Xuesaitong Capsule For Patients After Percutaneous Coronary Intervention For Unstable Angina: Study Protocol For a Randomized Controlled Trial

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Abstract

- **Background:** This study was designed to investigate the effect of Xuesaitong (XST) capsule added to conventional treatment in patients after percutaneous coronary intervention (PCI) for unstable angina (UA).
- **Methods:** This is a 12-week, randomized, multi-center, double-blinded, placebo-controlled clinical trial. A total of 120 patients with UA will be recruited and randomly allocated in a 1:1 ratio to receive XST or placebo (2 capsules twice per day) on the background of conventional treatment. The changed level of high-sensitivity C-reactive protein from baseline to week 12 is the primary outcome. Secondary outcomes include tumor necrosis factor- α , interleukin-6, platelet aggregation, blood lipid, angina symptoms and ST segment deviation in electrocardiogram. The safety of XST will be monitored during the trial.
- **Discussion:** This study will provide an evidence regarding the efficacy and safety of XST on the background of conventional medical treatment in patients after PCI for UA.
- **Trial registration:** Chinese Clinical Trial Registry, ChiCTR2000032152. Registered on 14 January 2020.

Introduction

Background and rationale {6a}

Unstable angina (UA) is a common type of coronary artery disease (CAD). Previous studies showed that 1-year mortality rate of patients with UA is about 10%^{1,2}. Percutaneous coronary intervention (PCI) alleviates the angina, shortens the duration of hospitalization^{1,3}, but does not reduce the longer-term mortality due to multiple factors such as stent thrombosis, inflammation, increased cytokine secretion, and stent-related endothelial damage^{4,5}. Although dual anti-platelet therapy prevents ischemic events^{4,5}, the risk of bleeding increases, even counters the benefits of revascularization. Therefore, there is an urgent need to explore treatment regimen that has a further favor impact on UA patients without the increase in bleeding risk.

The Xuesaitong (XST), derived from traditional Chinese medicine, *Panax notoginseng* (Burk.) F.H. Chen, is a widely prescribed Chinese patent medicine for CAD⁶. Previous evidence showed that the XST relieves anginal symptoms, inhibits inflammation and platelet aggregation^{7,8}. In addition, there is an evidence showing that XST is not associated with increased risk of bleeding⁹. Here, we hypothesize that, compared with conventional therapy alone, XST plus conventional therapy might be an optional treatment strategy for patients after PCI for UA.

Objectives {7}

This trial was designed to test whether XST in addition to conventional therapy has beneficial effects in patients after PCI for UA.

Trial design {8}

This study is designed to be a 12-week, randomized, multi-center, double-blinded, placebo-controlled clinical trial. The trial outline, including measurements at every 4 weeks and collection of biological samples at 0 and 12 weeks is illustrated in Fig. 1 and Table 1.

The study design is conducted in accordance with the principles of the Declaration of Helsinki (2013 version) and Good Clinical Practice guidelines following the theory that guides the appropriate use of TCM in clinical application. The study will follow the Recommendations for Intervention Trials guidelines and the completed checklist can be accessed in Additional file 1. All visits will be documented in Case Report Forms (CRFs), and the reports will be guided by the Consolidated Standards of Reporting Trials.

Methods: Participants, Interventions And Outcomes

Study setting {9}

A total of 120 patients will be enrolled in three hospitals in China: Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing, Fuwai Hospital attached to Chinese Academy of Medical Sciences, Beijing and Anzhen Hospital attached to Capital Medical University.

Eligibility criteria {10}

Diagnostic criteria

UA diagnosis was based on the criteria set by the European Society of Cardiology (ESC) in 2020¹.

Inclusion criteria

- (1) Patients aged between 40 and 75 years.
- (2) Patients diagnosed with UAP and have undergone PCI within 3 days.

Exclusion criteria

- (1) Patients with uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg, diastolic blood pressure ≥ 100 mmHg).
- (2) Patients with severe arrhythmia (atrial fibrillation with rapid ventricular response, atrial flutter, paroxysmal ventricular tachycardia).
- (3) Patients with a history of heart failure, pulmonary heart disease, rheumatic heart disease, myocarditis, cardiomyopathy, aortic dissection, pulmonary embolism.
- (4) Patients with peptic ulcer.

- (5) Patients with active rheumatic immune or tuberculosis or severe blood system diseases or malignant tumors.
- (6) Patients with serum alanine aminotransferase or serum creatinine > 2 times the upper limit of the normal reference value.
- (7) Pregnant and/or lactating women and/or women of childbearing age who require childbirth.
- (8) Patients allergic to the test drugs.
- (9) Those who have participated in other clinical trials within 1 month.

Who will take informed consent? {26a}

Strategies for achieving adequate participants are as follows. We will publicize our trial in the community, hospitals, and through the media. We will select from patients who meet the criteria for PCI who go to each branch for PCI surgery. For eligible subjects, researchers will give explanation to them, issuing informed consent to patients who are interested and agree to participate in the trial. Written informed consent, as is shown in Additional File 2, will be obtained from all participants prior to enrollment.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable. There is no plan for additional analysis.

Interventions

Explanation for the choice of comparators {6b}

See 6a.

Intervention description {11a}

The patients will be allocated to receive placebo (2 capsules twice per day) or XST (2 capsules twice per day), for 12 consecutive weeks. The appearance and smell of the placebo resembles the experimental drug, thus could not be differentiated. Both the XST soft capsule and the placebo will be provided by Kunming Shenghuo Pharmaceutical Co., Ltd. (Kunming, China).

Criteria for discontinuing or modifying allocated interventions {11b}

We fully respect the wishes of the participants that they can withdraw from the trial at any time. Once withdrawn, the researcher will record information including time, reason, whether adverse events (AEs) have occurred in the CRF.

Strategies to improve adherence to interventions {11c}

Patient compliance, which is calculated by the sum of the reclaimed boxes, will be recorded at week 4, 8 and 12. Medication compliance = (prescription volume-missed dose) / prescription volume × 100%. A medication compliance of ≥80% will be considered as good, but less than 80% will indicate poor compliance. Since we provide free laboratory tests, patients can undergo a follow-up check after PCI while participating this trial, thus the patient compliance presents to be good.

Relevant concomitant care permitted or prohibited during the trial {11d}

Based on the guideline issued by ESC in 2020, patients in both groups will receive the conventional cardiovascular medications (such as antiplatelet drugs, statins, nitrates, β-blockers, calcium antagonists, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers). The routine drugs used for chronic diseases will not be changed unless necessary. The usage, dosage and frequency of combined drugs during follow-up will be collected in detail in the CRF. Any other Chinese herbal decoction or Chinese patent medicine for the treatment of coronary heart disease is forbidden during the trial.

Provisions for post-trial care {30}

Currently we don't have further plan for post-trial care, but if the participants are interested, we will be willing to provide traditional Chinese medicine prescription.

Outcomes {12}

Primary outcome

The primary outcome, the change in high-sensitivity C-reactive protein (hs-CRP) from baseline to week 12, will be tested at baseline and week 12.

Secondary outcome

The secondary outcome will be as follows:

1. Reduction in tumor necrosis factor-α(TNF-α) and Interleukin-6 (IL-6) at week 12 compared with baseline.
2. Change in blood lipids assessed by the total cholesterol (TC), high-density lipoprotein cholesterol (HDL), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) from baseline to week 12.
3. Angina symptom score, including the intensity, frequency, duration of the chest pain and the amount of nitroglycerin, will be tested at week 0,4,8,12.
4. Change in platelet aggregation rate from baseline to week 12.
5. Change in ST segment and T-wave of electrocardiogram (ECG) will be followed at week 0,4,8,12.

Safety outcome

1.Coagulation function (such as prothrombin time, activated partial thromboplastin time, thrombin time or fibrinogen), blood, urine or stool routine as well as liver and renal function will be tested at week 0 and 12.

2.AEs such as cerebral or gastrointestinal hemorrhage and thrombocytopenia, will be monitored at every visit and recorded in the CRF.

Other outcomes

The other outcomes are as follows:

1.demographic data (age, gender, height, weight, ethnicity, occupation or complicated diseases)

2. influencing factors (risk factors, history of allergy and medication history)

3. combined medication

4. physical examination (body temperature, heart rate, heart rhythm and blood pressure)

Demographic data and the factors affecting the efficacy will be systematically recorded after enrollment while the general physical examination and the combined medication will be tested and recorded at week 0, 4, 8, and 12 of follow-up.

Participant timeline {13}

Sample size {14}

The sample size will be calculated on the basis of the change of hs-CRP. Based on the previous studies¹⁰, we hypothesize that, as compared with the conventional medical treatment, the level of hs-CRP will be 20% lower in the XST group after 12 weeks. Supposing type I error α or type II error of the hypothesis test is 0.05 or $\beta=0.1$ respectively, the sample size of the intervention group and the control group, which is calculated by PASS 11 software, is 48 cases. Assuming that 20% of the participants drop-out, the sample size should be 120 cases. Ultimately, each of the two groups would include 60 cases.

Recruitment {15}

Strategies for achieving adequate participants are as follows. We will publicize our trial in the community, hospitals, and through the media. We will select from patients who meet the criteria for PCI who go to each branch for PCI surgery. For UA patients who come to each branch for PCI and meet our criteria, researchers will give explanation to them, issuing informed consent to patients who are interested and agree to participate in the trial.

Assignment of interventions: allocation

Sequence generation {16a}

Eligible participants will be randomly assigned to either the XST or the placebo group, in a 1:1 ratio based on the randomization system of the Institute of Clinical Pharmacology of China Academy in Chinese Medical Sciences. The allocation sequence will be managed by people who are not involved in the trial and concealed from both participants and researchers. Not until the end of the trial will the allocation sequence be revealed.

Concealment mechanism {16b}

See 16a.

Implementation {16c}

See 16a.

Assignment of interventions: Blinding

Who will be blinded {17a}

All of the trial subjects, outcome assessors, analysts and the researchers will be blinded to the allocation.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Before the start of the trial, all personnel participating in the study will be trained to strictly follow the clinical trial protocol and adopt standard operating procedures. This will ensure quality control of the clinical trial and the implementation of the quality assurance system.

Plans to promote participant retention and complete follow-up {18b}

Throughout the follow-up period, the researchers will contact patients for completion of their follow-up and collect the outcome data.

Data management {19}

After using a unified research medical record for data collection, the researchers will use the drug clinical trial data management system of the Xiyuan Hospital of Chinese Academy of Chinese Medical Sciences (<http://www.xyedc.com/>) for data entry and management. The data entry will be carried out by double entry verification method. We will take the following measures to ensure the safety of the data: the research medical records will be kept in the designated place and the data will be managed by a dedicated person and only accessible by research-related staff. Besides, the privacy and confidentiality of the subjects will be protected. In addition, the files will be archived in chronological order with the latest file at the top and identified by the version number and date. In addition, a search directory will be set. If a file is archived separately, the location of the file will be recorded. All project files will be kept for 5 years

after the end of the clinical study. Only after the whole trial has completed will the entire research-related staff have access to the final trial dataset.

Confidentiality {27}

The detail personal information will not be published.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable. There are no biological samples collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

SPSS 23.0 will be used to analyze the data. The measurement data will be tested for normality by the Kolmogorov-Sminov method. Those that conform to the normal distribution will be described by mean $\pm$ standard deviation, while those that do not conform to the normal distribution will be described by the median (25% digits, 75% digits). Description: the count data will be described by the number of cases (percentage). For measurement data, the paired t -test will be used for intra-group comparison; for inter-group comparison, if the two groups meet normality and the variances between the two groups are equal, the independent sample t -test will be used; otherwise, the non-parametric Wilcoxon rank sum test will be employed. On the other hand, for categorical data, the chi-square test will be used for disordered outcomes, while the nonparametric Wilcoxon rank sum test will be used for ordinal data. A two-sided $P < 0.05$ will be used to evaluate the significance of the difference.

Interim analyses {21b}

We fully respect the wishes of the participants that they can withdraw from the trial at any time. Once withdrawn, the researcher will record information including time, reason, whether AEs have occurred in the CRF.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Not applicable. There will not be additional analyses.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

We will try our best to avoid withdrawals, drop-out and loss of participants. For cases that are lost to follow-up, we will conduct multiple imputation and sensitivity analysis. For withdrawal cases, we will use intentional analysis.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The trial protocol and clinical trial report will be made available by the major researchers. Reasonable requests for the concrete trial protocol should be directed to shidazhuo@126.com. Datasets during the current study will not be available due to data privacy.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

At the end of each natural year, we will make a summary to Beijing Administration of Traditional Chinese Medicine. Beijing Administration of Traditional Chinese Medicine will provide organizational support for us if necessary.

Composition of the data monitoring committee, its role and reporting structure {21a}

The Research Ethical Committee of Xiyuan Hospital will audit the trial, conducting every three months independently of investigators and the sponsor. The Research Ethical Committee will decide on any premature closure of the study.

Adverse event reporting and harms {22}

After the main investigator's consent, participants who are deemed to have had a serious adverse reaction will terminate the study, receiving free and reasonable corresponding medication. Subsequently, his or her specific intervention treatment will be unblinded by an individual that is independent of the trial.

Frequency and plans for auditing trial conduct {23}

Upon enrollment of initial 30 patients, personnel who are not directly involved in the clinical trial will conduct a systematic inspection of the trial-related activities and documents. They will evaluate standard operating procedures, relevant regulatory requirements and whether the trial is conducted in accordance with the trial protocol, at a frequency of every three months. The authenticity, timeliness, accuracy and completeness of the trial data will also be evaluated.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

If it is necessary to modify the research protocol during the trial, we will report to the ethical committee of each center and then the registration center.

Dissemination plans {31a}

Trial findings will be published through peer-reviewed international journals and conference presentations.

Discussion

We design this randomized, placebo-controlled, double-blind trial to explore a potential effective treatment for patients after PCI for UA.

Coronary stents damage the endothelium and activate the release of inflammatory cytokines, which accelerate the rupture of unstable plaques. The level of inflammatory cytokines is also a predictor of the occurrence of adverse cardiovascular events^{11–13}. Previous studies showed that PNS regulated the inflammation process by accelerating the release of anti-inflammatory cytokines and inhibiting the production of pro-inflammatory cytokines such as Hs-CRP, TNF- α and IL-6¹⁴. Here, we chose Hs-CRP as the primary outcome because it is not only a biomarker of inflammation, but also an independent predictor of major adverse cardiovascular events^{15,16}. The change level of other inflammatory cytokines like TNF- α and IL-6 were measured as the secondary outcomes.

Platelet and blood lipids play crucial roles in CAD^{17,18}. PNS has been demonstrated to promote lipolysis and reduce lipid synthesis, thereby improve the metabolism of serum lipids in multiple ways¹⁹. Aside from that, PNS inhibits platelet activation^{20,21}. Therefore, the blood lipid and the platelet aggregation rate will be assessed to test the effect of the XST.

The follow-up frequency was designed as once per month, for the reason that we can monitor patients for adverse reactions in a timely manner. In addition, we chose to draw blood at the time of enrollment and week 12 to reduce invasive testing and at the same time, ensure patient compliance to the greatest extent.

Previous studies have demonstrated better efficacy with the use of XST plus conventional drugs in UAP patients without PCI^{9,22}, but data on patients after PCI for UA is limited. Our study, therefore, will be the first to confirm the potential role of XST in such kind of patients.

The results might be underpowered to extrapolate to other races as the trial is only conducted in Beijing, China. In addition, the follow-up period will only last for 12 weeks, thus the long-term outcomes may not be verified.

The information obtained from this exploratory study will inform the decision to conduct a large-scale randomized controlled trial to test the efficacy of XST, which will add to the current high-quality evidence that is available for the management of UA.

Trial Status

The trial was initiated in November 2020 and is scheduled to be completed in December 2021. Currently, it is open for enrollment. The data will be available in mid- or late- 2022.

Abbreviations

ACS: acute coronary syndrome

AE: adverse event

CAD: coronary artery disease

CRF: Case report form

ESC: European Society of Cardiology

ECG: electrocardiogram

HDL: high-density lipoprotein cholesterol

Hs-CRP: high-sensitivity C-reactive protein

IL-6: interleukin-6

LDL-C: low-density lipoprotein cholesterol

PCI: percutaneous coronary intervention

PNS: panax notoginseng saponins

TC: total cholesterol

TCM: traditional Chinese medicine

TG: triglyceride

TNF- α : tumor necrosis factor- α

UA: unstable angina

XST: Xuesaitong

Declarations

Acknowledgements

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Authors' contributions {31b}

S DZ, as the major investigator of the study, proposed the concept for this trial and designed the study. Y YQ and L SY were major contributors to manuscript writing. L JW, Z YH, S L and M LN helped to revise the

manuscript critically. D WH, XM and D JP participated in the planning and designing of the study. All authors discussed, read, and revised the manuscript, and all approved the publication of this protocol.

Funding {4}

This study was supported by the 2019 Clinical collaboration capacity building project of Chinese and Western medicine for major and difficult diseases (residual angina after coronary revascularization). The Kunming Shenghuo Pharmaceutical Co., Ltd. Was only responsible for providing the drugs and didn't take any role in the trial such as the design of the trial, collection, management, analysis and interpretation of the data, writing manuscript or the decision to publish.

Availability of data and materials {29}

Contact the principal researcher for datasets if there are reasonable requests.

Ethics approval and consent to participate {24}

This study has been approved by the Ethics Committee of Xiyuan Hospital (Approval No. 2019XLA070-2), which has been registered in the Chinese Clinical Trial Registry (<http://www.chictr.org.cn/edit.aspx?pid=47984&htm=4>) as ChiCTR2000032152. Each participating center has obtained approval from its local institutional review board as well. The original ethical approval document is available in Additional File 3. Written informed consent will be obtained before participation from all subjects.

Consent for publication {32}

All authors have reviewed the final version of the manuscript and approved its publication. Written informed consent for the publication of trial data will be obtained from all the participants before enrollment.

Competing interests {28}

The authors declare that they have no competing interests.

Authors' information (optional)

Not applicable.

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Tables

Table1 The time of enrollment, intervention and assessment

	Enrolment	Allocation	Treatment-period		
TIME	<i>-1 week</i>	<i>0</i>	<i>Week 4</i>	<i>Week 8</i>	<i>Week 12</i>
ENROLMENT:					
Eligibility screen	✓				
Informed consent	✓				
Demographic data	✓				
Physical examination	✓		✓	✓	✓
Allergy and medication history	✓				
Combined medication	✓		✓	✓	✓
Allocation		✓			
INTERVENTIONS:					
<i>XST</i>		✓	✓	✓	✓
<i>placebo</i>		✓	✓	✓	✓
ASSESSMENTS:					
Hs-CRP		✓			✓
TNF- α		✓			✓
IL-6		✓			✓
platelet aggregation rate		✓			✓
blood lipids		✓			✓
angina pectoris symptom score		✓	✓	✓	✓
electrocardiogram		✓	✓	✓	✓
blood, urine and stool routine test		✓			✓
Coagulation function		✓			✓
side effects of drug interactions			✓	✓	✓
Renal and liver function		✓			✓
Adverse events		✓	✓	✓	✓
compliance			✓	✓	✓

Figures

Figure 1

Flow chart of the trial. UA: unstable angina; XST: Xuesaitong; hs-CRP: high-sensitivity C-reactive protein; TNF- α : tumor necrosis factor- α ; IL-6: Interleukin-6.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [trialschecklist.doc](#)
- [InformedConsentForm.docx](#)