



A randomized double-blind controlled study protocol on the efficacy and safety of Sangdantongluo granule in the treatment of post-stroke spasticity

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ABSTRACT

Introduction: Stroke is the first leading cause of mortality and disability worldwide, and post-stroke spasticity (PSS) is the common complication of stroke. Sangdantongluo Granule (Z20210481000), a modern patent Chinese medicine, is widely used in clinical practice to treat PSS. Whereas, there is limited evidence of effectiveness for Sangdantongluo Granule to treat PSS. This study will evaluate the clinical efficacy and safety of Sangdantongluo granule in the treatment of PSS.

Methods: and Analysis This multicenter, randomized, double-blind and placebo-controlled study will recruit 132 participants in China who develops PSS 15 days–90 days after stroke. Participants will be randomly assigned in an equal ratio to receive either Sangdantongluo granule or placebo for 2 months twice a day orally. The primary measure is the Modified Ashworth Scale (MAS), Secondary outcome measures include Composite Spasticity Scale (CSS), Simplified Fugl-Meyer Motor Scale (S-FM), National Institute of Health stroke scale (NIHSS), Modified Rankin Scale (mRS), Modified Barther Index (MBI), and Surface electromyography. Adverse events will be supervised throughout the trial. SPSS V. 26.0 statistical software will be used for statistical analysis. Enrolment will be started in April 2022.

Ethics and dissemination: The trial and protocol were approved by the Ethics Committee of Hunan Academy of Chinese Medicine Affiliated Hospital (No. [202102]20). We will report the results of this trial in a peer-reviewed journal.

Trial registration: ClinicalTrials.gov ChiCTR2100044544. Registered on 23 March 2021.

1. Introduction

Stroke nowadays is the highest disability-adjusted life-years lost of any illness all over China, with two million new cases per year. This situation will worsen as the consequences of population ageing and persistent high going of risk factors (smoking and hypertension) in China [1,2]. Post-stroke spasticity (PSS) is a common symptom of upper motor neuron injury with an incidence account for 30–80%, which arising from lesions to the reticulospinal or cortico-reticulospinal induced by stroke [3,4]. Muscle tension and stiffness of PSS usually be associated with forceless and loss of dexterity, making for disordered movement-control, just as inability to reach, grasp, and walk [5].

In the aspect of PSS management, rehabilitation is preferred as the basic treatment, including anti-spasticity limb position, joint mobility

training, and spastic muscle stretching slowly, but they show a relatively limited curative effect. Injection of botulinum toxin locally or oral muscle relaxants, for instance baclofen, benzodiazepines and dantrolene, have certain clinical efficacy, but with plentiful adverse effects, such as weakness, hypotension, memory impairment, dizziness, and so on, which restrict the widespread utilization of these medications in PSS [6,7].

Chinese herbal products are extensively used in PSS patients in China [8]. In accordance with the theory of Traditional Chinese Medicine (TCM), yin deficiency and blood stasis are the primary syndromes in PSS. Therefore, we prescribed Sangdantongluo granule to nourish yin and promote blood circulation in the treatment of PSS, which already be widely used in clinical practice for a long time and developed into Chinese patent medicine (Z20210481000). Sangdantongluo granule is

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composed of *Mori Fructus*, *Lycii Fructus*, *Salviae Miltiorrhizae Radix Et Rhizoma*, *Lumbricus*, *Siegesbeckiae Herba*, *Paeoniae Radix Alba*, *Gastrodiae Rhizoma*, *Smilax nipponica*, *Cicadae Periostracum*, and *Crataegi Fructus* (Table 1). In our previous research, we confirmed that Sangdantongluo granule can relieve spasticity of hemiplegia limbs and improve motor performance in PSS patients, but with poor supporting evidence. Therefore, we prepare to conduct a multicenter, randomized, double-blind and placebo-controlled study to evaluate the clinical efficacy and safety of Sangdantongluo granule in the treatment of PSS, which may be a novel proposed approach for PSS.

1.1. Objectives

The purpose of this study is to evaluate the clinical efficacy and safety of Sangdantongluo granule. Hypothesis of this study is that spasticity of hemiplegia limbs can be relieved by Sangdantongluo granule in PSS patients, compared with placebo.

1.2. Trial design

This is a multicenter, randomized, double-blind and placebo-controlled clinical trial. The aim of this trial is to evaluate the clinical efficacy and safety of Sangdantongluo granule in the treatment of PSS. The flow of this trial is presented in Fig. 1.

2. Methods: Participants, interventions and outcomes

2.1. Study setting

The clinical trial will be conducted at the Hunan Academy of Chinese Medicine Affiliated Hospital, Liling Hospital of Traditional Chinese Medicine and Ningxiang Hospital of Traditional Chinese Medicine in China, with a target sample of 132 participants.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

- (1) Western medicine diagnosis conforms to the diagnostic criteria of cerebral infarction;
- (2) TCM syndrome meets the criteria of yin deficiency and blood stasis syndrome;
- (3) Patients with limb hemiplegia and spasticity: the motor function evaluation criteria of hemiplegia in Brunnstrom 6 stage are above stage III, modified Ashworth score (MAS) ≥ 1 , and \leq grade 3;
- (4) Age ≥ 18 years and ≤ 80 years old;
- (5) conscious patients (GCS score = 15);
- (6) Duration ranges from 15 days to 90 days;
- (7) Patients who had not participated in other clinical trials in the last 3 months;
- (8) Patients or their family members agreed and signed informed consent.

Table 1

Components of Sangdantongluo granule.

Chinese name	Latin name	English name	Plant part
Sangshen	<i>Mori Fructus</i>	Mulberry	Fruits
Gouqizi	<i>Lycii Fructus</i>	Barbary wolfberry fruit	Fruits
Danshen	<i>Salviae Miltiorrhizae Radix Et Rhizoma</i>	Danshen root	Root
Dilong	<i>Lumbricus, Siegesbeckiae Herba</i>	Pberetima	Dry body
Baishao	<i>Paeoniae Radix Alba</i>	Debark peony root	Root
Tianma	<i>Gastrodiae Rhizoma</i>	Tall gastrodia tuber	Tuber
Dashenjin	<i>Smilax nipponica</i>	Large stretching bar	Root
Chantui	<i>Cicadae Periostracum</i>	Cicada slough	Carapacehard outer shell
Shanzha	<i>Crataegi Fructus</i>	Hawthorn fruit	Fruits

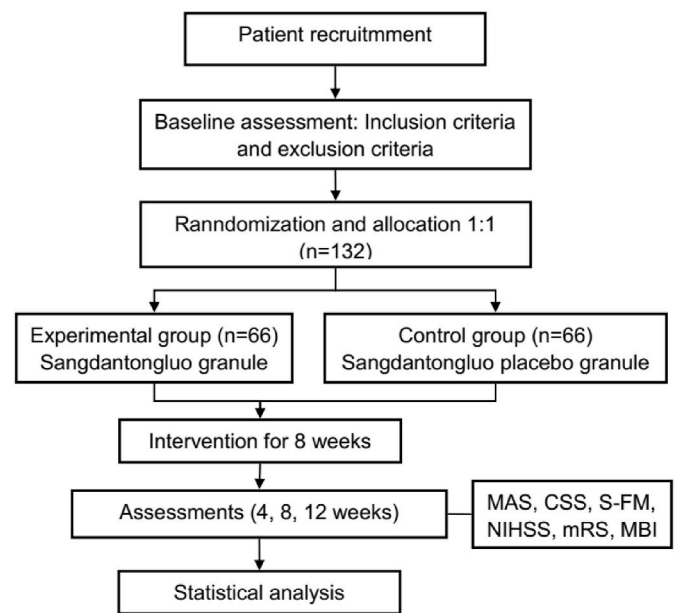


Fig. 1. Flow diagram of the trial process. MAS, Modified Ashworth Scale; CSS, Composite Spasticity; S-FM, Simplified Fugl-Meyer; NIHSS, National Institute of Health Stroke; mRS, Modified Rankin Scale; MBI, Modified Barther Index.

2.2.2. Exclusion criteria

- (1) Previous motor dysfunction, such as rheumatoid arthritis, limb surgery, joint deformities, multiple sclerosis, spinal cord injury, or neuromuscular lesions that affect limb activity;
- (2) Patients with a history of stroke and limb spasticity;
- (3) Patients with severe hepatorenal insufficiency (defined as ALT >2 times the normal upper limit or AST >2 times the normal upper limit). Severe renal insufficiency is defined as Cr > 1.5 times normal upper limit);
- (4) Complicated with other life-threatening diseases such as severe heart, liver, kidney and endocrine diseases with an expected survival time of less than 3 months;
- (5) Inability to understand and/or follow up research procedures and/or follow-up due to mental illness, cognitive or emotional disorders;
- (6) Allergic to Sangdantongluo granule;
- (7) Pregnant or lactating women.
- (8) Ischemic stroke caused by other non-arteriosclerosis, such as intracranial tumor, heart disease, blood disease, brain trauma and so on.

2.3. Who will take informed consent?

Patients with PSS will obtain written document about the study and determine whether they agree to sign the informed consent form to take part in this study.

2.4. Additional consent provisions for collection and use of participant data and biological specimens

Participants will be confirmed whether their clinical data can be used

or shared by related organization.

2.5. Interventions

2.5.1. Explanation for the choice of comparators

The Sangdantongluo granule placebo was chosen as the comparator to give evidence of the clinical efficacy and safety of Sangdantongluo granule in the treatment of PSS.

2.5.2. Intervention description

Eligible participants will be randomly distributed to experimental group or control group in a ration of 1:1. All participants will receive standard conventional treatments, under the Chinese Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack 2014 and Chinese Guidelines for early rehabilitation of stroke [9, 10]. Standard conventional treatments in the trial as follows:

- (1) Risk factor control: blood pressure, blood glucose and blood lipid management, smoking cessation, etc;
- (2) Antiplatelet agents: aspirin (100 mg, once per day) and/or clopidogrel (75 mg, once per day);
- (3) Conventional rehabilitation: anti-spasticity limb position, joint mobility training, and spastic muscle stretching slowly.

The experimental group will be treated by Sangdantongluo granule for 2 months twice a day orally on the basis of standard conventional treatments. While the control group will be treated by placebo granule, which be made from starch with the similar appearance, color, and odor also for 2 months twice a day orally.

2.6. Criteria for discontinuing or modifying allocated interventions

The criteria for discontinuation are as follows:

- (1) Condition aggravation during the study;
- (2) Participants who develop serious complications;
- (3) Participants with poor compliance, such as the use of experimental drug can not reach 80%;
- (4) Cases of breaking the blind or urgently unblinding;
- (5) Participants withdraw from the trial voluntarily.

2.7. Strategies to improve adherence to interventions

The number and time of taking medicine by every participant will be recorded. Similarly, unused drugs will be required to be returned and recorded during each visit.

2.8. Relevant concomitant care permitted or prohibited during the trial

Conventional rehabilitation and antiplatelet agents will be decided by physicians, and other TCM with the effect of nourishing Yin and promoting blood circulation is prohibited.

2.9. Provisions for post-trial care

Not applicable, there is no prospective harm from this trial.

3. Outcomes

3.1. Primary outcome measures

The primary measure of our study is the Modified Ashworth Scale (MAS), which to evaluate spasticity of hemiplegia limb at baseline, 1 month, 2 months, and 3 months after treated with Sangdantongluo granule. The MAS score ranges from 0 to 4, and the higher score indicates more severe spasticity [11].

3.2. Secondary outcome measures

- (1) Composite Spasticity Scale (CSS), to evaluate the spasticity of lower limb at baseline, 1 month, 2 months, and 3 months after treated with Sangdantongluo granule.
- (2) Simplified Fugl-Meyer Motor Scale (S-FM) [12], to assess the movement at baseline, 1 month, 2 months, and 3 months after treated with Sangdantongluo granule.
- (3) National Institute of Health stroke scale (NIHSS), to assess the neurological deficit at baseline, 1 month, 2 months, and 3 months after treated with Sangdantongluo granule.
- (4) Modified Rankin Scale (mRS), to evaluate the neurofunctional recovery at baseline, 1 month, 2 months, and 3 months after treated with Sangdantongluo granule.
- (5) Modified Barther Index (MBI), to evaluate the activities of daily living at baseline, 1 month, 2 months, and 3 months after treated with Sangdantongluo granule.
- (6) Surface electromyography, to evaluate the spasticity of hemiplegia limb at baseline, 2 months after treated with Sangdantongluo granule.

3.3. Participant timeline

Participant recruitment will begin in December 2021 and will end in December 2023. Time schedule of enrolment, interventions, assessments, and visits for participants are listed in Table 2.

3.4. Sample size

According to the literature, "Meng Wang, Shouguo Liu, Zhihang Peng et al. Tibetan Medicated Bathing Therapy for Patients With Post-stroke Limb Spasticity: A Randomized Controlled Clinical Trial" [13]. After the combined treatment of Tibetan medicated bathing therapy and conventional rehabilitation for 3 months, MAS changes were 0.27 ± 0.66 in conventional rehabilitation group, and 0.65 ± 0.75 in Tibetan medicated bathing group. We believe that Sangdantongluo granule should increase the change value of MAS by 0.1 compared with the Tibetan medicine bathing studied by Wang et al. With $\alpha = 0.025$ and test efficiency $1 - \beta = 0.8$, we will require at least 112 subjects. Considering the 15% attrition rate and the rounding principle, 132 participants in total (66 in each group) will be enrolled.

3.5. Recruitment

Three strategies will be undertaking to guarantee adequate participant enrolment:

- (1) posting recruitment advertisement in conspicuous places in hospital;
- (2) publishing and disseminating recruitment ads through WeChat, a popular social software in China;
- (3) introducing the clinical trial to PSS patients through the physician.

3.6. Assignment of interventions: allocation

3.6.1. Sequence generation

By using the method of block randomization, the random number grouping table is generated with the process statement of the SAS statistical software Proc Plan, and then the random assignment scheme is formed. The random allocation scheme, the selected area length and random initial seed parameters were taken as blind bottom, sealed and hidden in an opaque envelope, and handed over to the unit in charge of the project for safekeeping. In this study, patients were included and drug numbers were issued strictly according to the order of random assignment table numbers. The online randomization system was used

Table 2
Schedule of enrollment and assessments.

Time	Screening	Baseline	Treatment 1	Treatment2	Post-treatment follow-up
	D ₋₅ -D ₀	D ₁	4 weeks	8 weeks	12 weeks
Informed consent	✓				
Inclusion/exclusion	✓				
Demographic data	✓				
Medical history	✓				
Electrocardiograph	✓			✓	
Lab examination	✓			✓	
MAS		✓	✓	✓	✓
S-FM		✓	✓	✓	✓
CSS		✓	✓	✓	✓
NIHSS		✓	✓	✓	✓
mRS		✓	✓	✓	✓
MBI		✓	✓	✓	✓
Randomization		✓			
Adverse events		Record at any time			
Concomitant medication collection		✓	✓	✓	

Lab examination including: blood routine, liver and kidney function, cardiac enzyme, blood glucose, blood lipid, urine routine; MAS, Modified Ashworth Scale; S-FM, Simplified Fugl-Meyer; CSS, Composite Spasticity; NIHSS, National Institute of Health Stroke; mRS, Modified Rankin Scale; MBI, Modified Barther Index.

for the implementation of randomization. During the research process, researchers logged in the system to apply for the randomization codes assigned by the system in order.

3.7. Concealment mechanism

The random coding table will be generated by the central random platform and sealed by the GCP specialist in Hunan Academy of Chinese Medicine Affiliated Hospital, which will be submitted to the project leader for preservation. The drugs will be packaged and confirmed as a blinded treatment by a GCP specialist; the random codes will be mentioned on the drugs and the box label.

3.8. Implementation

The allocation sequence will be generated by professor Linyong Xu's team, an eminent statistician of Central South University in China. Neither the researcher nor the participants know the random sequences.

3.9. Assignment of interventions: Blinding

3.9.1. Who will be blinded

ALL researcher, participants, and statistician will be blinded throughout the course of trial.

3.10. Procedure for unblinding if needed

For emergency blinding, there will be an emergency envelope for every case, which is recorded the information about the coding and groups. It is necessary to check the drugs used by the patients in case of any serious event, and patients need to be treated. The investigator should report to the project leader before unblinding. The project leader decides to initiate unblinding and open the corresponding emergency envelope.

3.11. Patient and public involvement

Patients and public were not involved in the design of this study.

3.12. Data collection and management

3.12.1. Plans for assessment and collection of outcomes

In this 12-week trial, all participants will be treated with the Sangdantongluo granule or placebo for 8 weeks, with follow-up continuing for another 4 weeks. Independent assessors at each center, who were

trained before enrollment, will be responsible for duplicate measurements including MAS, CSS, S-FM, NIHSS, mRS, MBI, and standardized assessment of surface electromyography at 4 weeks, 8 weeks, and 12 weeks. Data will be recorded in the online electronic data collection system (EDC).

3.12.2. Plans to promote participant retention and complete follow-up

All investigators and doctors will be advised to treat the participants in a friendly and respectful way and encourage them to participate. All researchers also will be advised provide health consultation or pre-registration of specialist outpatient. The patients' round-trip fare will be reimbursed, which encourage them to finish the follow-up. The researchers will send reminders to the patients 2–3 days before each follow-up.

4. Data management

The electronic data collection system (EDC) will be used for on-line data acquisition in our clinical trial. In order to ensure the security and privacy of the original data, the research team will arrange full-time clinical research coordinator for data entry to avoid problems related to data transmission. The data management schedule will be arranged by the data administrator prior to the trial, which containing research objectives, general design, EDC system administrator, research man, data administrator, statistical analyst, data validation, database locking, and data security. After the completion of data management, the data management report will be written by the data administrator, and the statistical analysis will be conducted after the approval of the research institution, statistician and bid sponsor.

5. Confidentiality

The name and identity card number of patients will not be recorded in the data collection. The ID of patients will be showed initials, and outpatient or inpatient number. The researchers should not discuss the patients' condition and information in public areas, and patient data cannot be released in the media or on the internet. All documents will be stored confidentially and will only be accessible to members of the trial team. The online EDC will be assigned specific permissions to the different groups of researchers in the project to ensure the security and confidentiality of data. All data collected in the system will be backed up with reliable data and privacy security mechanisms, and desensitization technology will be adopted to ensure absolute privacy of the data of project participants. The data will be made available to other researchers upon request after the analyses and publication of primary

findings.

6. Statistical methods

6.1. Statistical methods for primary and secondary outcomes

Statistical analysis will be carried out by a professional team, who blinded to the whole course of the trial. The qualitative data of the two groups will be compared and analyzed by using chi-squared test or Wilcoxon test. And the quantitative data in accordance with the normal distribution will be compared and analyzed by using Student's t tests, whereas, the quantitative data which does not comply with the normal distribution will be compared and analyzed by using Wilcoxon test. The two-sided test will be adopted in the testing of hypotheses, and the test statistics and their corresponding P values will be offered. Two-side P value of ≤ 0.05 is regarded as statistically significant, and $P \leq 0.01$ as highly statistically significant.

6.2. Interim analyses

We will begin to conduct statistical analysis when the sample reaches 66. Principal investigator will decide whether to continue the experiment, according to the interim results.

6.3. Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Participants who discontinued will be excluded from statistical analysis, and missing data will be estimated by multiple imputation.

6.4. Plans to give access to the full protocol, participant level-data and statistical code

The full protocol, participant level-data and statistical code will be authorized by the corresponding author.

6.5. Oversight and monitoring

6.5.1. Composition of the coordinating centre and trial steering committee

The coordinating center is set up in Neurology Department of Hunan Academy of Chinese Medicine Affiliated Hospital. The primary investigator is the director of the department, who in charge of identifying potential recruits, acquiring consent, and messaging to the trial steering committee. The trial steering committee is set up in Good Clinical Practice office of Hunan Academy of Chinese Medicine Affiliated Hospital, whose responsibilities including revise and agreement of the protocol, supervising trial, reviewing progress of the trial and the paper for publication.

6.5.2. Composition of the data monitoring committee, its role and reporting structure

The data monitoring committee (DMC), who independent from the sponsor and free from competing interests, will ensure the interests of participants, the accurate of trial sheet and reported data, and follow of the registered protocol.

6.5.3. Adverse event reporting and harms

Adverse events, including symptom, time, duration, interventions taken and outcome, will be recorded and presented to researchers and ethics committee, who will decide whether to discontinue the treatment.

6.5.4. Frequency and plans for auditing trial conduct

The trial management team will meet every three months to review the study, and ethics committee will meet every six months to review the trial conduct.

6.5.5. Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

Once there are significant changes to the protocol, we will inform the sponsor, ethics committees and sub-centers.

6.5.6. Dissemination plans

The results will be published in peer-reviewed academic journals and shared with the general public and medical professionals.

7. Discussion

High cost on PSS brings out weightily economy burden for government, family and patients, due to the highly disability. Direct costs of PSS patients are fourfold as high in comparison with the stroke patients who do not have spasticity for the first year after stroke, which mainly because of the frequently hospitalization of PSS patients [14,15]. Consequently, effective spasticity management strategies are crucial to relieve the financial burden and elevate the quality of life of patient with PSS.

TCM is a generally accepted treatment with minimal side effects for PSS patients in China. There are increasing quantities of clinical studies on the treatment of PSS with TCM, such as orally Chinese herbal formulas, Chinese massage, acupuncture, medicated bath and so on [16–18]. The mechanism is related to modulation of gamma-aminobutyric acid and glutamate levels, reducing inflammatory response, and decreasing muscular tension [19–21]. Systematic review shows that oral or topical application of TCM is beneficial to relieving spasticity of the upper and lower limbs in PSS patients. Whereas, the methodological quality of these clinical researches is quite low, lacking suitable means for random sequence generation, allocation concealment. Most importantly, only a few studies had used appropriate placebo to blind researchers or participants [8].

Sangdantongluo granule (Z20210481000), a modern patent TCM, is mainly composed of Mori Fructus, Lycii Fructus, Salviae Miltiorrhizae Radix Et Rhizoma, and other 7 Chinese medicinal herbs. It is widely used in clinical practice to treat stroke, particularly PSS. Our previous research had confirmed that Sangdantongluo granule can relieve spasticity of hemiplegia limbs and improve motor performance in PSS patients. For the purpose of evaluating the clinical efficacy and safety of Sangdantongluo granule, we intend to conduct a multicenter, randomized, double-blind and placebo-controlled clinical study. We are aiming at providing high-quality evidence for Sangdantongluo granule in the treatment of PSS.

Abbreviations

PSS: Post-stroke spasticity; TCM: Traditional Chinese medicine; GCS: Glasgow Coma Scale; CSS: Composite Spasticity; S-FM: Simplified Fugl-Meyer; MAS: Modified Ashworth Scale; MBI: Modified Barther Index; mRS: Modified Rankin Scale; NIHSS: National Institute of Health Stroke; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; Cr: Creatinine; EDC: Electronic data collection system; DMC: Data monitoring committee.

Posted history

This manuscript was previously preprinted posting on Research Square: doi: <https://doi.org/10.21203/rs.3.rs-679035/v1>.

Authors' contributions

DW is the Chief Investigator. DW, LX, ZY, and YX designed the study. LX, YX, JJ, TY, RF, and YL will conduct the study. GM, RF and YX will analyze statistical data. All authors have read and agreed with the final manuscript.

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Availability of data and materials

All data will be provided by the corresponding author without any restriction.

Ethics approval and consent to participate

The trial and protocol were approved by the Ethics Committee of Hunan Academy of Chinese Medicine Affiliated Hospital (No. [202102] 20). The participants will be informed the trial protocols and consent before the trial begins, and their personal details will be kept confidential.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

No data was used for the research described in the article.

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None.

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