



Efficacy and Safety of Shenqisuxin Granule for Non-ST-segment Elevation Acute Coronary Syndrome: Study Protocol for a Randomized, Double-Blinded, Placebo-Controlled Trial

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Introduction: The Chinese herbal compound formula, Shenqisuxin granule (SQSX), promotes neovascularization and prevents in-stent restenosis in modern pharmaceutical studies and is expected to provide an effective strategy for non-ST-segment elevation acute coronary syndrome (NSTEMACS). Thus, this study aims to examine the efficacy and safety of SQSX for NSTEMACS and initially reveal its mechanism.

Methods/Design: The study is a randomized, double-blinded and placebo-controlled trial. A total of 66 participants will be randomly allocated to one of the following two groups. Participants in the SQSX group will receive conventional treatment plus SQSX, while the placebo group will receive conventional treatment plus placebo, both for 14 days. The primary outcome, hs-CRP, and secondary outcome the Seattle Angina Questionnaire (SAQ) will be assessed at baseline, 7 ± 3 days and 14 ± 3 days. At all visit windows, other indicators including creatine kinase (CK), creatine kinase-myocardial band (CK-MB), cardiac troponins I (cTnI), 12-lead electrocardiograph and the syndrome scores of Qi deficiency and blood stasis will be tested and metagenomic sequencing for intestinal flora will be performed. Echocardiography and safety assessment will be performed at baseline and 14 ± 3 days. Adverse events will be monitored during the trial.

Discussion: The purpose of the study is to examine the efficacy and safety of SQSX to improve NSTEMACS and initially reveal its mechanism.

Trial Registration: China Clinical Trial Registry, ChiCTR2000029226. Registered on January 19, 2020.

Keywords: Shenqisuxin granule, non-ST-segment elevation acute coronary syndrome, intestinal flora, randomized controlled trial, Chinese herbs

INTRODUCTION

Non-ST-segment elevation acute coronary syndrome (NSTEACS) is the most common type of acute coronary syndrome (ACS) (1, 2). Despite proven benefits of leading-edge ACS salvage strategies, NSTEACS has a high 1-year main adverse cardiovascular and cerebrovascular events (MACCE) rate of 8.7%, and is associated with a higher risk of long-term mortality (3–5). Thus, it is vital to improve the secondary prevention of NSTEACS and reduce the incidence of MACCE.

High-sensitivity C-reactive protein (hs-CRP) is regarded as an important indicator of the incidence of MACCE. Systemic vascular inflammation plays multiple roles in the presentation of ACS, and hs-CRP is positively associated with the incidence of future MACCE (6–8). The Seattle Angina Questionnaire (SAQ) is widely utilized in the assessment of angina symptoms. The cTnI is an important biomarker to indicate the progression of acute myocardial ischemia. In addition, the disturbed intestinal flora is implicated in forming atherosclerotic plaques (9, 10). The alterations in the intestinal flora are correlated with coronary artery disease (CAD) severity via the mediation of intestinal flora serum metabolites (11). The level of trimethylamine-N-oxide (TMAO) in NSTEACS patients is significantly higher than that in healthy people and is positively correlated with the risk of MACCE (11, 12). Most studies focus on Chinese herbal compounds that act directly on target cells or organs (13). Emerging evidence indicates that Chinese herbal ingredients cannot be absorbed into the blood circulation directly through digestion (14–16). Therefore, the intestinal flora might be an important pathway for Chinese herbs to function.

The Chinese herbal compound formula, Shenqisuxin granule (SQSX) is a novel patented drug (Chinese patent number ZL202010122712.6) for CAD. It comprises six herbs: Huangqi (Astragal Radix), Danggui (Angelicae Sinensis Radix), Danshen (Salviae Miltiorrhizae Radix Et Rhizoma), Ezhu (Curcuma Rhizoma), Huanglian (Coptidis Rhizoma) and Baizhu (Atractylodis Macrocephalae Rhizoma). Based on our previous pharmaceutical studies, the major ingredients of SQSX can activate phosphatidylinositol 3-hydroxykinase-protein kinase B (PI3K-Akt) signaling pathway and elevate the expression of VEGF mRNA in ischaemic myocardium of rats to promote neovascularization and angiogenesis (17). It can regulate the expression of Ang1/Tie2 and Ang2/Tie2 in hibernating myocardium and promote neovascularization and maturation to improve cardiac function (18). It's also proven that the ingredients of SQSX inhibit the proliferation of vascular smooth muscle cells in the in-stent restenosis minipig model induced by balloon injury, thereby preventing in-stent restenosis (19). At a time when the treatment of NSTEACS has run into a bottleneck, SQSX is expected to provide an effective strategy for further improvement of NSTEACS. Thus, this study aims to examine the efficacy and safety of SQSX for NSTEACS and initially explore its mechanism.

METHODS/DESIGN

Study Design

The randomized, double-blinded and placebo-controlled trial was endorsed by the Ethics Committee of Xiyuan Hospital, China Academy of Chinese Medical Sciences (Version No. XYYY-ASKY-1.1, January 1, 2021), and registered in the Chinese Clinical Trials Registry (ChiCTR2000029226). Our study conforms to the Helsinki Declaration and the Good Clinical Practice guidelines. It follows the Consolidated Standards of Reporting Trials Extension for Chinese Herbal Medicine Formulas 2017 (CONSORT-CHM Formulas 2017) recommendations and the Standard Protocol Items: Recommendations for Interventional Trials statements (SPIRIT) (20, 21). The study is currently underway at the Xiyuan Hospital, China Academy of Chinese Medical Sciences. Altogether 66 participants will be enrolled and randomly allocated to two groups. All participants will receive their respective interventions for 14 days. The clinical evaluations will be conducted at baseline (Visit 1), days 7 ± 3 (Visit 2) and 14 ± 3 (Visit 3), respectively. **Figure 1** depicts a schematic of the study design.

Participants

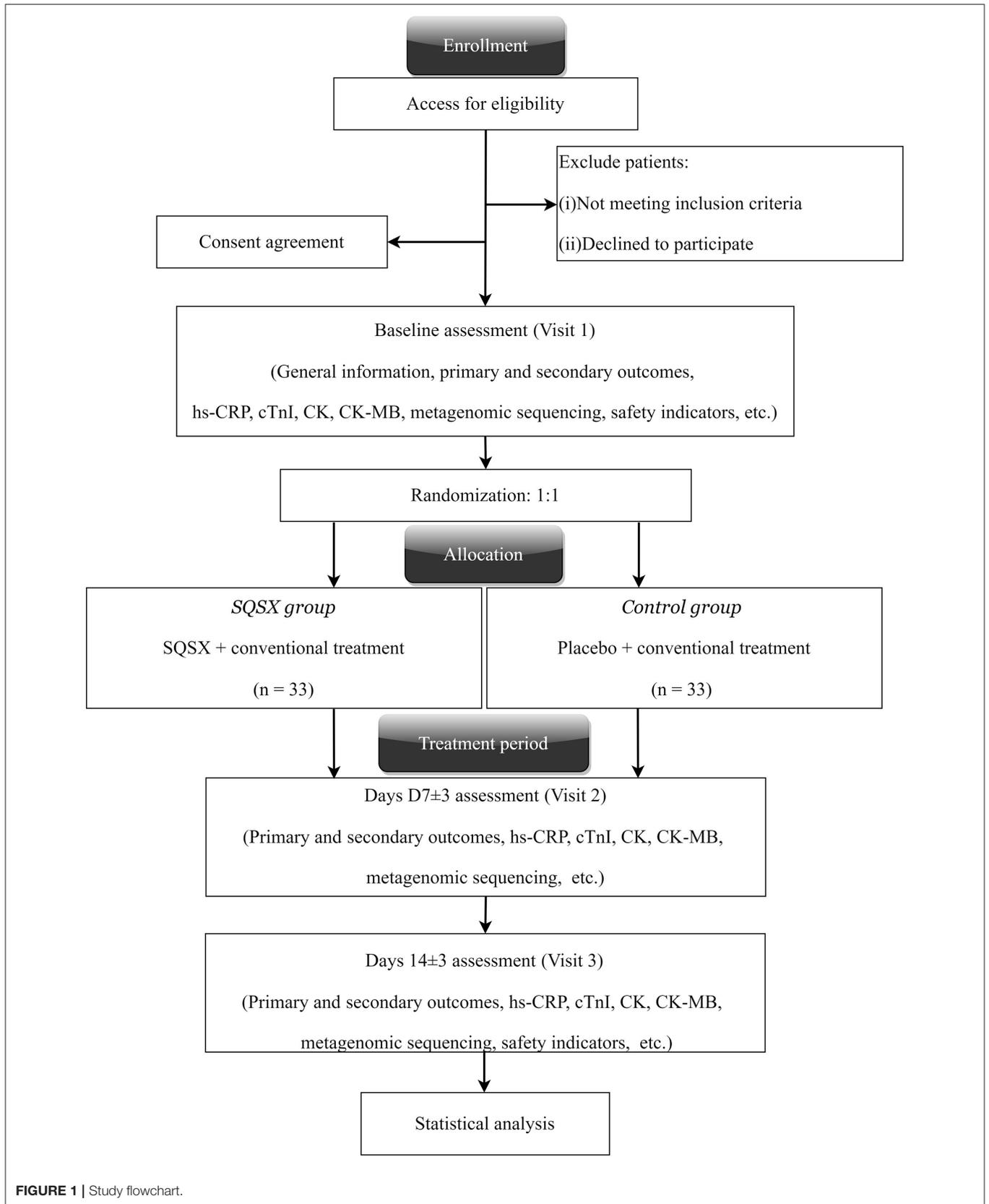
Specially trained research clinicians, the attending physician and general practitioners are responsible for the recruitment. Written informed consent is obtained for entry into the study.

Inclusion Criteria

Subjects who meet all of the following criteria are eligible to participate in the study: (1) diagnosed as unstable angina (UA) or non-ST segment elevated myocardial infarction (NSTEMI) according to the 2015 ESC guidelines for the management of NSTEACS (22); (2) diagnosed as the TCM syndrome of Qi deficiency and blood stasis according to the Guiding Principles For Clinical Research Of New Chinese Medicines (23); (3) age 40–60 years; (4) heart function is Killip grade I-II for subjects diagnosed as NSTEMI; (5) in-hospital patients; (6) written informed consent is obtained.

Exclusion Criteria

Any of the single conditions as follows would be excluded: (1) indication for renal insufficiency, blood serum creatinine (Scr) $> 220 \mu\text{mol/l}$ in males or $> 175 \mu\text{mol/l}$ in females; (2) significant abnormalities in liver function with alanine transaminase (ALT) and aspartate transaminase (AST) are 3 times above the upper bound of normal; (3) systolic pressure $> 160 \text{ mmHg}$ or diastolic pressure $> 100 \text{ mmHg}$ after controlled; (4) diabetic patients with random blood glucose $\geq 13.7 \text{ mmol/l}$ or glycosylated hemoglobin $\geq 9.5\%$; (5) Women who are pregnant, breast-feeding or preparing to be pregnant; (6) combined with acute cerebrovascular disease, severe hematopoietic diseases, psychiatric disorder, or malignant tumor; (7) intestinal disease with inflammation or malabsorption; (8) participated in other clinical trials within 3 months; (9) GRACE score > 140 points (high risk group with 1~3% in-hospital death rate) (24); (10)



immunosuppressants, hormones, drugs for gastrointestinal diseases, and drugs with a direct effect on intestinal flora are not permitted.

Outcomes Measures

The primary outcome, hs-CRP, and secondary outcome the SAQ will be assessed at baseline, 7 ± 3 days and 14 ± 3 days. At all visit windows, other indicators including creatine kinase (CK), creatine kinase-myocardial band (CK-MB), cardiac troponins I (cTnI), 12-lead electrocardiograph and the syndrome scores of Qi deficiency and blood stasis will be tested and metagenomic sequencing for intestinal flora will be performed (25). Echocardiography and safety assessment will be performed at baseline and 14 ± 3 days. All adverse events will be tracked throughout the study. **Table 1** lists the items measured as well as the data collection window.

Adverse Events

Negative or unintended clinical medical effects that occur after treatment are known as AEs, which can be manifested as symptoms, signs, and abnormal clinical or laboratory findings. During the study, all related AEs details will be documented on the CRF. UA/NSTEMI is an urgent condition. Several complications including STEMI, heart failure, malignant arrhythmia and even sudden cardiac death may occur. Therefore, first aid measures will be available under guidelines and standards to ensure the safety of patients.

Gut Microbial Profiling

Metagenomic sequencing will be used to analyze the spectrum of specific intestinal flora in NSTEACS patients after treatment with SQSX, revealing the mechanism of pharmacological effect from the intestinal flora perspective. The fecal collection kit and proper instruction for stool collection will be prepared for participants. Fecal samples will be stored in a laboratory freezer (-80°C) until metagenomic sequencing. The main steps of metagenomic sequencing are as follows: (1) genomic DNA is extracted and purified from feces using the QIAamp DNA kit; (2) genomic DNA is then fragmented to 350-bp by a Covaris crusher; (3) terminal repair, A-tailed, sequencing connector and other steps are performed to prepare a short cDNA library; (4) the library is then sequenced with Illumina HiSeq; (5) the sequence is assembled and finally analyzed for species and functional annotation.

Randomization and Blinding

The randomization will be conducted by the Institute of Clinical Pharmacology of Xiyuan Hospital, China Academy of Chinese Medical Sciences. The SAS software-generated random sequencing in blocks of four was used for randomization. Eligible patients are randomized into the SQSX or control group on a 1:1 basis. Researchers and outcome evaluators involved in this study know nothing about the details of the randomization sequence. All patients and physicians will be unaware of treatment allocation until the end of the study. Urgent letters revealing group and treatment allocation have been prepared.

If an emergency occurs, blind breaking and urgent measures may need.

Data Management and Monitoring

All participant data on the CRF will be input into the clinical trial data management system. To ensure the authenticity, accuracy and completeness of data, several effective procedures are used. First, data cleaning will consider missing data, questionable values and inconsistent dates. After that, the source data will be verified by the supervisor to check for consistency. Third, manual checks. Clinical monitors will be appointed by the quality assurance department of Xiyuan Hospital, China Academy of Chinese Medical Sciences to undertake regular monitoring visits on the trial's progress and completion.

Investigator Training and Quality Control

All investigators engaged in the study will be trained in standard operating procedure (SOP). The training includes screening of eligible subjects, standard collection and storage procedures for stool samples, and the use of evaluation scales, etc. All results will be reported by outcome evaluators trained in SOP standards to ensure their reliability and validity. In addition, to ensure relevant clinical data is collected as planned, researchers will establish close connection with patients through phone and WeChat groups.

Sample Size Calculation

The sample size was estimated using hs-CRP. Currently, the hs-CRP of NSTEACS decreased from 5.30 mg/L to 3.74 mg/L after 14 days of conventional treatment, with a decline rate of 29.43% (26). The hypothesis is that the treatment group could reduce the hs-CRP of NSTEACS by 35%. With a type I error rate of $\alpha = 0.05$ and a power of 80% (a type II error rate of $\beta = 0.2$), one arm requires a sample size of 27. With a 20% drop-out rate, we have to recruit a total of 66 patients. The following is the formula for calculating sample size (27):

$$n = 2 \left[\frac{(u_{\alpha} + u_{\beta})}{\delta/\sigma} \right]^2 + \frac{1}{4} u_{\alpha}^2$$

n , is the sample size required in each group, $\delta = \mu_1 - \mu_2$, is the difference between means of two groups, σ , is the standard deviation, u_{α} and u_{β} are the values of u corresponding to the test level α and type II error probability β , respectively.

Statistical Analyses

An independent biostatistician will perform statistical analysis. The result of recruitment, the specific reasons for data missing and the distribution of each statistical analysis data set will be described. The primary outcome, the change values of hs-CRP from recruitment to day 7 ± 3 , day 14 ± 3 and the day of revascularization, and the secondary outcome, the change scores in five dimensions of SAQ at the same time, are both continuous variables. For comparison between groups, the continuous variables will be described using means \pm SD, median, interquartile range, etc., and the Shapiro-Wilk normality test and Levene test for variance homogeneity will

be performed. A Student *t* test will be used to compare two groups that have a normal distribution with homogeneous variance, otherwise the Wilcoxon rank-sum test will be used. When some continuous variables are converted into categorical variables, these categorical variables will be described using rates, and the chi-square test or Fisher's exact probability method will be used. For comparison within groups, the paired *t* test or Wilcoxon signed-rank test will be used for continuous variables and the McNemar test for categorical variables. If there are baseline imbalances, Cox regression analysis, logistic regression and multivariate analysis of covariance will be used to adjust confounding variables. The longitudinal data with repeated measures will be analyzed using the linear mixed-effects model to assess associations. The safety analysis will tabulate a detailed description of the adverse reactions, adverse events and serious adverse events and compare the difference in incidence between two groups using Fisher's exact probability method. A difference of $P < 0.05$ at two-tailed test will be considered statistically significant in all analyses. The statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

After metagenomic sequencing is completed, microbiota community structures will be compared at different taxonomic levels. The abundance and diversity of intestinal flora will be analyzed. The relationship between microbiota composition and clinical outcomes will be investigated using univariate and multivariate linear and nonlinear mixed and regression models. Gene annotation will be conducted to study the function of the intestinal flora.

DISCUSSION

Based on our previous pharmaceutical studies, SQSX shows a good pharmacological effect of neovascularization and preventing in-stent restenosis. In clinical practice, it's also widely prescribed as a complementary medicine for CAD. Therefore, we would like to initiate a randomized, double-blind, placebo-controlled trial to examine the efficacy and safety of SQSX for NSTEACS. ACS is usually accompanied by gastrointestinal ulcers or bleeding (28, 29), and long-term use of antiplatelet drugs or combined use of multiple anticoagulant drugs causes gastrointestinal mucosal damage (30, 31). These pathological states of the intestinal mucosal barrier cause translocation and disturbance of intestinal flora (32). The disturbed intestinal flora and its metabolite TMAO are one of the reasons that promote the progression of CAD (12, 33, 34). As is well known, NSTEACS is at a critical stage from stable to unstable, which is likely to be accompanied by significant changes in the intestinal flora. We consider that SQSX could be an effective intestinal flora regulator, helping to ease the short-term symptoms of NSTEACS by improving intestinal flora disturbances and gastrointestinal tract injury. The study is possible to provide evidence for the use of intestinal flora modifiers in the treatment of ACS. The above hypotheses are still unclear, so we intend to verify in this trial.

There are three limitations to this work. First, the sample size of the study is small and might be biased. Therefore, two

subsequent clinical studies with a larger sample size ($n = 120$) will be launched this year as a follow-up supplement. Second, the biomarker hs-CRP is observed as a surrogate indicator for the incidence of MACCE and does not yet fully explain the efficacy. We'll determine whether or not to investigate the incidence of MACCE further according to the result. Third, we only control the effects of combined medications on the intestinal flora, and could hardly standardize the patient's eating habits and other multivariate factors that affect intestinal flora. We will educate patients and document their dietary and lifestyle habits to ensure consistency of multiple factors as much as possible.

To conclude, the purpose of the trial is to examine the efficacy and safety of SQSX for NSTEACS and explore the possible pharmacological mechanisms.

Trial Status

The trial was initiated in September 2020 and is presently recruiting participants. Currently, a total of 20 participants have completed the 14- days follow-up. However, no analysis has been conducted since the commencement of the trial.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The study conforms to the Helsinki Declaration. The study protocol was reviewed and approved by the Ethic Committee of Xiyuan Hospital, China Academy of Chinese Medical Sciences (2019XLA067-2). Written informed consent is obtained for entry into the study.

AUTHOR CONTRIBUTIONS

PW conceptualized and designed the study under the guidance of KC and XW drafted the manuscript, participated in the preliminary preparation of the study. MG reviewed the protocol for important intellectual content. XW and YD are responsible for the execution of the clinical trials. ShiS, SheS, SW, and YW helped to polish the manuscript. All authors read and approved the final manuscript.

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