Comparison of Buyang Huanwu Granules and Naoxintong Capsules in Treatment of Stable Angina Pectoris: Rationale and Design of a Randomized, Double-blind, Multicenter Clinical Trial

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ABSTRACT

Background: Stable angina pectoris (SAP) is seriously threatened the health of human life currently, and the mortality is in a continuous rising stage. The current treatment strategies mainly include pharmaceutical therapy and revascularization. In China, Buyang Huanwu granules (BYHW) and Naoxintong capsule (NXT) have been used in the treatment of SAP, but it is not clear which one is better in terms of relieving symptoms and improving quality of life. Therefore, we design a clinical trial to compare the efficacy and safety between NXT and BYHW in the treatment of SAP.

Methods: This is a randomized, double-blinded, parallel controlled, multicenter clinical trial protocol. On the basis of western medicine standardized treatment, a total of 128 SAP patients will be randomly divided into intervention group 1 (NXT group), intervention group 2 (BYHW group) and control group (placebo group) at a 2:1:1 ratio. A 2-week run-in period is required prior to randomization, and 1-week baseline period and 4-week treatment period are included in this study. The primary outcome is the efficacy rate of stable angina symptom score improvement; the secondary outcomes include the effect of electrocardiogram, Seattle Angina Questionnaire scores, and the nitroglycerin consumption.

Discussion: This study will evaluate the efficacy and safety between NXT and BYHW in the treatment of SAP. The results will provide critical evidence of the Chinese herbal medicine for SAP.

Trial registration Chinese Clinical Trials Registry ChiCTR1800015191. Registered on 13 March 2018. http://www.chictr.org.cn/showproj.aspx?proj=25818

Keywords Stable angina pectoris, Traditional Chinese medicine, Buyang Huanwu granules, Naoxintong capsules, randomized controlled trial
Administrative information

**Title (1)** Protocol for a randomized, double-blind, multicenter clinical trial to compare efficacy rate of stable angina symptom score improvement between Buyang Huanwu granules and Naoxintong gapsules for adults with stable angina pectoris

**Trial registration (2a and 2b).** Chinese Clinical Trials Registry, ChiCTR1800015191, registered on 13 March 2018.

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The National Natural Science Foundation of China and the National Key R&D Program for Modernization of Traditional Chinese Medicine were not involved in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.
Introduction

Background and rationale \{6a\}

In recent years, cardiovascular disease is one of the major causes of death globally, seriously threatening human life and health [1, 2]. The mortality rate due to cardiovascular diseases accounted for more than 40% of all-causes deaths in China [3]. Coronary artery disease (CAD), a common cardiovascular disease, is the leading cause of morbidity and mortality worldwide [4, 5]. Angina pectoris is the most common symptom of CAD, and a major cause of disability. Stable angina pectoris (SAP), as one of the common types of angina pectoris, is a chronic medical condition with an appreciable incidence of acute coronary events and increased mortality [6]. In 2017, the prevalence rate of SAP is 3.6% in China [7] and the numbers are rapidly increasing due to the aging, dramatic lifestyle changes, and expanding population of multiple risk factors for angina pectoris, such as hypertension, diabetes mellitus, etc. SAP significantly influences patients’ quality of life and places a heavy burden on society and healthcare systems [8]. As a consequence, it is now urgent that the society mounts a comprehensive attack on SAP, harnessing all available resources to slow, arrest, and possibly even reverse the epidemic of cardiovascular diseases [9].

The aim of SAP management is to stop or minimize symptoms, and to improve quality of life and long-term morbidity and mortality. Management options include lifestyle advice, drug treatment and revascularization using percutaneous or surgical techniques [10]. Pharmacological therapy is safe and beneficial for most patients, which remains the cornerstone treatment for SAP. Optimizing pharmacological therapy includes nitrates, beta-blockers, calcium channel blockers, antiplatelet agents, angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker, statins, etc. [11]. Despite advances in drug treatment and revascularization strategies over several decades, the prognosis of patients with SAP still remains poor, and the rate of mortality and rehospitalization are still high [11]. More and more SAP patients are
turning to complementary and alternative medicine to deal with the symptoms and signs of the disease.

The hemodynamic change caused by early coronary artery disease or atherosclerosis is the basic mechanism of SAP [11], which is similar from the perspective of traditional Chinese medicine (TCM) [12]. TCM has been used in China for more than 2000 years and plays a significant role in the treatment of SAP. Using the theoretical basis of TCM and modern complementary and alternative medicine, Buyang Huanwu granules (BYHW) and Naoxintong capsules (NXT) are widely used in the treatment of SAP, and both have shown to be effective for patients with SAP [13]. Modern clinical studies have shown that BYHW and NXT are both similar prescriptions for protecting vascular endothelial function, delaying the process of atherosclerosis, improving hemorheology indexes, reducing blood lipid, anti-inflammatory and antithrombotic, and have obvious protective effect on myocardial ischemia-reperfusion injury [13, 14]. Although BYHW and NXT have similar efficacy and application, their constituent herbs are different (Table 1) and there is no prospective data comparing the efficacy of the two in the treatment of SAP. Therefore, we designed a randomized, double-blinded, parallel controlled, multicenter clinical trial to compare the efficacy and safety of NXT and BYHW in the treatment of SAP.

**Objectives**

The objectives of this study are: (i) to evaluate the efficacy of NXT and BYHW in the treatment of SAP and (ii) to test whether NXT is more advantageous than BYHW for treating SAP.

**Trial design**

This study is a randomized, double-blinded, multicenter parallel-group, placebo-controlled clinical trial. The study consists of a 2-week placebo run-in period, 1-week baseline period and 4-week treatment period. The specific study procedures
are shown in Figure 1. The eligible patients will be randomly allocated to intervention
group 1, intervention group 2, and control group at the ratio of 2:1:1.

Methods: Participants, interventions and outcomes

Study setting [9]

This trial will be conducted in six participating sites, including the Second Affiliated
Hospital of Zhejiang Chinese Medical University, Hangzhou Xiaoshan District
Hospital of Traditional Chinese Medicine, Lishui Hospital of Traditional Chinese
Medicine, Fenyang Hospital of Shanxi Province, Affiliated Hospital of Shanxi
Chinese Medical University, and Luohe Hospital of Chinese Medicine.

Ethical review and general statements

This trial has been approved by the Research Ethics Committee of the Second
Affiliated Hospital of Zhejiang Chinese Medical University (No. 2017-Y-070-01), and
has been registered at the Chinese Clinical Trials Register (ChiCTR1800015191). In
order to guarantee standardized processes and the safety of all participants, our study
will be performed in accordance with the principles of Good Clinical Practices (GCP),
recommendations of the CONSORT [15] and SPIRIT [16] statements, and the
Helsinki Declaration. All participants will be informed about every detail of the trial
and provide written informed consent according to the Helsinki Declaration before
participating. To protect participants’ privacy, data forms and eCRFs involved in this
study will be maintained in secure storage at the coordinating center.

Eligibility criteria [10]

Patients will be included after written informed consent and enrolled in the study
when the inclusion and exclusion criteria are met.

Inclusion Criteria

Patients will be eligible for this study if they strictly meet the following criteria.
(1) Aged 40 to 75 years, both male and female;
(2) Diagnosis with SAP by the ‘Guidelines for diagnosis and treatment of chronic stable angina pectoris in 2007’ [17] and the ‘ACC/AHA2002 guideline update for the management of patients with chronic stable angina’ [18].
(3) Consistent with the diagnostic criteria of grade I ~ III of SAP;
(4) History of SAP within 1 month, or myocardial infarction (MI) 3 months ago.
(5) Undergone coronary revascularization or cardiac pacemaker surgery, and after 3 months of treatment, patients still had SAP;
(6) Volunteer to participate and sign informed consent.

**Exclusion criteria**

Patients who have any of the following criteria may not participate in this test.

(1) History of MI or coronary revascularization or cardiac pacemaker installation within 3 months;
(2) Patients with abnormal electrocardiogram (ECG), and ST segment declined more than 1 mm in resting 12-lead ECG;
(3) Patients with acute MI, severe angina pectoris, pulmonary embolism, aortic dissection, cardiomyopathy, aortic valve stenosis and other heart valve diseases, congenital heart disease, left bundle branch block, or electrolyte disturbance;
(4) Chest pain caused by severe cardiovascular neurosis, climacteric syndrome, cervical spondylosis, bone and joint diseases, the digestive system diseases and the respiratory system diseases;
(5) Patients with severe liver and kidney dysfunction (including dialysis patients) and active liver disease (including primary biliary cirrhosis and unexplained persistent liver dysfunction), and/or alanine aminotransferase (ALT), aspartate aminotransferase (AST)>1.5 times the normal upper limit, creatinine (Cr)> the normal upper limit and total bilirubin (TBIL) ≥2 times the normal upper limit;
(6) Other severe cardio-cerebro-vascular, liver, kidney, and hematopoietic system diseases, and those who have undergone major surgery recently;
(7) Psychiatric patients, patients with severe depression, alcohol addicts or history of substance abuse;
(8) Patients who are pregnant or lactating or have a positive pregnancy test at time of admission;
(9) Patients with allergic constitution, or allergic to the study drugs and its ingredients;
(10) Participation in other clinical trials in the previous 3 months;
(11) Patients who are judged as inappropriate by investigators.

Who will take informed consent? {26a}

Trained study staff (physicians or psychologists) provide verbal information about the trial, answer questions, and obtain written informed consent from potential trial participants.

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

On the consent form, participants will be informed that their data will be anonymized. This trial does not involve collecting biological specimens for storage.

Interventions

Explanation for the choice of comparators {6b}

Given the complexity of SAP, and the urgent need for evidence-based therapy approaches, we chose to add TCM on the basis of standardized treatments and compare the efficacy of NXT and BYHW in relieving stable angina symptoms (includes the frequency of angina attacks, duration and degree of pain).

The two interventions NXT group and BYHW group will be compared to placebo group to evaluate the efficacy of NXT and BYHW in the treatment of SAP, and further, the NXT group need to be compared to BYHW group to evaluate whether NXT is more advantageous than BYHW for treating SAP.
Intervention description {11a}

Eligible participants will experience a 2-week run-in period, 1-week baseline period and 4-week treatment period. The interventions during the treatment period are as follows:

- Intervention group 1 will receive NXT (0.4 g/ capsule, op, 4 capsules/tid) and granule placebo (5.5 g/bag, op, 1 bag/tid);
- Intervention group 2 will receive BYHW granule (5.5 g/bag, op, 1 bag/tid) and capsule placebo (0.4 g/capsule, op, 4 capsules/tid);
- Control group will receive capsule placebo (0.4 g/capsule, op, 4 capsules/tid) and granule placebo (5.5 g/bag, op, 1 bag/tid).

In the study, NXT, BYHW, capsule placebo, and granule placebo are provided by Shaanxi Buchang Pharmaceutical Co. Ltd. The capsule and granule placebos are similar to the study drug in smell, color, specification, packaging, property of contents and other features.

Criteria for discontinuing or modifying allocated interventions {11b}

Participants are allowed to withdraw at any time without having to give a reason. The withdrawal criteria are as follows: (1) participants request to withdrawal from the study; (2) exacerbation or deterioration that is clearly related to the treatment; (3) an allergic reaction that is clearly associated with the study drug; (4) participants showed comorbidities, complications, adverse events (AEs), or serious adverse events (SAEs) during the trial; (5) the use of forbidden drugs or receipt of prohibited treatment; (6) poor compliance, or the amount of drug used does not meet the regulations (<80% or >120%); (7) the blinding is uncovered or emergency unblinding is required.

If a subject withdraws from the trial, no additional data will be collected, but the existing data will be used for statistical analysis. The time of treatment or trial discontinuation and the reason for withdrawal will be documented on the CRF. Drop-out patients will not be replaced.
*Strategies to improve adherence to interventions {11c}*

In order to improve adherence to intervention protocols, during the treatment phase, we will distribute medicines once a week to grasp the patient’s drug consumption and monitor patient compliance in time. Face-to-face adherence reminder sessions will take place at the medicines dispensing process. After treatment, the package will be returned to the researchers.

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

Concerning standardized treatment, during the run-in period and treatment period, aspirin, statin lipid-lowering drugs, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) should be used. TCM formulations with a similar composition and efficacy to those of study drugs will not be allowed to be used. Researchers should record the concomitant medication truthfully, and maintain dose stability during the trial. The participants should be clinically stable in the last 1 month or receiving standardized treatment for ≥1 month and no modification of dosage or intravenous administration has been given.

Concerning emergency treatment, in the event of acute angina pectoris attack during treatment, participants should be treated with nitroglycerin first (one tablet at a time, with a sublingual administration, and can be repeated every 5 minutes until the pain is relieved. If the pain persists after the total amount reaches 3 tablets in 15 minutes, seek medical attention immediately). The treatment status should be recorded. If the participant’s condition deteriorates during treatment and it is not advisable to continue the trial, researcher should consider terminating the trial and switching to surgery or another type of clinical treatment, and the patients will be classified in the analysis as “treatment ineffective”.

*Provisions for post-trial care {30}*

If SAEs occur during the study period, the participants are also required followed up after the study period. Appropriate measures are taken to fully protect the interests of
participants such as outpatient or inpatient care or referral to other specialists.

Outcomes \{12\}

Primary outcome

The primary outcome is the efficacy rate of stable angina symptom score improvement \[19\]. The stable angina symptom score includes the number of angina attacks, duration and degree of pain. The indicators of baseline period (0 weeks) and treatment period (4 weeks) will be compared.

Secondary outcomes

The secondary outcomes are the effect of ECG \[20\], change in Seattle angina questionnaire (SAQ) scores \[21\], and the nitroglycerin consumption during the treatment period. Patients are asked to complete a SAQ (at baseline period and at the end of 4-week treatment), a 19-item self-administered questionnaire, to measure five dimensions of health. Researchers will record the nitroglycerin consumption during the treatment period and compare among groups.

Safety outcomes

Safety evaluations include vital signs (heart rate, respiration, body temperature, blood pressure); clinical laboratory tests (routine blood test, routine urinalysis, serum biochemistry, blood coagulation index, fasting blood glucose) and AEs.

Participant timeline \{13\}

The measurement items and time line for data collection in this study are displayed in Table 2.

Sample size \{14\}

The sample size is calculated using PASS 15 software (NCSS, Kaysville, UT), and driven by the efficacy rate of stable angina symptom score improvement. According
to the referenced literature [22,23], the efficacy rate in relieving stable angina symptoms of NXT is expected to be 85%, 70% for BYHW and 50% for placebo. Considering the drop rate of 20%, the estimated total sample size of 128 cases would achieve 80% statistical power (two sided with type I error rate of $\alpha =0.05$ and type II error rate of $\beta =0.2$) to detect a significant difference. According to the ratio of 2:1:1, there will be 64 cases in intervention group 1, 32 cases each in the intervention group 2 and control group.

**Recruitment**

The potential participants will be recruited by advertisement, oral promotion by researchers, hospital posters, and doctor referrals from the outpatients and inpatients of cardiovascular department.

**Assignment of interventions: allocation**

**Sequence generation**

Eligible participants are randomized in a 2:1:1 ratio into the intervention group 1, intervention group 2 or control group based on a computer generated (SAS 9.4 statistical software package PROC PLAN process) random sequence. The randomization sequence will be recorded by staff at the sponsor unit, and the randomized code of the trial drug is the unique identification code of participants. Eligible participants will be randomized in blocks of eight within each site and stratified by sites.

**Concealment mechanism**

The allocation sequence is implemented through sequentially numbered, opaque, sealed envelopes that are concealed until the interventions are assigned to a participant. Participants withdrawn from the trial will retain their randomization number (identification codes) if already given. New subjects must always be allotted a new randomization number.
Implementation {16c}

During this trial, the statistician generates the allocation sequence, the investigators enroll participants and assign participants to interventions based on opening the randomization number envelope.

Assignment of interventions: Blinding

Who will be blinded {17a}

To minimize ascertainment bias, all researchers, participants, physicians, drug administrators, and dispensing nurses will be blinded to the type of treatment until the study is completed.

Procedure for unblinding if needed {17b}

Unblinding will be available if participants experience severe adverse events (SAEs) or need to be rescued in an emergency situation. Once unblinded, the participant will withdraw from the study. Researchers should report the reasons to the inspector within 24h. The precise cause of unblinding, date of the adverse events (AEs), the treatment situation, and the results must be recorded in electronic case record forms (eCRFs).

Data collection and management

Plans for assessment and collection of outcomes {18a}

According to the requirements of GCP, the investigator shall fill in data to CRFs accurately, completely, and timely based on the original observations of subjects. The auditor shall monitor whether all CRFs have been completed correctly and are consistent with the source data, and issue questions at any time in case of any problem. If errors and omissions are made, the researcher shall be corrected promptly. All data will be stored securely in line with local data management arrangements. Data management will be implemented by Beijing Yilian Zhongkang Technology Co., Ltd.
Plans to promote participant retention and complete follow-up \{18b\}

To promote participant retention, at each medicine distribution visit, participants are scheduled by phone, sent message, and called the day before. Missed visits are rescheduled and followed up. The sponsor will provide compensation for transportation costs.

Data management \{19\}

CRFs are paper-based. Source data will be collected in each site from the investigator and will be transferred into the CRFs. Source data is stored in the respective center. The destruction of any paper files will be at least 5 years from the termination of the study and will be authorized by the sponsor and the principle investigator.

EpiData Software version 3.1 (the EpiData Association, Odense, Denmark) is used for storing outcome measurement data. Two personnel should undertake double-entry and proofreading independently to ensure the accuracy of the data input from CRF to EPidata. Electronic data files are backed up and password protected.

Confidentiality \{27\}

Participant identification numbers are used to track data collection documents. Interventionists’ paper documents (CRFs) are stored in a locked file cabinet. CRFs only use the first letter of the name to identify the participant, and does not include the participant’s home address. Access to electronic data is password protected and restricted to the research team. Data exchanged between research sites is de-identified, encrypted and password protected.

This protocol, CRFs and other documents and materials related to the trial will be kept strictly confidential and will not be disclosed to third parties unless expressly agreed by the principal investigator in advance. Staff of the investigators involved in this trial are also bound by the agreement.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use \{33\}
Participants are asked to give explicit consent for the blood samples collection and use. For blood sample collection, subjects are required to fast for 10 hours before each collection, draw 5 mL of blood and centrifuge, and store the serum in an Eppendorf tube at -70°C.

**Statistical methods**

**Statistical methods for primary and secondary outcomes {20a}**

The statistical analysis plan will be specified before data analysis. Statistical Analysis System v9.4 (or higher version) will be used for statistical analysis. Professional statisticians who are independent of all other processes of our study will carry out analyses.

For continuous variables, we will calculate the mean, standard deviation, median, minimum, maximum, and interquartile range. For categorical variables, we will describe various frequencies or percentages. The chi-square test or Fisher’s exact test will be used for categorical variables. For variables with a normal distribution, inter-group comparisons will be analyzed with one-way ANOVA, whereas pairwise comparisons before and after treatment will be performed with Student's t test. For data that does not have a normal distribution, intra-group or inter-group differences before and after treatment will be analyzed by the Wilcoxon rank-sum test. The proportion of patients with AEs will be compared using the chi-square test or Fisher’s exact test.

**Interim analyses {21b}**

Since the number of recruited cases is not large, no interim analysis is planned.

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

We will include sex, center, complication, concomitant medication as covariates in an analysis of covariance (ANCOVA) for statistical differences between groups by reducing the error variance.
Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data \{20c\}

This study will consistent with the CONSORT statement and intention-to-treat (ITT) principle, and the last observation carried forward method will be used for missing values. Cases in per protocol set (PPS) will be those who adhere to the protocol closely without the absence of baseline characteristics. Analysis of primary outcome and curative effect will be carried out using full-analysis-set and PPS approach. The safety analysis set will include all randomized patients who have accomplished at least one study visit. Participating centers will be required to sum-up participant numbers in each center and list participants who have been removed from PPS.

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

After the publication of the results of this trial, the de-identified version of the database will be available upon reasonable request for principal investigator.

Oversight and monitoring

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

The trial steering committee is composed of the principal investigator (Wan), on-site principal investigators of each hospital and co-investigators. Questions that arise during the research process will be submitted to the committee for decision-making. Principal investigator and on-site principal investigators are responsible for the overall management and coordinate operations of their respective centers. Principal investigator (Wan) is responsible for the overall management of financial and administrative operations. The on-site principal investigators are responsible for the research coordination and implementation of their respective sites.

Composition of the data monitoring committee, its role and reporting structure \{21a\}
This study commissioned Guoxin Pharmaceutical Technology (Beijing) Co., Ltd. to carry out clinical supervision and data monitoring, and set up safety officers to be responsible for security review. All the medical records of the subjects will be carefully assessed, and all harms and complications of the treatment will be reported. The harms will be categorized to AEs and SAEs as described in the AEs section. We will not conduct auditing between the participant sites during the trial. Safety officers review reports on recruitment, retention, and safety information for all participants twice per year, including AEs and SAEs.

Adverse event reporting and harms {22}

During the treatment period, all AEs and SAEs should be monitored and recorded at every study visit. Once AEs occurs, the researcher will evaluate whether AEs are related to the test drug and judge the severity of AEs. In cases of SAEs, the participating patients are asked to take immediate measures to protect their safety and report the events to the ethics committee within 24 hours. The classification and coding of AEs are formulated concerning Common Terminology Criteria for AEs version 4.03.

Frequency and plans for auditing trial conduct {23}

The trial includes close monitoring by the principal investigator, on-site principal investigators, and external agency. Annual progress reports are provided to the sponsor and principal investigator.

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

Any changes to the eligibility criteria, outcomes, or analyses will be reviewed by the trial steering committee and updated in ClinicalTrials.gov.

Dissemination plans {31a}
The results of this study will be disseminated through peer-reviewed publications, presentations at local, national, and international academic conferences, and reports to the funders. In addition, a summary of the primary outcome findings will be created in English and Chinese and shared with the study participants.

**Discussion**

SAP is closely related to the risk of cardiovascular death and recurrent MI, and has an impact on physical function and quality of life [24]. Recent years, the goal of treatment is to improve symptoms and quality of life, prevent cardiovascular events reduce the mortality and hospitalization rate of SAP. Nitrates, beta-blockers, calcium channel blockers, antiplatelet agents, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, statins, etc. are shown to be beneficial [11]. Despite some progress in the field of SAP treatment, the current prevalence and mortality remain high. There is still a need to develop new treatments and develop new drugs to achieve breakthroughs in SAP treatment.

TCM has gained increasing acceptance worldwide in recent years [22], and has accumulated rich experience in the long-term medical practice of preventing and treating SAP, and its understanding of SAP is also deepening. There have been some researches and reports on the treatment of heart failure with TCM. NXT and BYHW are drugs that use the theory of TCM to explore the pathogenesis and treatment of SAP, and they propose that the insufficiency of the heart-Qi and the obstruction of collaterals are the central link. BYHW was proposed by Wang Qingren in the Qing dynasty and has been used in the treatment of cardiovascular and cerebrovascular diseases for nearly 100 years. Under the guidance of the theory of “Inheriting the Essence, and Adherence and Innovation”, due to a weak ability of BYHW in activating blood circulation and dredging collaterals, NXT, was proposed and manufactured by Buchang Pharmaceutical Co., Ltd.. NXT (national medicine permission number: Z20025001), obtained drug production approval in 1993, awarded National Chinese Medicine Protection Certificate in 2014, and was included in the National Basic Drug List (2012 edition) and the Chinese Pharmacopoeia (2015...
Over the past two decades, NXT has been used to treat more than 100 million patients, and can significantly improve the total effective rate of cardio/cerebro-vascular diseases [25].

Modern clinical studies have shown that BYHW can significantly improve the effectiveness of angina pectoris, reduce the attack duration, pain degree, nitroglycerin consumption, and improve the blood lipid index [23]. NXT is the inheritance and innovation of the basic formula of BYHW. Li et al. systematically evaluated the efficacy and safety of NXT in the treatment of SAP, which included 44 literatures and 5130 patients. The results showed that NXT can significantly improve the ECG efficacy, relieve angina symptoms and improve the clinical efficacy [26]. In addition, there is evidence that both NXT and BYHW can protect vascular endothelial function, delay the process of atherosclerosis, improve hemorheological indicators, reduce blood lipids, anti-inflammatory and anti-thrombotic effects, and have obvious protective effect on myocardial ischemia-reperfusion injury [13]. Since the two Chinese patent medicines have similar indications, mechanisms and clinical efficacy on SAP, we design a protocol to observe the efficacy and safety of NXT and BYHW in the treatment of SAP.

However, this study has limitations. First, AEs will only be recorded and processed during the 4-week intervention period, which is relatively short, but the short-term results could encourage further prospective studies with different treatment regimens and longer follow-up. Second, due to the short intervention period, this study lacks long-term observations of mortality and cardiovascular events. A large-scale and long-term study in the future with mortality and cardiovascular events as the primary endpoint is expected.

In conclusion, under rigorous design and strict quality control, we expect that the results will provide valuable evidence to determine whether the effect of NXT is superior to BYHW for improving the symptoms of patients with SAP.

**Trial status**

The trial was initiated in June 2018 and will be completed by June 2022. The
recruitment is in progress. No analysis has been carried out since the beginning of the trial.

Abbreviations

ACEI: Angiotensin converting enzyme inhibitors; AEs: Adverse events; ALT: Alanine aminotransferase; AP: Alkaline phosphatase; APTT: Actived partial thrombolastin time; ARB: Angiotensin receptor blockers; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; BYHW: Buyang Huanwu granules; CAD: Coronary artery disease; Cr: Creatinin; ECG: Electrocardiogram; eCRFs: Electronic case record forms; FIB: Fibrinogen; GCP: Good clinical practices; INR: International normalized ratio; ITT: Intention-to-treat; MI: Myocardial infarction; NXT: Naoxintong capsule; PPS: Per protocol set; PT: Prothrombin time; SAEs: Severe adverse events; SAP: Stable angina pectoris; SAQ: Seattle Angina Questionnaire; SCr: Serum creatinine; TBIL: Total bilirubin; TCM: Traditional Chinese medicine; TT: Thrombin time; γ-GT: γ-glutamyl transpeptidase

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Authors’ contributions {31b}

HTW conceived and designed this study. YW and YHX wrote the manuscript with contributions from all authors. LZ, JHY, SWH, LPD, WF and PZ refined the protocol. All authors contributed to the review of the present manuscript and approved the final version.

Funding {4}

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Availability of data and materials {29}

Data and materials generated during the current study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participant {24}

The whole study process, the study protocol, and informed consent were approved by the Research Ethics Committee of the Second Affiliated Hospital of Zhejiang Chinese Medical University (approval number 2017-Y-070-01), and the Ethics Committee of Affiliated Hospital of Shanxi Chinese Medical University (approval number: 201902038). Written informed consent to participate will be obtained from all study participants.

Consent for publication {32}

Not applicable.

Competing interests {28}

All authors declare that they have no competing interests.

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Figure Legends

Fig. 1 Study flowchart

1. Recruiting SAP patients
   - Excluded
     - Not meeting inclusion criteria
     - Declined to participate
2. Signing an informed consent
3. Run-in period
   - (2 weeks before intervention)
4. Baseline period
   - (1 week before intervention)
   - Safety assessment
   - Efficacy indicators
   - Adverse events
5. Randomization
   - Intervention group 1
     - NXT + Standardized treatment
     - (n=64)
   - Intervention group 2
     - BYHW + Standardized treatment
     - (n=32)
   - Control group
     - Placebo + Standardized treatment
     - (n=32)
6. Efficacy and safety evaluation
   - (4 weeks after intervention)
7. Statistical analysis
8. Same as baseline period
### Table 1. Characteristics of the Investigational Product

#### Study drug 1: Naoxintong Capsule

- **Ingredients:** *Astragalus mongholicus* Bunge [Fabaceae; Radix Astragali], *Hirudo nipponia* Whitman [Hirudinidae; Whitmania pigra Whitman], *Boswellia carteri* Birdw., [Burseraceae; Boswellia carterii], *Commiphora myrrha* (T.Nees) Engl., [Burseraceae; Myrrha], *Salvia miltiorrhiza* Bunge [Lamiaceae; Salviae Miltiorrhizae Radix Et Rhizoma], *Achyranthes bidentata* Blume [Amaranthaceae; Achyranthes], *Neolitsea cassia* (L.) Kosterm. [Lauraceae; Cassia Twig], *Morus alba* L. [Moraceae; Mulberry Twig], *Spatholobus suberectus* Dunn [Fabaceae; Caulis Spatholobi], *Buthus martensii* Karsch [Buthidae; Scorpion];

- **Property:** capsule; the contents are brown to black brown powder; bitter in taste;

- **Specification:** 0.4g/ capsule;

- **Bach number:** 200593.

#### Placebo 1: Capsule placebo

- **Ingredients:** corn starch, silica, caramel (liquid), 2% NXT powder and sunset yellow;

- **With identical color, specification, packaging, property of contents and other features with Naoxintong Capsule;**

- **Bach number:** 200501.

#### Study drug 2: Buyang Huanwu Granule

- **Ingredients:** *Astragalus mongholicus* Bunge [Fabaceae; Radix Astragali], *Angelica sinensis* (Oliv.) Diels [Apiaceae; Angelicae Sinensis Radix], *Paeonia lactiflora* Pall. [Paeoniaceae; Paeoniae Radix Rubra], *Lumbricus rubellus* (Oligochaeta, Lumbricidae), *Ligusticum chuanxiong* Hort. [Apiaceae; Chuan xiong Rhizoma], *Carthamus tinctorius* L. [Asteraceae; Carthami Flos], *Prunus persica* (L.) Batsch [Rosaceae; Semen Persicae].

- **Property:** granule; the contents are brown to black brown granules; bitter in taste;

- **Specification:** 5.5g/ bag;

- **Bach number:** 200603.

#### Placebo 2: Granule placebo
• Ingredients: dextrin, 1% Ligusticum chuanxiong, bitterness SA, stevioside, lemon yellow, and chocolate brown;

• With identical color, specification, packaging, property of contents and other features with Buyang Huanwu granule;

• Bach number: 200601.
Table 2 Measurement items and time points for data collection.

| Item                                      | Run-in period (-14±1) day | Baseline period (-7~0) days | Intervention period (28 ± 4) days |
|-------------------------------------------|---------------------------|------------------------------|----------------------------------|
| **Basic information**                     |                           |                              |                                  |
| Informed consent                          | ×                          |                              |                                  |
| Inclusion/exclusion criteria              | ×                          |                              |                                  |
| Demographic data                          | ×                          |                              |                                  |
| Randomization                             | ×                          |                              |                                  |
| Record medical history and allergy history| ×                          |                              |                                  |
| Record complication and symptom           | ×                          |                              |                                  |
| Record concomitant medication             | ×                          |                              |                                  |
| Access to the "Doctor Tao" platform       | ×                          |                              |                                  |
| Urine pregnancy test                      | ×                          |                              |                                  |
| **Safety assessment**                     |                           |                              |                                  |
| Vital signs and physical examination      | ×                          | ×                            | ×                                 |
| Blood and urine routine examination       | ×                          | ×                            | ×                                 |
| Liver function (ALT, AST, AP, TBIL, γ-GT) | ×                          | ×                            | ×                                 |
| Kidney function (SCr, BUN)                | ×                          | ×                            | ×                                 |
| Coagulation function (PT, APTT, TT, FIB, INR) | ×                      | ×                            | ×                                 |
| Fasting blood glucose                     | ×                          | ×                            | ×                                 |
| **Efficacy indicators**                   |                           |                              |                                  |
| Stable angina symptom score               | ×                          | ×                            | ×                                 |
| Electrocardiogram                         | ×                          | ×                            | ×                                 |
| Seattle Angina Questionnaire              | ×                          | ×                            | ×                                 |
| Nitroglycerin consumption                 | ×                          | ×                            | ×                                 |
| **Other works**                           |                           |                              |                                  |
| Drug distribution                         | ×                          | ×                            |                                  |
| Drug recycling                            | ×                          | ×                            |                                  |
| Record adverse events and combined medication | ×                      | ×                            | ×                                 |
| Compliance judgment                       | ×                          | ×                            | ×                                 |

**Note:** ALT=alanine aminotransferase, AST=aspartate aminotransferase, AP=alkaline phosphatase, TBIL=total bilirubin, γ-GT=γ-glutamyl transpeptidase, SCr=serum creatinine, BUN=blood urea nitrogen, PT=prothrombin time, APTT=activated partial thromboplastin time, TT=thrombin time, FIB=fibrinogen, INR=international normalized ratio.