

# World Journal of *Clinical Cases*

*World J Clin Cases* 2022 July 26; 10(21): 7187-7619



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lei Wang*.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

July 26, 2022

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<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Case Control Study

# Efficacy of Guhong injection versus Butylphthalide and Sodium Chloride Injection for mild ischemic stroke: A multicenter controlled study

Wei-Wei Zhang, Jiang Xin, Guang-Yu Zhang, Qi-Jin Zhai, Hua-Min Zhang, Cheng-Si Wu

**Specialty type:** Neurosciences

**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B  
Grade C (Good): C  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Chen DDY, Canada;  
Garcia-Ballestas E, Colombia

**Received:** December 2, 2021

**Peer-review started:** December 2, 2021

**First decision:** January 10, 2022

**Revised:** February 7, 2022

**Accepted:** May 28, 2022

**Article in press:** May 28, 2022

**Published online:** July 26, 2022



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## Abstract

### BACKGROUND

Most studies on Guhong injection have involved a single center with a small sample size, and the level of clinical evidence is low.

### AIM

To assess the safety and efficacy of Guhong injection for mild ischemic stroke (IS).

### METHODS

A total of 399 IS patients treated at six hospitals from August 2018 to August 2019 were retrospectively analyzed. The patients were given Guhong injection (experimental group) or Butylphthalide and Sodium Chloride Injection (control group). Changes in National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores were observed before treatment and at 1, 2, and 3 wk after treatment in each group. The efficacy and safety of Guhong injection for IS

were assessed. Other medications taken by the patients were confounding factors for efficacy assessment. These factors were controlled by propensity score matching, and the results were further analyzed based on the matching.

## RESULTS

The marked response rates at three follow-up visits were 64.64%, 74.7%, and 66.7% in the experimental group, and 48.26%, 45.4%, and 22.2% in the control group. The marked response rates increased significantly in the experimental group compared with the control group ( $P < 0.05$ ). The overall response rate at the first visit (days  $7 \pm 2$ ) did not differ significantly between the two groups, but differed significantly at the second (days  $14 \pm 2$ ) and third visits (days  $21 \pm 3$ ) ( $P < 0.05$ ). The proportion of patients without any symptoms in the experimental group was significant different at the first visit ( $P < 0.05$ ), but not significantly different at the second visit. The two groups showed no significant difference in the baseline distribution of mRS scores. At the first and second visits, the change in mRS scores was -2 and -1 in the experimental and control groups, respectively, which were significantly different ( $P < 0.05$ ). After propensity score matching, the overall response rate and marked response rate were 97.29% and 100% in the experimental group ( $P > 0.05$ ) and 64.0% and 47.7% in the control group ( $P < 0.05$ ) at the first visit, respectively. The decreased NIHSS scores in the two groups were significant different ( $P < 0.05$ ). The overall response rate and marked response rate differed significantly between the two groups at the second visit ( $P < 0.05$ ). There was no significant difference in the incidence of adverse events between the two groups. No severe adverse events occurred in either group.

## CONCLUSION

Guhong injection is safe and more effective than Butylphthalide and Sodium Chloride Injection for treatment of IS.

**Key Words:** Guhong injection; Ischemic stroke; Propensity score matching; National Institutes of Health Stroke Scale

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**Core Tip:** Guhong injection, composed of aceglutamide and safflower aqueous extract, is widely used for the treatment of ischemic stroke (IS). For treatment of IS, Guhong injection has greater clinical efficacy and similar safety as Butylphthalide and Sodium Chloride Injection.

**Citation:** Zhang WW, Xin J, Zhang GY, Zhai QJ, Zhang HM, Wu CS. Efficacy of Guhong injection *versus* Butylphthalide and Sodium Chloride Injection for mild ischemic stroke: A multicenter controlled study. *World J Clin Cases* 2022; 10(21): 7265-7274

**URL:** <https://www.wjgnet.com/2307-8960/full/v10/i21/7265.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v10.i21.7265>

## INTRODUCTION

Ischemic stroke (IS) is the second leading cause of death worldwide and the leading cause of death in China[1], and accounts for 60%–70% of all strokes. According to the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018[2], the primary treatments for acute IS are as follows: First, to improve cerebral blood circulation, initiate revascularization, and restore blood flow as quickly as possible to salvage the ischemic semidark zone; and second, to protect the nerves, reduce ischemia/reperfusion injury, and inhibit the ischemic cascade to alleviate neurological deficits. In practice, few IS patients can receive timely treatment and achieve a good prognosis as most patients tend to miss the best time window for treatment[3]. In addition to anticoagulant, thrombolytic, antiplatelet, and vasodilator treatments, efforts should be made to restore microcirculation in the ischemic regions as quickly as possible to protect the brain nerves maximally.

Guhong injection, composed of aceglutamide and safflower aqueous extract, is a common drug for the treatment of cerebral ischemia/reperfusion injury[4]. Butylphthalide is a class I new drug for cerebral ischemia and has been widely used clinically[5]. Most studies that have compared the efficacy and safety of Guhong and Butylphthalide only involved a single center with a small sample size, and the level of evidence was low. Here, we conducted a multicenter retrospective cohort study to compare the safety and efficacy of Guhong injection and Butylphthalide and Sodium Chloride Injection for

treatment of IS.

## MATERIALS AND METHODS

### Patients

We recruited patients who were treated at six hospitals for IS between August 2018 and August 2019: Seventh Medical Center of PLA General Hospital, First Affiliated Hospital of Nanchang University, People's Hospital of Liaoning Province, Cangzhou People's Hospital, Second People's Hospital of Huai'an, and Ganyu District People's Hospital of Lianyungang. The clinical data were analyzed retrospectively. The number of patients included in each center is listed in [Table 1](#). Baseline information of the patients in the two groups is shown in [Table 2](#). All 399 patients conformed to the diagnostic criteria of the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018. Patients in the experimental group ( $n = 198$ ) received Guhong injection, and those in the control group ( $n = 201$ ) received Butylphthalide and Sodium Chloride Injection. There was no significant difference in age, height, weight, body mass index, heart rate, body temperature, or systolic and diastolic pressure between the two groups ( $P > 0.05$ ). The present study was approved by the Ethics Committee of the Seventh Medical Center of General PLA hospital (2020-001).

The inclusion criteria were: IS patients receiving treatment at the six centers from August 2018 to August 2019; aged 18–80 years; meeting the diagnostic criteria for IS; receiving treatment within 72 h after onset; suspect lesions confirmed by brain computed tomography/magnetic resonance imaging, which agreed with clinical manifestations, with the exclusion of cerebral hemorrhage; and complete medical records. The exclusion criteria were: Hemorrhagic stroke, transient ischemic attack, or other nervous system diseases; intravenous thrombolytic therapy or arterial embolectomy upon admission; any difficulty in efficacy assessment or incomplete medical records that interfered with efficacy assessment; incomplete medical records, including general information, diagnosis, and medical instructions; treated by other drugs containing safflower aqueous extract besides Guhong injection (Danhong injection and Safflor injection); and history of allergy to major components of the study drug (safflower and celery).

### Methods

Patients in the Guhong injection group (experimental group) received basic treatments plus Guhong injection, and 250 mL of normal saline was added to every 20 mL of Guhong injection. It was given once daily intravenously for 7–13 d consecutively. The Butylphthalide and Sodium Chloride Injection group (control group) received basic treatments plus Butylphthalide and Sodium Chloride Injection (SFDA Approval No.: H20100041; 100 mL: Butylphthalide 25 mg and sodium chloride 0.9 g) twice daily at 25 mg/mL. Each infusion lasted no less than 50 min, and the interval between two adjacent doses was no less than 6 h. Butylphthalide and Sodium Chloride Injection was given for 7–13 d consecutively. The basic treatments were the conventional systematic treatments, including: Intracranial pressure-reducing treatment, antiplatelet treatment, hypolipidemic treatment, hypoglycemic treatment, electrolyte disorder-correcting treatment, and nutritional support treatment. Neurological deficits were assessed using the National Institute of Health Stroke Scale (NIHSS). The NIHSS scores were compared between the two groups after treatment. The patients were followed after treatment at  $7 \pm 2$  d (first visit),  $14 \pm 2$  d (second visit), and  $21 \pm 3$  d (third visit). The efficacy assessment criteria were as follows[2,6]: Marked response: Symptoms and signs disappeared, and NIHSS score was reduced by  $> 46\%$  after treatment; mild response: Symptoms and signs improved significantly, and NIHSS score was reduced by  $\leq 45\%$  and  $\geq 18\%$ ; and no response: Symptoms were aggravated with the appearance of cerebral hernia, and the reduction in NIHSS scores did not meet the standard or improve considerably. Overall response rate was calculated as marked response rate + mild response rate. The calculation formula for the percentage change in NIHSS scores was:  $[(\text{total NIHSS scores before treatment} - \text{total NIHSS scores after treatment}) / \text{total NIHSS scores before treatment}] \times 100\%$ . The modified Rankin Scale (mRS) scores and their distribution at baseline and follow-up were compared. Safety analysis was conducted based on the patients' vital signs, routine blood tests, routine stool tests, liver and kidney function tests, electrocardiography (ECG), and adverse events. Efficacy assessment was analyzed using the basic, combined, and concomitant medications as confounding factors.

### Statistical analysis

Statistical analyses were conducted using SAS version 9.2 software. Count data and measurement data are expressed as percentages (%) and the mean  $\pm$  SD and were analyzed using the  $\chi^2$  test and  $t$  test, respectively. Comparison of measurement data among groups was conducted using the  $F$  test. The categorical data not obeying a normal distribution were analyzed by the Wilcoxon rank-sum test.  $P < 0.05$  indicated a significant difference. R was used to process the confounding factors of interest in efficacy assessment (basic, combined, and concomitant medications). Potential covariates were screened and entered into the propensity score matching analysis. Conditional logistic regression was used to calculate the propensity scores of the two groups. After performing the 1:1 nearest-neighbor matching,

**Table 1** Number of subjects recruited at each center

Center	Experimental group (n = 198)	Control group (n = 201)	Total (n = 399)
Seventh Medical Center of PLA General Hospital	0	92	92
First Affiliated Hospital of Nanchang University	38	32	70
People's Hospital of Liaoning Province	40	0	40
Cangzhou People's Hospital	31	42	73
Second People's Hospital of Huai'an	39	35	74
Ganyu District People's Hospital of Lianyungang	50	0	50

**Table 2** Baseline information of patients in the two groups

	Male (n, %)	Age (yr)	Height (cm)	Weight (kg)	Heart rate (beats/min)	Body temperature (°C)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Experimental group (n = 198)	109 (55.3)	65.57 ± 10.47	164.83 ± 7.28	65.12 ± 9.191	76.9 ± 14.34	36.42 ± 0.33	147.48 ± 23.20	84.23 ± 14.00
Control group (n = 201)	132 (65.7)	64.87 ± 10.75	Missing	Missing	78.2 ± 15.80	36.43 ± 0.34	150.30 ± 24.11	84.57 ± 14.43
Statistic	4.46	0.42	0.23	0.28	0.52	0.04	1.44	0.567
P value	0.35	0.674	0.6313	0.5939	0.603	0.965	0.15	0.57

we compared the efficacy between the two groups.

## RESULTS

### Comparison of NIHSS scores before and after treatment

Changes in the baseline total NIHSS scores at each follow-up visit are shown in Table 3. There were no significant differences in the NIHSS scores between the two groups at baseline ( $P > 0.05$ ). Compared with the baseline, the NIHSS scores of the experimental group at the first, second, and third visits were changed by  $-1.67 \pm 2.11$ ,  $-2.33 \pm 2.33$ , and  $-2.50 \pm 2.32$ , respectively. The NIHSS scores of the control group at these visits were changed by  $-1.25 \pm 2.62$ ,  $-1.45 \pm 2.36$ , and  $-1.67 \pm 4.12$ , respectively. The reduction in baseline NIHSS scores was greater at the three visits in the experimental group compared with the control group.

### Efficacy

The efficacy of the medications in the two groups is shown in Table 4. The marked response rates at the three follow-up visits were 64.64%, 74.7%, and 66.7% in the experimental group, and 48.26%, 45.4%, and 22.2% in the control group, respectively. The marked response rates were increased significantly in the experimental group compared with the control group ( $P < 0.05$ ). The overall response rates at the three follow-up visits were 98.48%, 100%, and 100% in the experimental group, and 99.01%, 98.59%, and 88.89% in the control group, respectively. The overall response rate at the first visit was higher in the control group than in the experimental group, but the difference was not significant. The overall response rates at the second and third visits were significantly higher in the experimental group than in the control group ( $P < 0.05$ ).

### Distribution of mRS scores before and after treatment

There were no significant differences in the distribution of varying degrees of disability at the baseline between the two groups ( $P = 0.3903$ ). At the first follow-up visit, the patients without any symptoms accounted for 60.1% in the experimental group compared to 44.8% in the control group ( $P > 0.05$ ). At the second visit, the patients without any symptoms accounted for 55.4% in the experimental group compared to 41.8% in the control group ( $P > 0.05$ ). At the first visit, the change in the mRS score was -2 in three patients (1.5%) in the experimental group, -1 in 140 patients (70.7%), and 0 in 55 patients (27.8%). In the control group, the change in the mRS score was -2, -1, and 0 in 0, 90 (44.3%), and 111 (55.7%) patients, respectively. The percentages of patients with a change of -2 and -1 were significantly different between the two groups ( $P < 0.05$ ). At the second visit, the change in the mRS score was -2 in three patients (3.6%), -1 in 78 patients (94.0%), and 0 in two patients (2.4%) in the experimental group. In

**Table 3** Changes in baseline total National Institutes of Health stroke scale scores at each follow-up visit

	Experimental group (n = 198)	Control group (n = 201)	Rank-sum test	P value
Baseline (day 0)	3.40 ± 2.08	3.63 ± 2.72	0.495	0.621
Visit 1 (days 7 ± 2)	1.75 ± 2.03	2.34 ± 2.37	1.588	0.056
Relative to baseline	-1.67 ± 2.11	-1.25 ± 2.62	300.727	< 0.0001
Visit 2 (days 14 ± 2)	1.65 ± 1.90	2.45 ± 2.26	8.138	< 0.0001
Relative to baseline	-2.33 ± 2.33	-1.45 ± 2.36	222.404	< 0.0001
Visit 3 (days 21 ± 3)	2.33 ± 1.63	5.0 ± 3.54	2.207	0.016
Relative to baseline	-2.50 ± 2.32	-1.67 ± 4.12	16.19	< 0.0001

**Table 4** Efficacy of medications in the two groups, n (%)

		Experimental group (n = 198)	Control group (n = 201)	$\chi^2$	P value
Visit 1 (days 7 ± 2)	Marked response	128 (64.64)	97 (48.26)	11.60	0.003
	Mild response	67 (33.84)	102 (50.75)		
	No response	3 (1.51)	2 (0.99)		
Visit 2 (days 14 ± 2)	Marked response	62 (74.7)	64 (45.4)	835.36	< 0.0001
	Mild response	21 (25.30)	75 (53.2)		
	No response	0	2 (1.41)		
Visit 3 (days 21 ± 3)	Marked response	4 (66.7)	2 (22.2)	887.40	< 0.0001
	Mild response	2 (33.3)	6 (66.7)		
	No response	0 (0)	1 (11.1)		
Visit 1 (days 7 ± 2)	Overall response	195 (98.48)	199 (99.01)	0.121	0.728
	No response	3 (1.52)	2 (0.99)		
Visit 2 (days 14 ± 2)	Overall response	83 (100)	139 (98.59)	403.127	< 0.0001
	No response	0	2 (1.41)		
Visit 3 (days 21 ± 3)	Overall response	6 (100)	8 (88.89)	9.63	0.0019
	No response	0	1 (11.11)		

the control group, the percentages of patients with a change of -2, -1, and 0 were 0, 69 (48.9%), and 74 (33.0%), respectively. The percentages of patients with a change of -2 and -1 were significantly different between the two groups at either visit ( $P < 0.05$ ) (Table 5).

### Adverse events

Adverse events were divided into three categories based on their causal relationship with the investigational drug: Definitely related, possibly related, and uncertain. Twelve patients (6.06%) in the experimental group and 13 (6.47%) in the control group experienced adverse events, but none of the adverse events were related to the study drug. There was no significant difference in the incidence of adverse events between the two groups ( $P > 0.05$ ). No severe adverse events occurred in either group during treatment.

### Analysis of confounding factors

The concomitant and combined medications used were divided into 11 major types: Concomitant medication for respiratory diseases; concomitant medication for digestive diseases; concomitant medication for genitourinary diseases; concomitant medication for coronary heart disease; concomitant medication for other diseases; combined medication based on vitamins; combined medication based on free-radical scavengers; combined medication based on calcium ion antagonists; combined medication based on cerebrovascular dilators; combined medication based on neurotrophic agents; and combined medication based on Chinese patent medicine. The above covariates were put into the logistic regression model. The 1:1 nearest-neighbor matching was performed, with the matching tolerance set to 0.2.

**Table 5** Distribution of modified Rankin scale scores in the two groups

	Experimental group (n = 198)	Control group (n = 201)	Rank-sum test	P value
<b>Baseline</b>			1.88	0.3903
No symptom	15 (7.6)	48 (23.6)		
No significant disability	132 (66.7)	95 (47.8)		
Mild disability	38 (19.2)	41 (20.2)		
Moderate disability	7 (3.5)	9 (4.4)		
Moderately severe disability	6 (3.0)	8 (3.9)		
Severe disability	0	0		
<b>Visit 1 (days 7 ± 2)</b>			11.66154	0.020
No symptom	119 (60.1)	89 (44.8)		
No significant disability	57 (28.8)	86 (42.4)		
Mild disability	16 (8.1)	17 (8.4)		
Moderate disability	6 (3.0)	7 (3.4)		
Moderately severe disability	0	2 (1.0)		
Severe disability	0	0		
<b>Visit 2 (days 14 ± 2)</b>			6.098	0.192
No symptom	46 (55.4%)	59 (41.8%)		
No significant disability	29 (34.9%)	62 (44.0%)		
Mild disability	8 (9.6%)	15 (10.6%)		
Moderate disability	0	4 (2.8%)		
Moderately severe disability	0	1 (0.7%)		
Severe disability	0	0		

### Analysis after propensity score matching

Before propensity score matching, the two groups did not differ significantly in the use of the following medications: Concomitant medication for respiratory diseases; combined medication based on free-radical scavengers; combined medication based on neurotrophic agents; and combined medication based on Chinese patent medicine. After the matching, 111 matched patients in terms of medication were obtained in the two groups. After propensity score matching, the overall response rate and marked response rate were 97.29% and 100% in the experimental group ( $P > 0.05$ ) and 64.0% and 47.7% in the control group ( $P < 0.05$ ) at the first visit, and 100% and 100% and 75.51% and 45% at the second visit, respectively ( $P < 0.05$ ). At the first visit, compared with the baseline, the NIHSS score decreased by  $-1.61 \pm 0.620$  in the experimental group compared to  $-1.26 \pm 0.481$  in the control group ( $P < 0.05$ ). At the second visit, the NIHSS score decreased by  $-2.27 \pm 0.569$  in the experimental group compared to  $-1.32 \pm 0.652$  in the control group ( $P < 0.05$ ). After propensity score matching, the good prognosis rate assessed by mRS at the first visit was 99.1% in the experimental group and 98.2% in the control group ( $P > 0.05$ ). At the second visit, the good prognosis rate was 100% in both groups ( $P > 0.05$ ). The distribution of six degrees of disability assessed by mRS was not significantly different between the two groups, namely, no symptoms, no significant disability, mild disability, moderate disability, moderately severe disability, and severe disability (Table 6).

## DISCUSSION

The pathological process of IS is related to several factors. Therefore, intervention is possible for any process in the ischemic cascade. Guhong injection, composed of aceglutamide and safflower aqueous extract, is a common drug for the treatment of cerebral ischemia/reperfusion injury[7,8]. Aceglutamide and safflower aqueous extract can work synergistically and have antiplatelet and antithrombotic actions. Aceglutamide is decomposed into glutamic acid after passing through the blood-brain barrier. Glutamic acid can improve nerve cell metabolism, maintain normal stress response of nerve cells, and lower blood ammonia level, thereby improving brain function[9]. Glutamic acid is also involved in

Table 6 Propensity score matching between the experimental group and control group

Factors	Before propensity score; Experimental group (n = 198)	Control group (n = 201)	P value	After propensity score; Experimental group (n = 111)	Control group (n = 111)	P value
Combined medication based on vitamins	-0.331	0.288	0.25	0.375	0.91	0.34
Combined medication based on Chinese patent medicine	0.539	0.31	0.082	0.147	0.17	0.68
Combined medication based on neurotrophic agents	0.575	0.225	0.011	-0.193	0.467	0.494
Combined medication based on free-radical scavengers	-1.823	0.245	0	-0.017	0.003	0.955
Concomitant medication for respiratory diseases	-1.182	0.44	0.007	-0.032	0.003	0.953
Concomitant medication for genitourinary diseases	-0.638	0.557	0.252	0.279	0.197	0.657
Concomitant medication for coronary heart disease	0.414	0.423	0.328	0.512	1.085	0.298

signal transmission in the central nervous system. Glutamic acid can be converted into glutathione in astrocytes. Glutathione is shown to have antioxidative effects and has neuroprotective activity against cerebral ischemia and nervous system diseases. Guhong injection is a vasodilator[10], which improves blood perfusion in cerebral ischemia/reperfusion injury[11]. Guhong injection can clear oxygen free radicals, thereby reducing the calcium ion level in the brain tissues of rats with ischemia/reperfusion injury[12,13]. Zhou *et al*[14] found that Guhong injection improved the neurological deficit scores in a rat model of cerebral ischemia and reduced the ischemic infarct volume. Further investigation showed that Guhong injection protected the rat brain tissues or brain microvascular endothelial cells (BMECs) against ischemic/reperfusion injury or oxygen glucose deprivation (OGD)-induced injury by repairing the brain microvascular system and mitochondria. Guhong injection inhibited cell apoptosis by activating the PI3K/Akt pathway in cerebral ischemia. Guhong injection may be an effective drug against cerebral ischemia as it maintains the antiapoptotic effect and integrity of the brain microvascular system and mitochondria. Wang *et al*[15] showed that Guhong injection plus Naoxingtong decoction were protective against cerebral ischemia/reperfusion injury in rats. The number of rat BMECs and superoxide dismutase level were higher in the combined treatment group than in the monotherapy group. These two indicators were significantly higher in the medication groups than in the nonmedication group. The apoptosis rate of rat BMECs and malondialdehyde level were significantly lower in the combined treatment than in the monotherapy group. They were both significantly higher in the medication groups than in the nonmedication group. Based on the pharmacological features of Guhong injection, several clinical studies of Guhong injection for other diseases are being carried out (ChiCTR1900022902)[15]. Coronary microvascular disease (CMVD) is a cardiovascular disorder with normal coronary arteriographic findings but with myocardial ischemia or microcirculatory disorder. Angina is a common symptom of CMVD, which is also a pathogenic feature of coronary heart disease. A multicenter randomized controlled trial (RCT) is currently being conducted to evaluate the efficacy and safety of Guhong injection compared with placebo in CMVD. In this trial, 260 eligible patients were randomized into the experimental group and the control group at a 1:1 ratio. The treatment lasted 10 d, with an 8-wk follow-up. Efficacy is the primary endpoint to be assessed. Secondary endpoints include quantitative scores of traditional Chinese medicine (TCM) syndrome (a series of symptoms and signs in TCM), average frequency of angina attacks, ECG changes, inflammatory response and endothelial function indicators, and myocardial metabolites. Butylphthalide is a novel type of anti-IS agent independently developed in China. Being fat-soluble, butylphthalide can pass through the blood-brain barrier[16-18]. It is reported that butylphthalide can improve the mitochondrial function of the cerebrovascular endothelial cells, increase levels of NO and prostacyclin, inhibit glutamic acid release, and reduce intracellular calcium and arachidonic acid concentrations[19,20]. Butylphthalide can inhibit free oxygen radicals, improve *in vivo* antioxidase activity, protect against cerebral ischemia *via* multiple targets, and improve local blood perfusion in the brain tissues. It can also prevent energy exhaustion induced by cerebral ischemia, delay the onset of ischemic brain edema and thrombosis, and improve nerve function[21,22].

Many clinical trials have investigated the efficacy and safety of Guhong injection and Butylphthalide and Sodium Chloride Injection for cerebral IS[23-30]. One meta-analysis including 1498 patients with acute cerebral infarction from nine RCTs indicated a significant difference in overall response rate between the Guhong injection and control groups. The neurological deficit scores were also significantly

different between the Guhong injection group and the control group. Adverse events were rare or mild. These results confirmed the safety of Guhong injection[23]. Another meta-analysis focused on the efficacy and safety of butylphthalide, which included seven RCTs with 796 patients. Among them, 396 patients received Butylphthalide and Sodium Chloride Injection and 400 received conventional treatment. A systematic review showed that compared with the conventional treatment group, NIHSS scores decreased significantly in the Butylphthalide and Sodium Chloride Injection group at days 11 and 21, and the Barthel index increased markedly. The results showed that Butylphthalide and Sodium Chloride Injection alleviated neurological deficits at days 11 and 21 after the onset of acute IS. The patients' physical function was also improved. Butylphthalide and Sodium Chloride Injection was proved to be effective and worthy of clinical application[24]. We recruited 399 patients from six hospitals. Apart from a shorter length of hospital stay, Guhong injection outperformed Butylphthalide and Sodium Chloride Injection in improving NIHSS and mRS scores. This finding remained unchanged after propensity score matching. Based on the vital signs, routine blood tests, and liver and kidney function tests, we found no significant differences between the two groups in safety and incidence of adverse events. A few adverse events observed were not related to the study drug, and no severe adverse events occurred. Thus, Guhong injection displayed good safety in our study.

For efficacy assessment, other medications used in the two groups were considered confounding factors, which were handled by propensity score matching. After confirming that the medication use was balanced between the two groups, we further assessed the efficacy. Finally, 11 medication regimens involving drugs other than Guhong injection and Butylphthalide and Sodium Chloride Injection were put into the model as covariates, and propensity score matching was carried out. After the matching, the marked response rate of the experimental group was significantly higher than that of the control group. However, the overall response rate was only slightly reduced. The decrease in the NIHSS score was greater relative to the baseline in the experimental group than in the control group.

There were some limitations to the present study. First, the patients were only recruited from six hospitals, and selection bias was inevitable. Second, the follow-up with mRS assessment was short. In the future, the follow-up may be prolonged to 3 mo or longer to assess the long-term efficacy of Guhong injection. In addition, it is necessary to conduct large-scale RCTs or real-world studies of Guhong injection for cerebral IS to guide safe and reasonable drug use in the clinic.

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## CONCLUSION

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Guhong injection compared with Butylphthalide and Sodium Chloride Injection increases the response rate and shortens the length of hospital stay in patients with IS. Guhong injection has greater clinical efficacy for IS.

## ARTICLE HIGHLIGHTS

### **Research background**

Efforts should be made to restore microcirculation in ischemic regions as quickly as possible to protect the brain nerves maximally, and there are many neuroprotective drugs in clinical application.

### **Research motivation**

Most studies on Guhong injection have involved a single center with a small sample size, with a low level of clinical evidence.

### **Research objectives**

To assess the safety and efficacy of Guhong injection for mild ischemic stroke (IS).

### **Research methods**

IS patients who met the inclusion and exclusion criteria were enrolled from six hospital in China and divided into two groups treated with Guhong injection or Butylphthalide and Sodium Chloride Injection. The National Institute of Health Stroke Scale (NIHSS) scores and modified Rankin scale (mRS) were compared between the two groups after treatment. Conditional logistic regression was used to calculate the propensity scores of the two groups. After performing the 1:1 nearest-neighbor matching, we compared the efficacy between the two groups.

### **Research results**

The marked response rates were increased significantly in the experimental group compared with the control group. The overall response rate was significantly different at the second (days 14 ± 2) and third visit (days 21 ± 3). At the first and second visits, the change in mRS scores was -2 and -1 in the two

groups, which were significantly different. There was no significant difference in the incidence of adverse events between the two groups. No severe adverse events occurred in either group. The results showed that Guhong injection had greater clinical efficacy than Butylphthalide and Sodium Chloride Injection for IS in a large sample.

### Research conclusions

The research suggested that Guhong injection compared with Butylphthalide and Sodium Chloride Injection increases the response rate and shortened the length of hospital stay in patients with IS. Guhong injection has greater clinical efficacy for IS.

### Research perspectives

Further study on the mechanism of Guhong injection for treatment of IS is required.

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## FOOTNOTES

**Author contributions:** Zhang WW wrote the paper; Wu CS, Xin J, and Zhang GY supervised the report; Zhao LD contributed to the analysis; Zhang HM provided clinical advice; all authors designed and performed the research, and gave final approval for the version to be submitted.

**Institutional review board statement:** The present study was approved by the Ethics Committee of the Seventh Medical Center of General PLA hospital (2020-001).

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** There are no conflicts of interest to declare.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at [amy\\_1119@163.com](mailto:amy_1119@163.com).

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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**S-Editor:** Liu JH

**L-Editor:** Wang TQ

**P-Editor:** Liu JH

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