Clinical Evaluation of Compound Salvia Droplet Pills in the Treatment of Stable Angina Pectoris:Study Protocol for a Randomized Double-blind Control Trial

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SUBJECT AREAS
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Abstract

Background SAP (Stable Angina Pectoris, SAP) is a clinical syndrome characterized by acute and temporary myocardial ischemia and hypoxia due to an increase in the myocardial load resulting from a fixed severe stenosis of the coronary artery. Its' characteristics include paroxysmal pressure pain or tightness in the prothorax, primarily retrosternal pain, which can radiate to the precordium and upper left ulna. It often occurs during physical exertion and lasts for several minutes. Traditional Chinese Medicine (TCM) has unique advantages in treating this disease due to holistic, dynamic and dialectical system of thought regarding life and diseases. Clinical efficacy is the basis for the survival and development of Traditional Chinese Medicine. Scientifically evaluating the clinical efficacy of such TCM treatments is of great importance for promoting its' modernization and internationalization. In this study, we aimed to observe the therapeutic effects of Compound Salvia Droplet Pills on patients with SAP (Qi deficiency and blood stasis), as shown by a standardized clinical study on the treatment of SAP by means of supplementing qi and activating blood circulation by taking TCM treatments for CHD, thereby providing a practical and valuable clinical treatment approach.

Methods A randomized, controlled trial was designed to evaluate the efficacy and safety of Compound Salvia Droplet Pills for the treatment of SAP. A proposed total of 60 patients with SAP (Qi deficiency and blood stasis type) are to be entered into the study. The patients shall be randomly assigned to treatment groups (compound Salvia Droplet Pills, 10 pills/time, 3 times a day, + aspirin enteric - coated tablets 100mg/time, once a day) or the control group (compound Salvia Droplet Pills mimetics, 10 pills/time, 3 times a day, + aspirin enteric - coated tablets 100mg/time, once a day), duration of 28 ±1, and follow-up for 14 ± 3 days. Primary outcome measures: angina pectoris symptom scores and TCM syndrome scores. Secondary outcome measures: ECG, incidence and mortality of cardiovascular events, etc.

Discussion This is a randomized controlled trial for Compound Salvia Droplet Pills to treat SAP on the basis of conventional therapy, to preliminarily evaluate the efficacy in the treatment of patients with SAP (angina symptoms, signs and reducing the use of vasodilator drugs, etc.), and follows up on the short -term prognosis of patients to provide clinical evidence for the use of compound Salvia Droplet

Pills in patients with SAP.

Background

Coronary Heart Disease (CHD) refers to a heart disease from vascular stenosis or occlusion caused by coronary artery atherosclerosis or myocardial ischemia and hypoxia or necrosis caused by coronary functional changes (spasms) [1]. CHD is a common cardiovascular disease. In modern industrialized countries, the number of deaths caused by CHD accounts for approximately one third of all deaths. With the social and economic development, people's living habits and lifestyle have undergone tremendous changes in China; with an increasing aging trend, so too the incidence of CHD will increase year by year. According to the statistics from the Ministry of Health, there were more than 500, 000 deaths due to CHD at the beginning of this century, and in 2004, the number of deaths attributed to CHD accounts for 50% of total number of heart disease deaths. CHD has become one of the main diseases which poses a threat to people’s health in China. Therefore, active prevention and treatment of CHD is a major research topic that challenges medical practitioners throughout the world.

The names “CHD” and “angina pectoris” do not exist in Traditional Chinese Medicine, but physicians from all ages have given further elaborations on their syndromes, etiologies, pathogenesis, and relevant prevention and treatment measures, which have mainly been dispersed throughout the “heartache”, “chest obstruction”, “cardiac obstruction” and “severe palpitation” range etc. At present, CHD is mainly classified within the scope of a chest obstruction and heartache etc., forming a unique system of syndrome differentiation in Chinese medicine regarding CHD. TCM’s consensus on the pathogenesis of CHD and Stable Angina Pectoris, is that it is due to an intrusion of cold evils, improper diet, emotional disorder, and physical disability, etc. These pathogenic factors will cause diseases in isolation, or cause imbalances in the Qi and blood, yin and yang, to produce a variety of pathological changes, i.e. cold coagulation, phlegm stasis, qi stagnation, blood stasis, and eventually a dysfunction of the internal organs. The real syndrome is primarily phlegm and blood stasis, while the deficiency syndrome is primarily due to the relationship with the internal organs such as a cardiac and renal yin deficiency, cardiac and renal yang deficiency, cardiac qi deficiency with blood stasis,

and phlegm stasis. The characteristics of pathogenesis are “chronic diseases intruding into collaterals, heart vessel blockage stasis or qi stagnation and blood stasis”.

TCM has unique advantages in treating this disease due to its’ holistic, dynamic and dialectical understanding of life and diseases. Clinical efficacy is the basis for the survival and development of Traditional Chinese Medicine. Scientifically evaluating the clinical efficacy of such TCM treatments is of great importance for promoting its’ modernization and internationalization. In this study, we aimed to observe the therapeutic effect of Compound Salvia Droplet Pills on patients with SAP (Qi deficiency and blood stasis) as shown by a standardized clinical study on the treatment of SAP by means of supplementing qi and activating blood circulation taking TCM treatments for CHD, thereby providing a practical and valuable clinical treatment approach. In addition, relevant indexes were measured using statistical methods to evaluate the efficacy of traditional Chinese medicines in the treatment of SAP and the improvement of traditional Chinese medicine symptoms, to define the effectiveness and safety of all evaluation indexes regarding its’ efficacy, and provide an objective basis for research on the clinical efficacy evaluation index of Chinese medicine.

Compound Salvia Droplet Pills (Compound Salvia Droplet Pills, CSDP) is a new type of efficient, quick-acting pure traditional Chinese medicine preparation made according to TCM theory and modern medical technology. This drug is made of Salvia, Panax notoginseng and borneol, and contains the active ingredients are the water-soluble Salvia and Panax Notoginseng Saponins. It is effective in promoting blood circulation, removing blood stasis, regulating Qi, and easing pains. It is primarily indicated for chest obstructions caused by Qi stagnation and blood stasis which exhibit chest tightness, precordial tingling, and CHD angina symptoms. Modern pharmacological research shows that [2], Panax Notoginseng Saponins, the main active ingredient of Panax notoginseng is pharmacologically active in dilating blood vessels, increasing coronary blood flow, decreasing myocardial oxygen consumption, inhibiting platelet aggregation, lowering blood viscosity, and enhancing body functions etc. Salvia miltiorrhiza [3] can dilate arteries and peripheral blood vessels, increase blood flow, improve microcirculation, shorten red blood cell recovery periods, increase reticulocytes, promote tissue repair, and alleviate myocardial ischemia, hypoxia, infarction and other

problems relating to cardiac function. Drug approval number: SFDA approval number: Z10950111 (specification: 90 pills per bottle).

Objective

The objective of this study is to observe the therapeutic effect of Compound Salvia Droplet Pills on the heart function and TCM syndromes of patients with CHD with stable angina pectoris (Qi deficiency and blood stasis).

Methods And Design

Program Design

This study is a randomized, single-blind, controlled trial. All cases were outpatients. Sixty subjects were randomly allocated to treatment and control groups. The specific technical route is as shown in Figure 1.

Subjects

Sample Size

This study was a clinical pilot trail. According to expert suggestions, the total sample size was set at 60 cases (the case dropout rate was controlled to within 20% during the trial), of which 30 cases were allocated to the treatment group and 30 cases to the control group.

The formula for calculating sample size is as follows:

Diagnostic Criteria

(1) CHD Diagnostic Criteria:

1) Has a history of myocardial infarction, with or without receiving revascularization (PCI or CABG) treatments;

2) Coronary angiography or coronary CTA indicates at least one major branch of the lumen diameter stenosis has narrowed by over 50%, with or without receiving revascularization treatments.

Diagnosis can be made if patient conforms with one of the above criteria.

(2) SAP Diagnostic Criteria

With reference to the Symposium of National Integrative Medicine Prevention and Treatment of Coronary Heart Disease, Angina and Arrhythmia’s “Reference Standard for Diagnosis of Coronary

Heart Disease” [4] revised in September 1979, this disease was graded by referring to “Guidelines for the Diagnosis and Treatment of Chronic SAP”[5].

(3) Grading Standards [5]:

Grade I: General daily activities, such as walking and going upstairs, do not cause angina, but nervousness, rapid or sustained exertion may cause an angina attack;

Grade II: Daily physical activities are slightly restricted. Fast walking or going upstairs, ascending to a higher elevation, walking or going upstairs after a meal, walking in the cold or wind, emotional excitement may induce an angina attack, or result in an attack occurring within several hours after waking up. Under normal circumstances, walking at normal pace on flat ground for over 200m, or going up more than one flight of stairs is restricted;

Grade III: Daily physical activities are obviously restricted, under normal circumstances, walking for 100 - 200m at a normal pace or climbing one flight of stairs may cause angina pectoris;

Grade IV: Angina symptoms may occur during mildly strenuous activities or during rest.

(4) Differentiation Criteria for TCM Qi Deficiency and Blood Stasis Syndrome

According to the prescription compositions and functional indications of Compound Salvia Droplet Pills and with reference to *Guiding Principles for Clinical Studies on New Drugs for the Treatment of CHD with Angina Pectoris*[6] and *Chinese Medicine Industry Standard of the People's Republic of China • Criteria of TCM Syndromes* [7], CHD with angina pectoris of blood stasis and qi stagnation syndromes was chosen as observation syndromes.

Blood stagnation and Qi stagnation syndromes

Primary symptoms: Chest tightness and/or chest pain;

Secondary symptoms: Cardiac palpitations, shortness of breath, suffocation, painful distension over hypochondrium;

Tongue Appearance: Dark tongue, or dark purple or weak spots, thin white fur;

Pulse: Taut and uneven pulse.

Diagnosis can be made if primary and secondary symptoms are present, and in combination with the tongue appearance and pulse considerations.

Inclusion criteria

1) Complies with the Western medical diagnosis of angina pectoris; more than two weekly attacks of grade I - III stable exertional angina pectoris;

2) Qi deficiency and blood stasis TCM syndrome differentiation;

3) ECG shows ischemic changes or treadmill exercise trail showed as positive;

4) Aged between 18 to 70 years old;

5) Signed the informed consent form.

Exclusion Criteria

1) Patients with confirmed coronary heart disease with acute myocardial infarction, or severe angina pectoris and other heart diseases, severe neurosis, menopausal syndrome, or chest pains caused by cervical spondylosis;

2) Patients with grade III or higher hypertension, severe cardiopulmonary insufficiency, severe arrhythmia (rapid atrial fibrillation, atrial flutter, paroxysmal ventricular tachycardia, etc.);

3) Patients with serious primary hepatic, renal, hematopoietic system, or mental diseases;

4) Patients under 18 years of age or over 70 years of age, pregnant or breast-feeding women, or any patient with an allergic constitution;

5) Patients who have had surgery and a bleeding tendency in that least four weeks, or have taken clopidogrel, warfarin, or any anticoagulant other than aspirin;

6) Patients have participated in other clinical trials within the last month.

Randomization

The trial was conducted by the Tianjin Institute of Chinese Medicine Clinical Evaluation using the Central Randomization System (CRS) to achieve central randomized distribution and centralized drug delivery. The age and sex were used as central random control factors, among which, age was divided into categories of 18 to 50 years, and 51 to 70 years. Subjects were dynamically randomized to maintain the balance between groups and avoid selective bias of the cases. The drug distribution and inventory information were monitored in a real-time, and drugs were replenished in a timely manner to effectively avoid a unnecessary surplus of drugs and to greatly save manpower and

material resources.

Blinding Method

Compound Salvia Droplet Pills and aspirin were used as solid preparations. To reduce the bias of the trial, a double-blind single simulation blinded design was used to divide the two groups; where A is the trail group and B is the control group. Compound Salvia Droplet Pills and aspirin were used on the trail group, and Compound Salvia Droplet Pills mimetics and aspirin were used on the control group. To reduce the test bias, researchers, patients and statistical experts were under blindfold conditions during the trial.

Intervening Measures

All research cases received basic routine western medical treatment according to the *Guidelines for diagnosis and treatment of chronic SAP*[5]. In combination with patients' cardiac function, antiplatelet drugs and statins lipid-lowering drugs were used providing no contraindications were exhibited. Medications were selected according to the complications and relevant guidelines; all Chinese medicine preparations other than the trail drugs were prohibited.

The specific posology of the trail drug was as follows:

Treatment Group: Compound Salvia Droplet Pills, 10 pills/time, 3 times a day, + aspirin 100 mg/time, once a day;

Control group: Aspirin 100 mg/time, once a day.

Duration of treatment: 28 ± 1 days.

Outcome Measures

Primary outcome measures

The primary outcome measures of this study included improvements of the angina pectoris symptoms and TCM syndromes. These two indices were measured before and after treatment, and used to

determine the condition of the angina symptoms, which was an easy task to implement. TCM syndromes were evaluated according to the primary and secondary symptom scores.

Secondary Outcome Measures

A Therapeutic evaluation was conducted according to changes in the objective indices combined with physiochemical examinations before and after treatment.

ECG’s can reflect changes in cardiac electrical activity generated in each cardiac cycle. Most patients may have temporary ST segment shift caused by myocardial ischemia, so common responses include ST segment depression of subendocardial myocardial ischemia (≥ 0.1 m V), patients recovered after the episode subsided. There were some instances of T-wave inversion. For patients with normal T-wave continuous inversion, the T-wave may become upright during an episode.

In addition, the incidence conditions of end-point events were observed to analyze the incidence of cardiovascular events and rehospitalization rate.

Safety Indices

Safety checks included vital signs, physiochemical examinations and evaluation of adverse events. The measured vital signs included blood pressure and heart rate; physiochemical examinations included routine blood, urine, stools and occult blood, hepatic and renal functions. The routine stool and occult blood trails were adopted to prevent the use of drugs for anti-platelet aggregation and anticoagulants, which may lead to gastrointestinal bleeding.

Adverse events were recorded during the treatment phase. The prognosis of adverse events was observed until the adverse reactions disappeared or were alleviated.

Data Collection

We collected three types of data including basic information (gender, age, previous medical history, medication, etc.), disease evaluation (angina pectoris symptom score, TCM syndrome score) and physiochemical trails (ECG, coagulation, etc.). For specific items and interviews, refer to Table 1.
The data and information were entered into the medical records and case report forms by the researchers. The medical records were designed giving consideration to facilitating the researchers entering of data and data traceability. the original patient's name, contact information, physiochemical trail reports, etc. were retained; the case report forms were designed to facilitate data entry; patients personal information was kept confidential and the patients were distinguished by code.

Recruitment

Advertising: Use doctors' influence to advertising through the media, e.g. the maximum circulation of newspapers in cities, WeChat subscription platform, etc. to post recruitment information.

Community hospital recruitment: Collecting cases from community hospitals through questionnaires.An effective questionnaire reward is given to the doctors. Then follow up the drug using situation from patients. Or advertising in the community hospital to recruit and public the result by doctors, and attract patients to the researcher's hospital to organize the health lecture centrally.

Data Analysis

The data analysis shall be conducted by the Tianjin Institute of Chinese Medicine Clinical Evaluation Institute using SAS 9.3 statistical software. Due to the different data categories, the T-test and test were adopted.

Discussion

Compound Salvia Droplet Pills are the preferred drug [8] for the clinical treatment of CHD with angina pectoris. Its efficacy in alleviating angina pectoris has been widely recognized, especially in improving the signs and symptoms, quality of life, exercise tolerance, long-term prognosis (reducing the

mortality and re-admission rate due to angina pectoris) of patients with angina pectoris, which has been validated through clinical studies [9-12].

Compound Salvia Droplet Pills are composed of Panax notoginseng, Radix Salviae Miltiorrhizae and borneol. It is effective in pain relief and activating circulation to remove blood stasis [14]. Panax notoginseng tastes sweet and warm, with favorable analgesic and hemostatic effects. Radix Salviae Miltiorrhizae tastes bitter and cold, and highly effective in activating blood and dissolving stasis. Borneol tastes spicy and cool and highly effective for inducing resuscitation. Its main component, Radix Salviae Miltiorrhizae, can resist platelet aggregation, oxygen free radical activation, and vascular endothelial proliferation; when combined with Panax notoginseng and borneol, it can not only directly regulate blood lipids and lower blood viscosity, but also improve the hemodynamic disorders [14]. In addition, it functions to repair vascular endothelial cells. By reducing the negative influence on hemodynamics such as stenosis, sclerosis and embolism, the blood circulation is smoother, which reduces the total myocardial ischemic load [15], and therefore improves the disease conditions. Domestic studies have confirmed [16] that, PAGM, SV, LDL and HDL were significantly improved, cardiac function-related indices were also improved significantly, indicating on one hand the ability to facilitate obvious improvements in the hemodynamic indices, and on the other hand, Compound Salvia Droplet Pills have a better auxiliary effect on ameliorating hemodynamic disorders. In addition, it is possible that Compound Salvia Droplet Pills can concurrently improve hemodynamic parameters and vascular functions.

This study has three characteristics: (1) Subjects were selected from patients with underlying CHD with stable exertional angina pectoris. The disease populations and conduct studies according to the main causes of angina pectoris and the main treatment types were fully clarified. (2) The study is a superiority trial drawing comparisons with a conventional aspirin monotherapy. (3) The main efficacy indicators were the improvement rate of angina pectoris symptoms and the effective rate of TCM syndromes. The clinical efficacy evaluation method of traditional Chinese medicine was used, that is, “a combination of illness and symptoms, system segmentation, multidimensional indexes” [17].

Indices which reflected the advantages and characteristics of TCM, combined with the conventional efficacy evaluation of western medicines were selected; and the incidence of endpoint events was observed.

Trial Progress

The trial began on November 1, 2017, as of October 1 2018, a total of 60 patients were enrolled in the study. The study is expected to conclude in February 30, 2019. The clinical trial registration number is ChiCTR - IPR - 17012014.

Declarations

Ethics approval and consent to participate:

This study has been reviewed by the leading institute Tianjin University of Traditional Chinese Medicine (TJUTCM - EC20170003) and the Ethics Committee of participating hospitals. The research protocol and informed consent form conformed with the scientific and ethical requirements. Before admission, all subjects or their legal guardians shall sign an informed consent form. Aspirin and compound Salvia droplet pills were purchased in “ BaoKang ”hospital through the normal route.

Consent for publication:

“Not applicable”

Availability of data and material:

The datasets generated and/or analysed during the current study are not publicly available due [The clinical trial project has not completed.] but are available from the corresponding author on reasonable request.

Competing Interests:

The authors have no other relevant affiliations or financial involvement with any organization or entity

with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Authors’ contributions:

All authors have read and approved this version of the article, and due care has been taken to ensure the integrity of the work. Neither the entire paper nor any part of its content has been published or has been accepted elsewhere. It is not being submitted to any other journal. ZL and JC took part in the design of the study,performed the literature survey and drafted the the manuscript. ZW and RG took part in the design and implementation of the study.HW and CL was responsible for central randomization management.WZ was responsible for statistical analysis.AS principal Investigator,JC played a key role in the professional design of the study.

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Table 1. Trial Flow Chart

Item \ Research stage	Screening/ Inclusion	Evaluation after Administering Medication	F
Time	Within 48 h	28 ±1 d	14 ±3 d
Basic treatment	√	√	
Determine inclusion or exclusion	√		
Sign informed consent form	√		
Fill out general information	√		
Medical history, treatment history, and allergy history	√		
Current medication condition	√		
Acquire central randomized number	√		
Designate the research drugs	√		
Score angina pectoris symptoms	√	√	
Score Chinese medicine symptoms	√	√	
12-channel ECG	√	√	
Blood coagulation	√	√	
Cardiovascular events		√	
Re-hospitalization			
Blood pressure, heart rate	√	√	
Recording of adverse events		√	
Routine blood, urine and stools + occult blood	√	√	
Hepatic and Renal functions (fasting)	√	√	
Research drug recovery record		√	
Trial completion conditions			
CRF audit			

Table 1: Trial Flow Chart

Figures

Figure 1

Technical route chart

Supplementary Files

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