ORIGINAL RESEARCH

Efficacy of Getong Tongluo Capsule plus Clopidogrel Hydrogen Sulfate Tablets Therapy Assisted by Home Rehabilitation Guidance in Convalescents from Cerebral Infarction

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ABSTRACT

Background • Cerebral infarction (CI) is one of the leading causes of death in middle-aged and elderly people, and there is a need to focus on overall rehabilitation during the recovery period of CI in the clinic, to provide a more reliable guarantee for the health of patients.

Objective • To observe the therapeutic efficacy of Getong Tongluo Capsule (GTC) plus Clopidogrel hydrogen sulfate tablets (CHST) therapy assisted by home rehabilitation guidance in convalescents from CI, to provide clinical reference and evidence for future CI management.

Methods • CI convalescents who visited the Fourth People's Hospital of Haikou City between 2016 and 2021 were selected as the research participants. Based on the assistance of home rehabilitation guidance, 44 patients receiving CHST treatment and 56 patients receiving GTC + CHST treatment were assigned to a control group (CG) and research group (RG), respectively. The blood viscosity of the two groups was compared before and after treatment. In addition, patients were assessed by the National Institutes of Health Stroke Scale (NIHSS), Mini-Mental State Examination (MMSE), Fugl-Meyer Assessment (FMA), Modified Barthel index (MBI), and Self-rating Anxiety/Depression Scale (SAS/SDS) scores. Finally, the adverse reaction rate was counted.

Results • The post-treatment blood viscosity decreased in both cohorts and was lower in RG compared with CG ($P < .001$). Regarding various scale scores, NIHSS, SAS, and SDS were lower in RG than CG, while MMSE, FMA, and MBI were higher ($P < .001$). The adverse reaction rate was not significantly different between groups ($P = .587$).

Conclusion • GTC + CHST therapy assisted by home rehabilitation guidance is effective in the treatment of CI patients in the convalescent stage and is worth recommending. (*Altern Ther Health Med.* 2024;30(6):259-263).

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INTRODUCTION

Cerebral infarction (CI) is an irreversible damage to brain tissue caused by abnormal local blood circulation due to multiple factors, accompanied by brain tissue ischemia, hypoxia, and necrosis of brain tissue, with high mortality and disability rates.[1] As a high-risk disease among the middle-aged and elderly, CI afflicts 3 million cases yearly worldwide, eventually causing deaths in more than 50% and leaving the survivors experiencing irreversible neurological injury sequelae.[2,3] Depending on the pathogenesis, CI can be categorized as large artery atherosclerotic CI, cardiogenic embolic CI, and small artery occlusive CI, and regardless of the type of CI, there is a great potential threat.[4] Recent years have witnessed a marked decline in the mortality rate of CI as a result of constant advances in medical technology, but the sequelae have greatly reduced patients' quality of life and affected their physical and mental health.[5] CI convalescence, namely within 6 months of onset, is the best secondary prevention period for patients,[6] during which CI convalescents receive corresponding drug treatment and rehabilitation intervention to improve symptoms such as numbness of limbs and language impairment.[7] Currently, the preferred treatment scheme for CI convalescents is based on modern Chinese medicine, supplemented by Western medicine, which can alleviate patients' symptoms and prevent the disease from progressing on the premise of ensuring therapeutic safety.[8]

Getong Tongluo Capsule (GTC) is a blood-regulating agent and due to its circulation-promoting and stasis-removing effects as well as its positive influence on improving nerve function, increasing cerebral blood flow, and reducing blood viscosity, it is commonly used in clinical practice for the meridian obstruction syndrome due to blood stasis in the convalescence period of

ischemic stroke.[9] In addition, Pueraria flavone, the main component of GTC, accounts for 80% of the pharmaceutical ingredients.[10] In modern pharmacological research, Pueraria flavone can dilate coronary artery blood vessels, reduce myocardial oxygen consumption, restore coronary and cerebrovascular blood flow, promote blood circulation, and enhance myocardial contractility and immunity, which facilitates the recovery of patient's neurological function; moreover, it has been shown to reduce the activities of calcium ion and superoxide dismutase in brain tissue caused by repeated cerebral ischemia, ameliorate brain edema, reduce oxygen consumption in brain tissue and improve the protective effect of brain tissue.[11] Clopidogrel hydrogen sulfate tablets (CHST), a platelet antagonist that can inhibit platelet aggregation, can be used to prevent and treat cardiovascular and cerebral arterial circulatory disorders caused by high platelet aggregation, thus effectively relieving brain ischemia and avoiding reperfusion damage.[12] GTC plus CHST therapy is a relatively novel treatment integrating traditional Chinese and Western medicine, which was first used to treat coronary heart disease, and has now been indicated to contribute to excellent treatment outcomes for CI.[13] However existing research is still not comprehensive, and the application of GTC and CHST still lacks reliable medication guidance.

In recent years, the application value of home rehabilitation guidance in convalescent stage CI has been increasingly high, with many studies pointing out its great application value in improving patient prognosis.[14,15] Since 2016, the Fourth People's Hospital of Haikou City has carried out extensive home rehabilitation guidance in various departments with excellent results. Therefore, this study observes the effectiveness of GTC + CHST in CI convalescents under the guidance of home rehabilitation, which has important reference significance for the selection of CI convalescent treatment in the future.

MATERIALS AND METHODS

Participants

With the approval of the hospital Ethics Committee, 100 convalescent CI patients admitted between 2016 and 2021 were selected as the research participants. The enrolled patients were all diagnosed with first-onset CI by Cephalometric MRI and other imaging data and were in the convalescent phase rather than the acute phase, with complete case data and high compliance. The exclusion criteria were severe dysfunction of the heart, liver, kidneys, and other organs, brain trauma, brain tumors, blood disorders, endocrine and/or mental disorders, drug allergies, and referrals.

Group allocation

Forty-four cases were treated with CHST (control group, CG) and 56 were treated by GTC + CHST therapy (research group, RG). During the treatment, all subjects received home rehabilitation guidance. All patients included were informed and signed informed consent. The two groups had similar clinical baseline data ($P > .05$, Table 1).

Table 1. Baseline information table

	Control (n = 44)	Research (n = 56)	t or χ^2	P value
Age	56.3±4.8	55.6±5.8	0.645	.520
Gender				
Male	27 (61.4)	38 (67.9)		
Female	17 (38.6)	18 (32.1)		
BMI (kg/m^2)	28.0±1.4	28.1±1.4	0.355	.724
Past medical history			1.170	.919
Hypertension	16 (36.4)	21 (37.5)		
Diabetes mellitus	13 (29.5)	18 (32.1)		
None	15 (34.1)	17 (30.4)		
Smoking			0.282	.595
Yes	26 (59.1)	36 (64.3)		
No	18 (40.9)	20 (35.7)		
Drinking alcohol			0.331	.565
Yes	25 (56.8)	35 (62.5)		
No	19 (43.2)	21 (37.5)		

Intervention

Before discharge, the rehabilitation physician conducted a comprehensive health assessment for the patient, based on which relevant disease awareness education was given to the patient and his/her family members. In addition, the patients were instructed on daily medication, diet, exercise, emotional regulation, etc., and told to take medication on time. Dietary precautions were also explained, such as limiting the intake of oil and fat, strictly following the principle of a low-fat and low-salt diet, eating more fresh fruits, vegetables, and coarse grains, and quitting smoking and drinking. Furthermore, patients were advised to conduct rehabilitation training step by step according to their conditions, including limb motor function training and daily living ability training. Meanwhile, massage stimulation was given mainly to the affected limb, and the force was applied according to the patient's bearing capacity. Moreover, the patients were encouraged and supported, and the negative emotions were promptly intervened and channeled. What's more, medical staff sent rehabilitation-related knowledge to the WeChat group from time to time and asked patients about their rehabilitation training status. Patients were evaluated in the clinic at least once a month, and the program was adjusted according to their needs.

Treatment methods

Both groups received basic routine care such as blood pressure control circulatory stabilization and symptomatic management. Patients in CG were given oral CHST (Lepu Pharmaceuticals, Inc., SFDA Approval No. H20123115), 75 mg/time/d. RG was given oral CHST (same dosage as CG) and GTC (Anhui Joyfar Pharmaceutical Co., Ltd., SFDA Approval No. Z20060439), of which GTC was administered 2 capsules per time, 2 times a day. Both groups were treated continuously for 3 months.

Outcome measures

Three milliliters of fasting venous blood were collected before and after treatment for the detection of high blood viscosity, low whole blood viscosity, and plasma viscosity using a blood flow analyzer. The National Institutes of Health Stroke Scale (NIHSS, 0-42 points)[16] and Mini-Mental State Examination (MMSE, 0-30 points, 0-9 is severe dementia, 10-20 is moderate dementia, 21-26 is mild dementia, and 27-30 is normal)[17] were adopted for neurological function

assessment, with higher NIHSS and lower MMSE indicating worse neurological function. In addition, the Fugl-Meyer Assessment (FMA, upper + lower extremity motor function 0-100 points)[18] and Modified Barthel Index (MBI, 0-100 points)[19] were employed for mobility assessment of patients, with the score of both scales in direct proportion to mobility. Patients' psychological states were also evaluated using the Self-rating Anxiety/Depression score (SAS/SDS, 20-80 points)[20]; higher SAS and SDS scores were associated with more serious anxious and depressive symptoms. Finally, the adverse reactions of the two groups were counted.

Statistical analysis

This study employed SPSS version 23.0 for data analyses. Categorical and continuous variables were statistically described as percentages and mean ± standard deviation, respectively. To identify statistical significance (threshold: $P < .05$), a chi-square test was carried out for categorical variables, while a *t* test and a paired *t* test were used for inter-group and intra-group comparisons (before and after treatment) of continuous variables, respectively.

RESULTS

Comparison of pre-treatment scores of various scales

The pre-treatment scores of MMSE, NIHSS, FMA, MBI, SAS, and SDS of both groups are shown in Table 2, which revealed no statistical difference between groups ($P > .05$).

Comparison of post-treatment neurological function

An elevation in the MMSE score was observed in both groups, with that being (27.02±3.22) and (23.80±2.26) in RG and CG, respectively, showing a higher MMSE in RG ($P < .05$, Figure 1A). While the post-treatment NIHSS decreased in both groups, especially in RG ($P < .05$, Figure 1B).

Comparison of post-treatment mobility

Increased FMA and MBI scores were found in both patient cohorts after treatment, with those being (74.82±6.67) and (79.91±7.52) in RG, respectively, versus (69.18±6.53) and (73.43±5.86) in CG. The inter-group comparison revealed higher post-treatment FMA and MBI scores in RG as compared to CG ($P < .05$, Figure 2).

Comparison of post-treatment psychological state

Marked reductions in SAS and SDS were identified in both groups after treatment, and the SAS and SDS scores in RG were (39.04±7.39) and (38.63±5.48), respectively, lower than those in CG ($P < .05$, Figure 3).

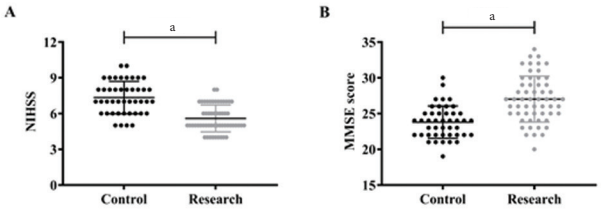
Comparison of pre-and post-treatment hemodynamics

The two groups were not statistically different in pre-treatment high blood viscosity, low whole blood viscosity, or plasma viscosity ($P > .05$). After treatment, the blood viscosity of both cohorts decreased evidently ($P < .05$), with reduced high blood viscosity, lower whole blood viscosity, and plasma viscosity in RG compared with CG ($P < 0.05$, Figure 4).

Table 2. Pre-treatment scores of various scales

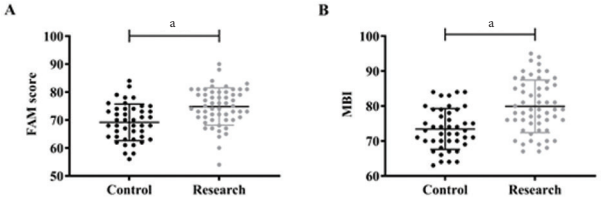
Group	MMSE	NIHSS	FMA	MBI	SAS	SDS
Control (n = 44)	16.59±2.56	15.41±2.78	53.73±6.31	62.30±5.92	57.07±8.04	54.93±5.49
Research (n = 56)	16.54±2.85	14.93±2.96	53.36±7.39	62.54±5.37	56.32±6.15	52.82±6.54
t	0.10	0.83	0.26	0.21	0.53	1.72
P value	.92	.41	.79	.83	.60	.09

Figure 1. Post-treatment neurological function. A, comparison of MMSE score. B, comparison of NIHSS.



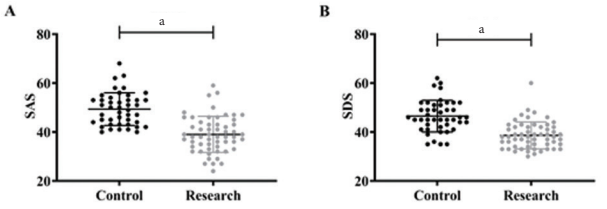
[a]$P < .001$

Figure 2. Post-treatment mobility. A, comparison of FMA score. B, comparison of MBI.



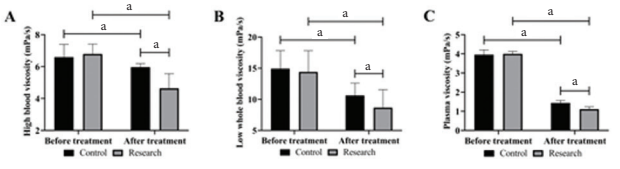
[a]$P < .001$

Figure 3. Post-treatment psychological state. A, comparison of SAS. B, comparison of SDS.



[a]$P < .001$

Figure 4. pre- and post-treatment hemodynamics. A, comparison of high blood viscosity. B, comparison of low whole blood viscosity. C, comparison of plasma viscosity.



[a]$P < .05$

Table 3. Adverse events

Group	Dizziness and headache	Gastrointestinal discomfort	Skin rash	Constipation	Total incidence
Control (n = 44)	2 (4.55)	1 (2.27)	0 (0.0)	1 (2.27)	4 (9.09)
Research (n = 56)	2 (3.57)	2 (3.57)	1 (1.79)	2 (3.57)	7 (12.50)
χ^2					0.293
P value					.587

Comparison of adverse events

The adverse reaction rate was 12.50% in RG and 9.09% in CG. Both groups suffered from adverse events such as occasional dizziness and headache, gastrointestinal discomfort, and constipation, but had no difference in the total incidence of adverse events ($P > .05$, Table 3).

DISCUSSION

In this study, we found a more significant improvement in NIHSS and MMSE scores in RG after treatment, suggesting a better neurological rehabilitation status of patients in RG, similar to previous research results.[21,22] In addition, patients in RG showed lower blood viscosity than CG after treatment, demonstrating that GTC + CHST therapy is markedly effective in treating CI and can significantly improve the hemodynamics of patients. As known, hemorheology can effectively reflect the macroscopic properties of blood flow, including blood viscosity and blood deformability. Following a stroke, patients experience damaged vascular function, atherosclerosis thrombosis, elevated blood viscosity, and reduced blood fluidity, all of which will reduce blood flow in ischemic areas, further intensifying brain tissue damage and promoting disease progression.[23] CI patients are shown to have higher coagulation and lower anticoagulation and fibrinolysis, which are closely related to disease progression.[24] After the occurrence of acute CI, platelet aggregation, decreased erythrocyte mobility, and increased blood viscosity in patients not only lead to hemodynamic disorders, but also increase peripheral vascular resistance that elevates blood pressure, decreases erythrocyte deformability and reduces oxygen uptake, aggravating ischemia, and hypoxia, and exacerbating CI.[25] CHST, as a second-generation adenosine diphosphate (ADP) receptor antagonist, has a selective blocking effect on ADP receptors. It is an inactive prodrug that needs to be metabolized by the liver into an active thiol metabolite, which can hinder ADP from binding to platelets by rapidly and irreversibly binding to platelet receptors, thereby inhibiting platelet aggregation.[26] When CHST enters the gastrointestinal tract by oral administration, the blood drug concentration can quickly reach the highest value without being influenced by food. Therefore, it has a fast-onset anti-platelet aggregation effect, which can achieve the purpose of inhibiting platelet aggregation, improving cerebral blood supply, alleviating nerve function damage, and controlling the disease.[27] In our previous study, we also found that GTC and CHST had excellent improvement in neurological function in patients with hypertensive encephalopathy, ischemic stroke, etc., which can also support our findings.[9,28] Therefore, when CHST is used in combination with GTC, the hemodynamics of patients can be improved significantly and effectively, and the nerve injury can be repaired more ideally, which is undoubtedly of great significance to the prognosis and rehabilitation of CI patients. Similarly, higher post-treatment FMA and MBI scores were determined in RG versus CG, which verifies the above viewpoint and confirms that CHST + GTC have a more ideal effect on nerve repair after CI and greatly avoids the disability risk of patients. When investigating drug safety, we found no significant inter-group difference in the adverse reaction rate, confirming that the combination of CHST and GTC has stable safety. Previous studies also highly affirmed the safety profile of CHST + GTC,[29,30] which supports our findings.

Finally, in the comparison of the psychological state, an obvious improvement was observed in both cohorts, which may be due to the positive effect of home rehabilitation treatment. In previous studies, we can see that the negative psychological situation of patients with CI is generally serious due to factors such as the harm of the disease, lack of rehabilitation knowledge, and economic pressure,[31] which not only greatly affects patients' treatment compliance, but may also lead to treatment discontinuation due to patients' loss of confidence in treatment.[32] Under the intervention of home rehabilitation guidance, rehabilitation knowledge popularization and health education can be effectively carried out, and the community can make patients and their families understand the importance of rehabilitation treatment, to encourage them to actively participate and cooperate to obtain comprehensive rehabilitation. In this way, patients' negative emotions can be significantly mitigated, which undoubtedly has important positive significance for the long-term treatment of CI.

However, because this paper is a retrospective analysis, the researcher was not involved in the collection of information and relied on information from others, which may have led to misclassification or recall bias. Second, there may still be room for optimization and improvement of medication regimens for patients. Third, due to the short study period, we could not evaluate the influence of CHST + GTC on the long-term outcomes of CI patients. These are also areas that need to be optimized and improved in the follow-up research.

CONCLUSION

CHST + GTC therapy assisted by home rehabilitation guidance has marked effects in the treatment of convalescent CI patients, which can effectively enhance patients' neurological function and mobility, reduce blood viscosity, and maintain the normal operation of hemodynamics. In future clinical treatment of CI convalescents, CHST combined with GTC therapy can be selected as the treatment scheme to provide a more reliable guarantee for the prognosis and safety of patients. At the same time, it is also recommended to carry out home rehabilitation guidance in all diseases requiring long-term treatment, which is conducive to reducing patients' negative psychology and improving the quality of treatment.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Not applicable.

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