The Effect of Acupuncture as Adjunctive Therapy for Chronic Stable Angina (A Randomized Clinical Trial)

STUDY PROTOCOL

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1. Background

Chronic stable angina (CSA) is a common cardiovascular condition that endangers a patient's life quality and longevity, which is characterized by severe chest pain and discomfort in the left anterior chest or adjacent areas caused by myocardial ischemia[1]. Stable angina affects more than 7.8 million people in the United States, with an annual incidence of over 500,000 new cases[2]. Despite the declining incidence of myocardial infarction, the prevalence of angina remains high, and direct costs in the United States in 2000 have been estimated at up to $75 billion[3]. As for China, the prevalence of angina is 2.4 % among males and 3.2% among females[4], which makes it a serious social problem, considering its large population base. In China, a large majority of CSA patients resort to acupuncture and other traditional Chinese medicine (TCM) therapies in addition to conventional drugs for treatment and recurrence prevention[5,6], though discrepancies still exist concerning the effectiveness and efficacy of acupuncture therapy for angina.

Acupuncture, well known as an oriental healing technique that originated from ancient China, has been used as a treatment method in Asia for over 2,000 years. Nowadays, the therapeutic effect of acupuncture is gradually being recognized in the western world. The National Institutes of Health (NIH) Consensus has recommended acupuncture as an alternative and complementary treatment for many health conditions [7]. As demonstrated in several international clinical trials 20 years ago, acupuncture is effective for CSA[8] in reducing disease duration[9], anginal attack and

nitroglycerin consumption [10], as well as for improving cardiac work capacity [11]. Similarly, clinical trials [12,13] and case observations [14-17] from China in recent decades, accompanied with TCM experts' opinions [18], have consistently confirmed that CSA patients may benefits from traditional acupuncture therapy. Importantly, large amount of animal experiments have already validated the myocardial protective effect of acupuncture for cardiac ischemia[19,20] and reperfusion via inhibition of the beta(1)-adrenoceptor signaling pathway [21,22] and regulation of myocardial enzyme level [23,24]. However, these Chinese clinical trials or observations and international randomized controlled trials (RCTs) are not adequate enough to act as high-quality evidence for clinical decision making, as a result of inadequate methodology design and small sample size [25]. Therefore, clinical trials with sufficient sample size and sound methodology design are necessary and meaningful to clinical practice.

Notably, there is a remarkable paradox in the aforementioned international clinical trials validating the effectiveness of acupuncture for CSA, which is the specificity of real acupoint when compared with sham acupoint [8-11]. In TCM theory, multifaceted factors contribute to therapeutic effect of acupuncture [26], among which, the selection of optimal acupoint is vital. As to acupoint selection, the traditional acupuncture theory emphasizes the indications and property of different acupoints, which is known as acupoint specificity[27]. Acupoint specificity has been widely acknowledged and considerably utilized as the basic law of traditional acupuncture practice. To elaborate, acupuncturists would always prefer to choose acupoints on the

disease-affected meridian(s) for preferable treatment effect based on TCM patterns resulting from syndrome differentiation [28]. Nevertheless, many reviews, meta-analyses and clinical trials have merely demonstrated a statistical difference, but not clinical significance between real acupoint and sham point for various diseases[29-36]. These studies have drawn the attentions of many researchers and further aroused controversy regarding the existence of acupoint specificity. In 2010, the American Association of Acupuncture came to a consensus agreement and announced in a white paper that acupoint specificity was one of these two main paradoxes of forthcoming acupuncture research[28]. Hence, clinical trials assessing the meridian-involved acupuncture specificity is of great significance for guiding clinical practice as well as for inspiring basic research in acupuncture.

2. Study Aims

We have designed a clinical trial to primarily investigate the effect of acupuncture, in addition to routine care, among patients with CSA. Furthermore, we investigated whether acupuncture on the acupoints of disease-affected meridian (DAM) was more efficacious than acupoints on the non-affected meridian (NAM) or sham acupuncture (SA) or waiting list (WL).

3. Research Design and Methods

3.1 Design

This study was a multicenter, assessor and statistician blinded, RCT in China. In this study, 404 participants in sum would be randomly assigned to the four groups through central randomization in a 1:1:1:1 ratio (Figure 1). Eligible participants will be recruited from outpatient clinics and inpatient departments of Cardiology in the following five clinical centers in different regions of China: Chengdu University of Traditional Chinese Medicine, Hunan University of Traditional Chinese Medicine, Guiyang University of Traditional Chinese Medicine, Shaanxi University of Chinese Medicine, and Yunnan Provincial Hospital of Traditional Chinese Medicine.

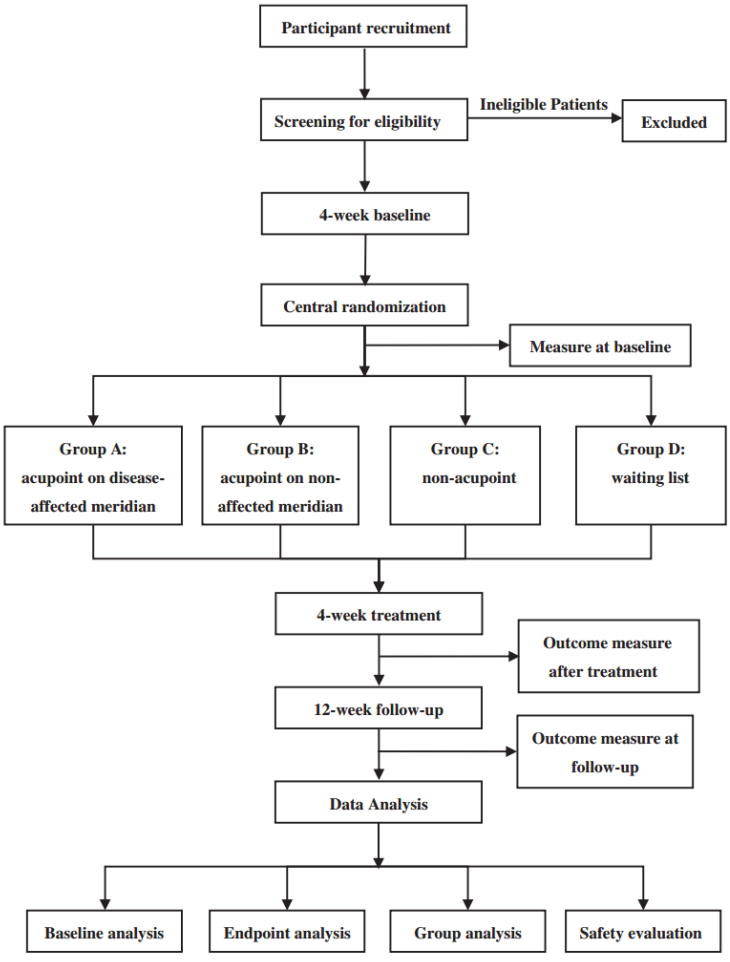

Figure 1 Trial profile

3.2 Randomization

The central randomization is performed by the Company of Brightech-Magnsoft Clinical Information Management System (CIMS). Allocation to the treatment groups uses a stratified block dynamic randomization method with permuted block, which is automatically under the control of a central computer system. The website and mobile messages will be used to send randomization information (including the participants' name in pinyin format, gender and date of birth) to the center. To guarantee allocation concealment, randomization will be done by an independent researcher. An independent assessor will interview the participants and perform the screening. Random numbers and group assignment will be confirmed through email or short message service (SMS) to the independent assessor immediately. This procedure guarantees that randomization concealment is adequate, and not influenced either by the acupuncturists or by the participants. Participants allocated to groups will be blinded to their treatment allocation; however blinding is clearly not possible in the WL control group. We shall endeavor to ensure that participants begin the trial with the same expectations of effectiveness by informing them that all the treatments provided are effective. All participants will be assessed and the results analyzed by professionals blinded with respect to the allocations of the different treatments.

3.3 Ethical Requirements and Registration

The Consolidated Standards of Reporting Trials (CONSORT) statement

(http://www.consort-statement.org/home/) has been used as a framework for developing the study methodology. The protocol of this study was approved by the Ethics Committee of the Teaching Hospital of Chengdu University of TCM (Chengdu, China) in June 2012 and is in accordance with the Declaration of Helsinki. The trial protocol has permission number 2012KL-005. The trial was registered in ClinicalTrials.gov with approval number NCT 01686230. All participants have provided written informed consent to be included in the trial.

3.4 Setting and participants

Participants will be: informed (verbally and through a print-out) of the possible risks associated with the study; instructed to complete the angina diary; told that they can withdraw from the trial at any time without specifying reasons; and told they can provide written informed consent before enrollment voluntarily. Before randomization, all eligible patients will be informed of the details of the study and all the benefits and risk that they may take from this trial. Particularly, participants will be clearly told about the equal chance of allocation to any one of the four groups before signing the informed consent. Meanwhile, they will be given enough time to decide whether they join in the trial or not. Lastly, participants will be included voluntarily by signing the written informed consent. However, due to the principle of blinding, only patients allocated to WL group will be told to wait for free treatments till the completion of study; while allocation information will be strictly restrained to patients in the other three groups.

4. Inclusion and Exclusion Criteria

4.1 Inclusion criteria

Eligible participants should match the diagnostic criteria for CSA set by according to the classification criteria of the American College of Cardiology and the American Heart Association (ACC/AHA)[37]. They must:

- men or women between 35 and 80 years of age;
- presence of angina for more than 3 months with attacks occurring at least twice weekly at baseline;
- no significant change in the frequency, extent, nature and inducing and alleviation factors of angina attacks during the baseline;
- provided written informed consent by themselves.

4.2 Exclusion criteria

Participants with any of the following conditions will be excluded:

- age ≤35 or age ≥80;
- presence of acute coronary syndrome (including acute myocardial infarction and unstable angina), severe arrhythmias (severe atrioventricular block, ventricular tachycardia, heartbeat influencing the flow dynamics in supraventricular tachycardia, frequent heartbeat and premature beat and especially premature ventricular contractions), atrial fibrillation, primary cardiomyopathy and valvular heart disease;
- psychiatric, allergic, or blood disorders; poorly controlled or uncontrolled blood

pressure or blood glucose;

- other severe primary disease not effectively controlled;
- heart disease treated with acupuncture within the previous 3 months;
- pregnancy or lactation;
- undergoing other clinical trials.

5. Interventions

In order to ensure the safety of participants, fulfill ethic necessities and improve the prognosis of patients with angina pectoris, we adhered to the European and Chinese Guidelines for the management of patients with chronic stable angina recommendation [37,38]. All participants in the four groups will receive same basic treatment. In addition, according to the guidelines and clinical conditions in China, we shall prescribe antianginal drugs for patients suffering acute angina attack.

The initial acupuncture treatment scheme originates from the clinical practice of TCM. The final scheme was discussed and revised according to advice of clinical acupuncture experts who were consulted in China. Participants in the acupuncture groups will receive 12 sessions of acupuncture treatment over 4 weeks. In each session, participants in all groups except for WL will receive acupuncture treatment bilaterally three times per week and each session will last for 30 mins. Each group shares the same basic treatment including health education and basic drug therapy. The whole study period is 20 weeks including a 4-week baseline period, a 4-week

treatment period and a 12-week follow-up. We required each participant to record the details of each angina attack and remission in angina diaries. The angina diaries should be kept from baseline to 12 weeks after randomization. All outcomes will be assessed at baseline period and in the 4th, 8th, 12th and 16th weeks after randomization, according to the diaries and related checks.

5.1 Basic treatment

Basic treatment includes health education and primary drugs. We recommend lifestyle modification including increasing exercise, limiting alcohol consumption, weight loss, quitting smoking, etcetera for all patients in health education. Basic medication includes aspirin (100 mg once a day); metoprolol (25 mg twice a day); ramipril (5 mg once a day); and atorvastatin (20 mg once every night)[37,38]. Basic treatment lasted from baseline to the completion of the follow-up period.

5.2 Antianginal therapy

Antianginal therapy includes nitroglycerin, nifedipine tablets and *suxiao jiuxin wan*[39]. In emergency cases of angina attack, participants will be instructed to administer one kind of medicine according to previous treatment history and personal contraindication. Basically, for all patients, we recommend nitroglycerin. Regardless of the type of medicine, participants are required to carefully record the details of medicine, including name, administration time and dosage. Researchers will provide these three drugs to standardize the basic treatment for free: Nitroglycerin (Beijing Yimin Pharmaceutical Co., Ltd., Beijing, China) with State Food and Drugs

Administration (SFDA) (China) registration number (H11021022), sublingual dose of 0.5 mg (one tablet); Nifedipine Tablets (CSPC Pharmaceutical Group Limited, Shijiazhuang, China, SFDA: H13021315), oral dose of 10 mg (one tablet); *Suxiao Jiuxin wan* (SX) (Zhongxin Pharma Tianjin No. 6 Traditional Chinese Medicine Factory, Tianjin, China, SFDA: Z12020025), sublingual dose of 5 to 10 pills. Other antianginal drugs would be considered to violate the study protocol, for which the patient would be eliminated.

There will be one treatment group receiving acupuncture stimulation at acupoints on the DAM, and three different control groups undergoing acupuncture stimulation at acupoints on a NAM, NA and no intervention, respectively, in addition to routine care. The location and needling methods for acupoints and non-acupoints are demonstrated in Table 1. The name/code and location of the acupoints are consistent with the WHO standards [40].

Table 1. Details of groups

Group	Interventions	Acupoints	Manipulation
Acupoint on disease- affected meridian	Acupuncture and basic treatment	Neiguan (PC6) Tongli (HT5)	Both points are punctured bilaterally and perpendicularly 2 to 4 cm
Acupoint on non-affected meridian	Acupuncture and basic treatment	Taiyuan (LU9) Kongzui (LU6)	Both points are punctured bilaterally and perpendicularly 2 to 4 cm.
Non-acupoint	Acupuncture and basic treatment	1) On the front arm of deltoid muscle and biceps brachi junction. 2) On the ulnar side of the arm, half way between the epicondylus medialis of the humerus and the ulnar side of the wrist.	Both points are punctured bilaterally and perpendicularly 3 to 5 cm.
Waiting list	Basic treatment		

5.3 DAM group

Based on TCM theory, angina pectoris commonly affects the heart and pericardium meridian, and acupoints located on these two meridians are essential components of acupoint prescription for heart diseases in acupuncture clinics. Thus, we selected Neiguan (PC6) and Tongli (HT5) as obligatory acupoints. PC6 has profoundly been regarded as the key acupoint for curing heart and chest disease in Chinese medicine. As clinically indicated, PC6 can improve cardiac function, enhance myocardial contractility, increase coronary artery blood flow and myocardial oxygen supply and relieve angina pectoris [41-43]. HT5 functions to calm the spirit and regulate heart rhythm. The combination of HT5 and PC6 are frequently used to treat angina

pectoris and arrhythmia clinically [44].

5.4 NAM group

In this group, we selected Taiyuan (LU9) and Kongzui (LU6), both of which belong to Lung Meridian of Hand Taiyin. This meridian and its related acupoints in clinical acupuncture practice are not the preferred choice for treating angina pectoris [45]. Nevertheless, they are located inside the forearm, which makes it a suitable control because acupoints chosen in the DAM group are located in the same body area.

5.5 NA group

We will provide non-acupoint acupuncture treatment for patients in the NA group, in which pre-validated sham acupoints [46] and real insertion of acupuncture needles at bilateral non-acupoints will be administrated, but without achieving a '*deqi*' sensation.

5.6 WL group

Participants in this group will receive no acupuncture-related intervention while the trial is in process, but will receive a free 12-session acupuncture treatment over 4 weeks after the completion of the study.

The doctors performing all treatment procedures have at least 5-year experience of acupuncture treatment and a TCM license. All acupoints will be punctured with disposable stainless steel needles (0.25 mm × 40 mm; 0.25 mm × 25 mm; Suzhou Huatuo Medical Appliance Co., Ltd., Suzhou City, China). The needles will be manipulated in a lifting and thrusting technique combined with twirling and rotating

manner until the patient feels numbness or other acupuncture sensation (known as '*deqi*'). Then, an auxiliary needle (0.18 mm × 13 mm) will be inserted to 2 mm away from the acupuncture needle to a depth of 2 mm. No manipulation will be delivered to the auxiliary needle. Acupuncture needles and auxiliary needles will be separately connected to an electrode-powered by HANS-200A stimulator (Nanjing Jisheng Medical Technology Company, Nanjing city, China), to induce stimulation to further activate acupoint for 30 min with 2 Hz, rarefaction wave. The electrical stimulation intensity will be adjusted from 0.1 mA to 2.0 mA to make the patients feel comfortable. After retaining for 30 min, all needles will be withdrawn with clean cotton balls pressed to the skin to prevent bleeding.

6. Outcome Measurement

The primary outcome was the change in frequency of angina attacks from baseline to 16 weeks based on the angina diaries over 4-week baseline through weeks 16. The secondary outcome measures are:

- average severity of angina as assessed with visual analogue scale (VAS) score;
- the Seattle Angina Questionnaire (SAQ);
- improvement of exercise capacity assessed by Six minutes' walk test;
- rescue medication intake;
- the heart rate variability (HRV) as recorded by Holter monitor;
- the Canadian Cardiovascular Society (CCS) angina grading;

- Zung Self-Rating Anxiety Scale (SAS) and Zung Self-rating Depression Scale (SDS);
- acupuncture expectation value;
- number of participants with adverse events (AEs) and serious adverse events (SAEs).

Detailed time points of outcome assessments are provided in **Table 2**.

Table 2 Timetable of treatment and outcome collection

Period	**Baseline**	**Inclusion**	**Treatment**	**Follow-up**		
Measurement		1	2	3	4	5
Week	-4	0	4	8	12	16
Patients						
Informed consent						
Inclusion/exclusion criteria	×	×				
Medical history	×					
Medical examination	×					
Combined disease treatment	×	×	×	×	×	×
Physical examination	×					
Outcomes						
Angina diary	×	×	×	×	×	×
The frequency of angina attack	×	×	×	×	×	×
The dosage of rescue medication	×	×	×	×	×	×
Angina pectoris grade		×	×			
The pain severity of angina(VAS)	×	×	×	×	×	×
SAQ score		×	×	×	×	×
Six minutes' walk test		×	×			
SAS and SDS		×	×	×		×
24 hours dynamic ECG		×	×			
Cardiovascular events			×	×	×	×
Trial evaluation						
Patient's compliance			×			×
Reasons of drop-out or withdrawals			×			×
Adverse events						×
Safety evaluation						×

ECG, dynamic electrocardiograph; SAQ, Seattle Angina Questionnaire; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; VAS, Visual Analogue Scale.

7. Adverse Events and Safety

For the sake of patient safety, prevention measures and emergency medical plans will include well-equipped treatment rooms, emergency department, cardiovascular specialist and first-line clinical physicians. All adverse events (AEs) associated with acupuncture would be recorded during the treatment and the follow-ups; these AEs include bleeding, hematoma, fainting, serious pain, local infection, etcetera. On the other hand, AEs commonly associated with the anti-anginal drugs (basic therapy) will be documented as well, (for example, headaches, dizziness, nausea, flushing, abdominal pain, etcetera) [47]. Serious adverse events (SAE) are defined as death or life-threatening events, which may require inpatient hospitalization, cause prolongation of existing hospitalization, or even result in persistent or significant disability/incapacity and need intervention to prevent permanent impairment or damage. If participants suffer any AE/SAE, all details will be documented and reported. Furthermore, SAE will be reported to the principal investigator and the ethics committee immediately so that they can make a decision on whether the patient should withdraw from the trial.

8. Drop-outs

Patients who withdraw from the trial for any reason will be considered a drop-out. The common reasons for dropping out including AEs, poor compliance with the protocol, unsatisfied efficacy, withdraw and quit, and others. Investigators should

complete the case report form (CRF) and record the reason for dropping out. All the information from participants who have dropped out will be used for intention-to treat (ITT) analysis.

9. Data Management

All CRFs for each patient should be filled in by study staff in each clinical center timely. All data, including the time of angina onset, duration, severity and rescue medication use based on angina diary, questionnaires, assessment scales, physical examinations, treatment compliance and screening details will be filed accurately in CRFs. Medical histories, original documents and CRFs will be stored in the clinical study office. Researcher staff will double-entered all data in electronic CRFs which produced by the Brightech–Magnasoft CIMS. The CRFs and electronic CRFs are identical. When the data entry is complete, the database will perform consistency check automatically. Whenever inconsistencies are found, the data will be rechecked and corrected in according to the CRFs and original documents.

10. Training for Study Physicians

All physicians who enroll participants and assessors who collect data must attend training classes to ensure all practices at each hospital are identical. The training classes comprise theoretical and practical lessons. Physicians must pass the training test to understand the purpose and content of the trial, treatment strategies and quality

control. Additionally, to maintain quality control, quality monitoring will be carried out by Brightech–Magnasoft CIMS, and specially trained physicians will check all trial processes.

11. Calculation of Sample Size and Statistical Analyses

11.1 Calculation of sample size

The sample size calculation was based on a previously study by Richter A. et al. [48]. According to which, the clinical effect difference value of the two groups was 4.5. In this study, we incorporated the early clinical pretest, the difference of clinical effect for frequency of weekly angina attacks (DAM and NA) was estimated to be 4.2. Standard deviation for each of the four groups was 8.5 times ($\alpha = 0.05$; $1\text{-}\beta = 0.90$). According to the estimation with NQuery Advisor (Version 4.0, Statistical Solutions Ltd, Ireland), in the bilateral testing, 352 cases are required in this study with 88 cases for each group. Considering a 15% dropout, therefore, 404 participants in sum should be included in this trial with 101 for each group.

11.2 Statistical analyses

All data in this trial will be assessed by Brightech–Magnasoft CIMS, with SPSS version 13.0 (SPSS, Chicago, IL, USA) and SAS version 9.3 (SAS, Cary, NC, USA). All analyses will be done on the ITT population (i.e., any participant randomized regardless of whether he/she receives any treatment). Missing data will be replaced according to the principle of the last observation carried forward method. In addition,

the per-protocol (PP) population will be analyzed. The results of ITT and PP analyses will be compared to ascertain if the results are consistent. Moreover, analysis of variance (ANOVA) for repeated measures will be used for numerical variables. The Chi-square test will be used for categorical variables. $P<0.05$ will be considered significant.

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