

Shuxuetong for Prevention of recurrence in Acute Cerebrovascular events with Embolism (SPACE) trial: rationale and design

Hong-Qiu Gu ¹, Xue-Wei Xie,¹ Jing Jing,¹ Xia Meng,¹ Wei Lv,¹ Jian-Dong Yu,¹ Xiang-Ping Lv,¹ Hao Li ¹, Yi-Long Wang,^{1,2} Yong-Jun Wang ^{1,2,3,4}

To cite: Gu H-Q, Xie X-W, Jing J, et al. Shuxuetong for Prevention of recurrence in Acute Cerebrovascular events with Embolism (SPACE) trial: rationale and design. *Stroke & Vascular Neurology* 2020;0. doi:10.1136/svn-2019-000293

H-QG, X-WX, JJ and XM contributed equally.

Received 21 October 2019
Revised 23 November 2019
Accepted 6 December 2019



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¹China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

²Vascular Neurology, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

³Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, Beijing, China

⁴Center for Stroke, Beijing Institute for Brain Disorders, Beijing, China

Correspondence to

Dr Yong-Jun Wang;
yongjunwang@nccrncd.org.cn

ABSTRACT

Backgrounds Embolic stroke is one of the main mechanisms of ischaemic stroke. Even if treated with recommended antithrombotic agents, stroke recurrence remains high. The Shuxuetong injection, a purified extract of traditional Chinese medicine widely used for thrombus diseases in clinical practice in China, could be a promising agent to prevent stroke recurrence.

Aims To describe the design of the Shuxuetong injection for prevention of recurrence in acute ischaemic stroke with embolism mechanisms.

Design The Shuxuetong for Prevention of recurrence in Acute Cerebrovascular events with Embolism (SPACE) trial is a multicentre, randomised, double-blind, placebo-controlled, parallel-group, superiority trial to evaluate the efficacy and safety of Shuxuetong injection in reducing recurrence or silent new ischaemic lesions on patients with acute embolic stroke within 10 days. An estimated 2416 patients with embolic stroke within 72 hours of symptom onset from 80 hospitals will be randomly assigned to one of two groups receiving Shuxuetong injection or placebo injection for 10 days. The primary endpoint is symptomatic or asymptomatic new cerebral infarction within 10 days after randomisation.

Conclusion The SPACE Trial will provide valuable evidence for the efficacy and safety of Shuxuetong injection for the prevention of stroke recurrence in patients with imaging-defined embolic stroke.

Clinical trial registration NCT03090113.

INTRODUCTION AND RATIONALE

Stroke is the second leading cause of death worldwide and the leading cause of death in China.^{1–4} Ischaemic stroke can be further divided into embolic stroke and non-embolic stroke by stroke mechanisms.⁵ Different stroke subtypes require different strategies for acute management and secondary prevention of stroke.⁶ Embolic stroke, the most common subtype of ischaemic stroke, caused by brain embolism which can originate from any of several well established potential embolic sources, including cardiogenic embolism (the mitral or aortic valves or the left cardiac chambers, etc), artery-to-artery embolism

(proximal cerebral arteries or the aortic arch, etc) and other causes (paradoxical embolism, etc).⁵

American Heart Association/American Stroke Association guidelines recommend antiplatelet treatment after non-cardioembolic ischaemic strokes, and anticoagulant therapy after cardioembolic ischaemic strokes.^{7–8} Although patients receive the recommended therapy, the risk of recurrence remains high. Previous studies showed that dual antiplatelet therapy with clopidogrel plus aspirin was more effective than aspirin alone in patients with transient ischaemic attack and ischaemic stroke due to artery-to-artery embolism.^{9–10} Furthermore, the Aortic Arch Related Cerebral Hazard Trial showed a potential benefit in dual antiplatelet treatment compared with warfarin in patients with embolism of the thoracic aorta.¹¹ Long-term oral anticoagulation is another increasing treatment option for embolic stroke.¹² However, concerns regarding extended use of dual antiplatelet or anticoagulant persist due to increased risk of bleeding. Therefore, more effective strategies for patients with embolic stroke need to be explored.

The Shuxuetong injection, a purified extract of leech and earthworm, has been widely and safely used to treat thrombus diseases in clinical practice.⁵ In view of traditional Chinese medicine, both leech and earthworm have the effects of promoting blood flow, activating meridians and dispersing blood stasis. The main components of Shuxuetong are hirudin (a specific thrombin inhibitor) and lumbrokinase (a strong fibrinolytic enzyme); both of them have a substantial effect on improving blood flow.¹³ Thus, the Shuxuetong injection has been widely used for patients with acute ischaemic stroke. However, the effect of Shuxuetong injection for embolic stroke has not been well evaluated in large sample-sized,

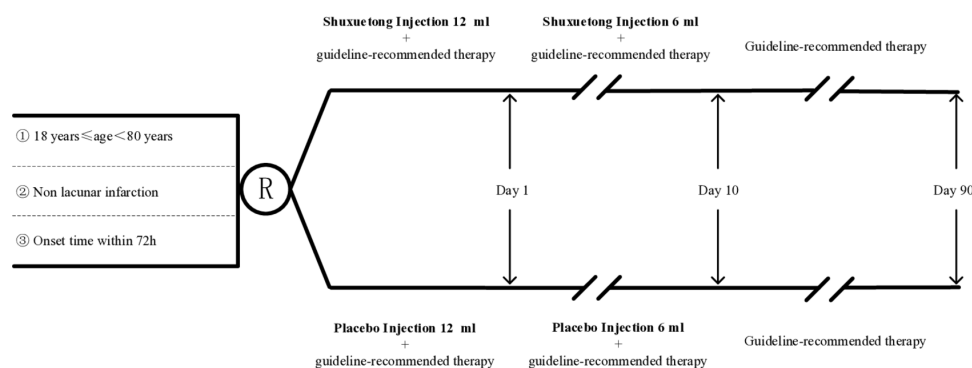


Figure 1 Flow chart of the Shuxuetong for Prevention of recurrence in Acute Cerebrovascular events with Embolism (SPACE) trial.

well-designed randomised clinical trials with clinical end points such as stroke recurrence, bleeding, and so on.¹⁴

This study described the rationale and design of the Shuxuetong for Prevention of recurrence in Acute Cerebrovascular events with Embolism (SPACE) trial to investigate whether Shuxuetong injection was superior to placebo injection in reducing the 10-day symptomatic or asymptomatic new cerebral infarction for patients with acute embolic stroke.

METHODS

Design

SPACE is a multicentre, randomised, double-blind, placebo-controlled, parallel-group, superiority trial. Patients are randomised 1:1 to Shuxuetong injection or placebo injection (normal saline) within 72 hours of the onset of symptoms of acute embolic stroke and followed for 90 days after randomisation (figure 1). Blood samples of all patients were collected at baseline and 10 days after randomisation. All patients included in the current study routinely completed image evaluation during hospitalisation as follows: brain MRI (3.0T or 1.5T) and diffusion-weighted MRI (DWI) and fluid-attenuated inversion recovery (FLAIR) sequence must be included as the Digital Imaging and Communications in Medicine (DICOM) format. Image data were collected and analysed in the image research centre of Beijing Tiantan Hospital centrally. All patients provided written informed consent. All outcomes and major bleeding events will be adjudicated by an independent clinical event adjudication committee.

Patient population

For this randomised clinical trial, an estimated 2416 subjects will be enrolled from approximately 80 sites in China. The detailed inclusion and exclusion criteria are listed in box 1.

Randomisation

The randomisation will be stratified by participating hospitals. In each stratum, patients will be randomly assigned to the Shuxuetong injection treatment group or placebo injection treatment group in blocks to ensure

approximate balance (1:1) allocation. The randomisation code list will be generated centrally by an independent statistician with SAS V.9.4. The patient kits will be packaged in accordance with this randomisation code list. Both Shuxuetong injections and placebo injections will be wrapped in opaque plastic bags in order to not reveal the colour of these two injections by independent nurses who are not involved in this study. The first dose of study medication is administered to the patient as soon as possible after randomisation at visit 1.

Treatment

At visit 1 (randomisation), eligible patients are randomly assigned to one of two treatments:

- Treatment 1: Shuxuetong injection 12 mL loading dose on day 1, followed by 6 mL daily doses from day 2 to day 10 in addition to guideline-recommended therapy.
- Treatment 2: Placebo injection 12 mL loading dose on day 1, followed by 6 mL daily doses from day 2 to day 10 in addition to guideline-recommended therapy.

The first dose of study medication is given as soon as possible at visit 1. Subsequent maintenance doses are given in the following days. At the end of 10 days of study treatment, patients are treated with guideline-recommended therapy.

Primary outcomes

The primary outcome of the trial is new symptomatic or asymptomatic ischaemic lesion(s) within 10 days, as confirmed by DWI or FLAIR at baseline and 10 days after randomisation. The new ischaemic lesion was defined as¹ new lesions on DWI or FLAIR image outside the region of the acute lesion on baseline DWI/FLAIR image, or² new lesions on DWI or FLAIR with decreased apparent diffusion coefficient within the region of the acute lesion on baseline DWI.¹⁵

Secondary outcomes

The secondary end points within 10 days include (1) Symptomatic ischaemic stroke. (2) Asymptomatic ischaemic stroke. (3) The National Institutes of Health Stroke Scale (NIHSS) Score increase. Other secondary end points at 90

Box 1 Inclusion and exclusion criteria

Inclusion criteria

- ▶ At least 18 years old and less than 80 years old.
- ▶ Acute ischaemic stroke, brain MRI showed non-lacunar infarction (subcortical infarction ≤ 1.5 cm).
- ▶ Onset within 72 hours.
- ▶ Patients or their family members are willing to sign the informed consent form.

Exclusion criteria

- ▶ Intracranial haemorrhage: intracerebral haemorrhage, subarachnoid haemorrhage and so on.
- ▶ Transient ischaemic attack.
- ▶ Lacunar infarction.
- ▶ History of acute stroke within 6 months.
- ▶ Clear diagnosis of other causes of ischaemic stroke (arterial dissection, arteritis, vasospasm, etc).
- ▶ The acute infarct lesion is more than one-half lobe in size.
- ▶ Preceding modified Rankin Scale Score ≥ 2 .
- ▶ Cumulative usage of traditional Chinese medicine activating blood circulation more than three times after onset, including but not limited to Danhong, Xueshuantong, Xuesaitong, Ginkgo biloba, sodium ozagrel, Salvia miltiorrhiza, ligustrazine, Erigeron breviscapus, and so on.
- ▶ Chronic liver disease, liver and kidney dysfunction, lifted alanine aminotransferase (>3 times the upper limits of normal), lifted serum creatinine (>2 times the upper limits of normal).
- ▶ History of coagulopathy, systemic bleeding, thrombocytopenia or neutropenia.
- ▶ Blood pressure $<90/60$ mm Hg or $\geq 220/120$ mm Hg after treatment.
- ▶ Patients with serious heart or lung disease, in the judgement of clinical study staff, would not be suitable to participate in the trial.
- ▶ Patients with atrial fibrillation who were scheduled or likely to receive anticoagulant therapy with unfractionated heparin or low molecular weight heparin within 2 weeks after randomisation.
- ▶ A medical condition likely to limit survival to less than 3 months or any other condition judged by the clinic team to likely limit the adherence to study procedures.
- ▶ Known allergies for ingredients of the drug, allergy history for food or drug.
- ▶ Pregnant, currently trying to become pregnant, or of childbearing potential and not using birth control.
- ▶ Participation in another clinical trial within 30 days.
- ▶ Unable to understand and/or comply with the study procedures and/or follow-up studies due to mental illness, and cognitive or emotional disorders.

days after stroke onset include (1) Recurrent symptomatic stroke. (2) Recurrent symptomatic ischaemic stroke. (3) Combined vascular events (including recurrent symptomatic stroke, myocardial infarction or vascular death). (4) Disability or death (defined as modified Rankin Scale range from 3 to 6).

Safety outcomes

The primary safety outcome is major bleeding events, including fatal or life-threatening major bleeding and other major bleeding events, using the PLATElet inhibition and patient Outcomes Study definition.¹⁶ Other safety outcomes within 10 days include (1) Symptomatic

intracranial haemorrhage. (2) Asymptomatic intracranial haemorrhage. (3) All-cause mortality. (4) Adverse events (AE). (5) Severe adverse events (SAEs). Safety outcomes at 90 days after stroke onset include (1) Symptomatic intracranial haemorrhage. (2) All-cause mortality. (3) AEs. (4) SAEs. SAEs were defined as vital events leading to death, threatening life, prolonged hospitalisation, persistent or severe disability or dysfunction, congenital abnormalities or birth defects, or other medical events that can be identified as SAEs, according to the researchers.

Sample size

The estimated sample size for the study is 2416 subjects. With a sample size of 2416 patients, the study has 90% power to detect a relative risk reduction of 20% with an assumed 30% event rate of primary outcome in the control group at two-sided α of 0.05 with the t-test for two independent proportions. Sample size calculation is based on the primary outcome with inflation to account for 5% loss to follow-up.

Statistical analyses

The results will be analysed according to the 'intention-to-treat' principle. However, sensitivity per-protocol analysis may also be conducted. Baseline characteristics will be summarised by treatment groups. For the primary hypothesis, the event rate of a composite outcome of symptomatic and asymptomatic new cerebral infarction within 10 days after randomisation, lower in treatment groups than that in control group, will be tested by χ^2 tests. Binary logistic regression will be used as well to estimate OR and 95% confidence interval (CI). Shuxuetong will be considered superior to placebo with regard to the primary end point if the upper limit of the 95% CI for OR is less than 1.00. χ^2 tests and binary logistic regression will be used to compare secondary primary and safety outcomes with in 10 days between treatment groups. The cumulative incidences of secondary primary outcomes at 90-day will be estimated by the Kaplan-Meier method and will be compared using the log-rank test between treatment groups. The Cox proportional hazards model will also be used to estimate the hazard ratio (HR) and 95% CI. No internal analyses are planned in this study.

Subgroup analyses

In order to examine the consistency of the treatment effect, the following subgroup analyses are planned (with the primary study outcome as the dependent variable): age (>65 years vs ≤ 65 years), sex (female vs male), body mass index (≥ 25 vs <25), systolic blood pressure group (≥ 140 mm Hg vs <140 mm Hg), diastolic blood pressure (≥ 90 mm Hg vs <90 mm Hg), disease history of hypertension, diabetes mellitus, stroke, smoking, hypercholesterolaemia, NIHSS Score at admission (≥ 3 vs <3), Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, main arterial stenosis, infarction pattern, cryptogenic embolism and symptom onset to randomisation time. No α adjustments

are planned; therefore, all subgroup analysis will be interpreted as explorative analysis.

DISCUSSION

People who experience an embolic stroke are at substantial risk for major stroke and other ischaemic events in the subsequent days, even if antithrombotic agents are administered. China has extensive experience in the use of traditional Chinese medicines for stroke therapy. There are over 100 traditional Chinese medicines used for stroke therapy in China, and the Shuxuetong injection is one of the most widely used therapy since the year 1999. However, in the era of evidence-based medicine, traditional Chinese medicine has encountered a strong challenge from clinicians due to a shortage of evidence-based efficacy.^{17 18} Although preclinical researches on Shuxuetong injection can be found in the literature, the effective components and related structures and formulas are not well determined yet. Published clinical research evaluated nerve injury, blood lipid metabolic indexes and coagulative function indexes.¹⁴ However, high-level evidence from the large sample size, well-designed randomised clinical trials with primary clinical end points (such as stroke recurrence, bleeding, etc) are limited. Therefore, whether the result of the SPACE Trial is positive or negative, it will provide valuable evidence of the test for efficacy and safety of the Shuxuetong injection for prevention of symptomatic or asymptomatic new cerebral infarction after an acute embolic stroke.

Twitter Yi-Long Wang @yilong

Acknowledgements The authors thank all participating hospitals, their physicians, nurses, and other personnel who participated in the study, and the SPACE Steering Committee members.

Contributors H-QG, X-WX, JJ, HL, Y-LW and Y-JW conceived the study and oversaw all scientific aspects of its implementation. H-QG, X-WX and JJ drafted the manuscript. XM, WL, X-PL and J-DY recruited hospitals and operated the SPACE programme.

Funding This work was supported by grants from the Ministry of Science and Technology of the People's Republic of China [2017YFC1310901, 2017YFC1307905, 2018YFC1312903], grants from Beijing Municipal Administration of Hospitals' Mission Plan [SML20150502], grants from National Natural Science Foundation of China [81600999], grants from Beijing Municipal Science & Technology Commission [D171100003017002, D151100002015003] and grants from National Science and Technology Major Project [2014ZX09201022-010, 2017ZX09304018] and Mudanjiang Youbo Pharmaceutical Co., Ltd.

Competing interests The SPACE programme is an investigator-initiated study and mainly funded by the Ministry of Science and Technology of the People's Republic of China. Mudanjiang Youbo Pharmaceutical Co., Ltd partly funded this programme; however, the company was not involved in the study design, data collection, data cleaning, data analysis, data interpretation and manuscript writing.

Patient consent for publication Not required.

Ethics approval The ethics committee of Beijing Tiantan Hospital, ID: KY2016-045-03.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request at yongjunwang@nccr.cn

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ORCID iDs

Hong-Qiu Gu <http://orcid.org/0000-0003-1608-1856>

Hao Li <http://orcid.org/0000-0002-8591-4105>

Yong-Jun Wang <http://orcid.org/0000-0002-9976-2341>

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