebral ischemia and hypoxia[15,16]. Atorvastatin is a widely used lipid-lowering drug that reduces the number of Low-Density Lipoprotein (LDL-C) receptors[17], increases LDL-C excretion and reduces LDL-C levels[18,19]. Extensive clinical studies have shown that low-fat treatment of ischemic stroke could mitigate inflammatory responses and inhibit plaque formation[20,21]. In TCM, ischemic stroke is known as blood stasis obstruction. Different TCM evidence in patients with cerebral infarction leads to different degrees of carotid atherosclerosis. Phlegm and blood stasis are caused by abnormalities in the metabolism of qi, blood and body fluids. The production and presence of pathological products such as phlegm and stasis affect Qi, forming a vicious circle that causes the disease, with phlegm stasis blocking the meridians and paralysis of the meridians. Hence, phlegm and stasis blocking are considered the main pathogenesis of cerebral infarction in TCM. Radix *S. miltiorrhiza* has analgesic, blood-activating, blood-nourishing, calming, blood-cooling and stasis-removing properties. Polyphenolic acid, the main water-soluble active component of Radix *S. miltiorrhiza*, was extracted from Radix *S. miltiorrhiza* by some researchers and it was suggested that salvianolic acid inhibited lipid peroxidation and provided preferable therapeutic effects in the management of cardiovascular and cerebrovascular diseases[22], which was confirmed by the results of the present study. Zhang used Radix *S. miltiorrhiza* polyphenols as an adjunct to intravenous thrombolysis for acute ischemic stroke and showed better results and hemodynamic improvement, which is consistent with the results of the present study. The mechanism may lie in the stimulation of energy metabolism in neurons, improvement of blood supply to brain tissue and promotion of aerobic metabolism. The results of the present study are consistent with the results of previous studies, which all concluded that the application of salvianolic acid in patients recovering from ischemic stroke provides significant therapeutic benefits, which may be linked to the stimulation of neuronal energy metabolism, improvement of blood supply to brain tissues and promotion of aerobic metabolism. Salvia polyphenolic acid inhibits platelet aggregation, reduces red blood cell aggregation and blood viscosity, improves cerebral ischemia and protects neurological and ischemic brain tissue by improving blood rheology and promoting neurological recovery. It also decreases the arteritis response through antioxidants, scavenges free radicals, inhibits platelet aggregation and regulates lipid metabolism and endothelial cell function[23,24]. The results of animal tests showed that salvia polyphenolic acid could reduce the serum levels of Interleukin (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) in mice and play an increasingly important role in the inflammatory response to atherosclerosis with increasing doses. The advantage of TCM in treating cerebral infarction lies in the differentiation of diagnosis and individualized treatment, which fully embodies holistic and personalized treatment with few side effects and features a good application prospect.

This study has the following limitations; the nature of the experiment led to some clinical study questions that could not be addressed. The nature of the design resulted in a limited patient selection, a small sample size and no follow-up, which may have biased the results. Long-term functional effects and long-term prognosis need to be further investigated. Future studies with long-term follow-ups and a larger sample size will be performed to provide more reliable data.

Salvia polyphenolic acid significantly ameliorates the stroke status of ischemic stroke patients, promotes the recovery of neurological functions, significantly enhances the patient's living ability and therapeutic effects and optimizes the patient's limb and cognitive functions, thus effectively improving the quality of life and promoting the patient's recovery.

**Conflict of interests:**

The authors declared no conflict of interests.

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