Clinical Trial Protocol

Myocardial infarction secondary prevention study (MISPS)

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Background

Traditional Chinese medicine (TCM), especially herbal medicine, has been widely used in China and now is also being increasingly used in other countries for the treatment of cardiovascular diseases. Although many studies have demonstrated that certain Chinese herbal products are effective and safe for the treatment of cardiovascular diseases, most of these lack sufficient quality. Therefore, large randomized clinical trials and further scientific research to determine its safety, effectiveness are necessary. Qishen YiQi Dipping Pills (QSYQDP) is a herbal preparation clinically used in the treatment and prevention of coronary artery disease. Preliminary observations have shown its safety and effectiveness. Methods/Design This randomized, controlled trial will recruit 3600 patients with a history of myocardial infarction. Patients will be randomized into two groups by a Centr-Randomized System. One group receives QSYQDP, the other group receive aspirin. This trial protocol will describe eligibility criteria, detailed information on the treatment definition, blinding, endpoints, statistical methods, sample size determination, data management, legal aspects, and the current status of the trial. Discussion This trial is one of the first randomized, controlled clinical trial to evaluate the efficacy and safety of traditional Chinese herbal medicine in the treatment and secondary prevention of coronary artery disease. The results of this study should help to define the role of TCM in modern medical care, as well as to provide the management strategy for CAD patients in China and other countries. (J Geriatr Cardiol 2006; 3(2):116-9.)

Background

During the past decades, numerous large clinical trials have confirmed the effectiveness of antiplatelet drugs, β-receptor blockers, angiotensin-converting enzyme inhibitors (ACEIs), lipid regulating agents, anti-hypertensive agents and interventional therapy on reducing morbidity and mortality of acute myocardial infarction (AMI). However, coronary artery disease still remains the leading cause of death in many developing countries, including China, as well as developed countries.10-12

Traditional Chinese medicine (TCM), especially the herbal medicine, has been widely used in China for the treatment and prevention of CAD. TCM has also been increasingly used in many other countries, including the United States and European countries.13 Many clinical studies showed that TCM could ameliorate the frequency and extent of angina, reduce the dosage of nitroglycerin, and prevent reoccurrence of AMI.14 The supposed mechanisms include dilating coronary artery, improving myocardial ischemia, reducing myocardial oxygen consumption, improving the function of blood vessel endothelium, and regulating lipid metabolism, etc.15 Furthermore, TCM generally showed few and mild side effects, making it and optimal alternative for the secondary prevention of cardiac events.

"Qishen YiQi Dipping Pills (QSYQDP)" is a patent Chinese herbal medicine formulation comprising of Radix Astragali, Radix Salviae Miltiorrhizae and other herbs. In a preliminary study of 18 healthy volunteers, QSYQDP showed similar antiplatelet effect as aspirin, but with fewer side effects.

In this article, we describe a randomized, multicenter study to test the hypothesis that QSYQDP, in combination with other standard treatment for patients with previous MI, is as effective as, or superior to aspirin, in reducing major adverse cardiac events, with comparable, or less side-effects or drug-related complications.
Methods/Design

Design
Randomised controlled multicenter study with blind evaluation by an independent observer and blind, independent analysis.

Inclusion criteria
- Acute myocardial infarction within 28 days to 2 years prior to evaluation.
- Corresponding with syndrome of thoracic obstruction heartache of deficiency of vital energy and blood stasis through differentiation of symptoms and signs of TCM
- Age ≤ 65 years old
- Informed consent is given.

Exclusion criteria
- Age > 65 years old
- Patients with previous PCI or CABG
- Severe heart failure (NYHA Class IV)
- Severe, uncontrolled hypertension (systolic pressure ≥ 180 mmHg and/or diastolic pressure ≥ 110 mmHg)
- Tachycardia and arrhythmias (e.g., atrial fibrillation with rapid ventricular rate, atrial flutter, paroxysmal supraventricular tachycardia)
- History of severe disease in other major organ systems, such as liver, kidney and hemopoietic system or cancer.
- Psychosis
- Peptic ulcer with active bleeding or other hemorrhagic diseases
- Pregnancy or in lactation
- Allergic to aspirin
- Already registered in other clinical trial within three months

Ethical criteria
The ethical validity of this study has been analyzed and approved by the corresponding ethical and research committees at the healthcare centers involved. The study design expressly guarantees the patient’s right to privacy and informed decision-making. The study also complies with the norms for Good Clinical Practice (GCP) and the Edinburgh 2000 revision of the Helsinki Declaration. All the patients who participate give their written, informed consent to the clinical research methods applied. During the development of the study, audits will be performed, according to the criteria of the Research and Ethics Committee and the healthcare center’s Quality Committee, independently of the external audits (research funding provider) that may be required.

Criteria and procedures for withdrawal from the study
A patient may be withdrawn from the study at any time, either at will or by decision of the researcher. The reasons for interrupting participation in the study will be recorded on the summary page of the Case Report Form (CRF). The following procedure is to be followed when a patient withdraws from the study:

- Assess the relevant study variables
- Record any adverse events
- Evaluate the taking of rescue medication
- Indicate the possible co-interventions carried out
- Record the date and reason for withdrawal

Intervention and control
Patients will be randomized into the QSYQDP group (receiving QSYQDP and aspirin placebo) or aspirin group (receiving aspirin and QSYQDP placebo). The QSYQDP, aspirin and their respective placebo medications will be prepared by the Tasly Group (Tianjin, China) and appear identical. Medication administration and data collection will be performed in a double-blind manner, such that neither the patient nor the healthcare personnel will be aware of the medication assignment.

Concomitant medication and treatments
Patients will receive concomitant therapies in both groups as recommended by the current American College of Cardiology / American Heart Association guidelines. This will include smoking cessation counseling and the administration of beta blockers, angiotensin converting enzyme inhibitors, and lipid lowering medications. Target LDL values and blood pressure will be those recommended as per current guidelines and will be assessed during the study follow-up period. Other Chinese medicine and antiplatelet preparations will not be taken by patients.

Outcome measures

Primary outcomes
The primary outcomes of this study will be death from any cause and the major adverse cardiovascular events, including: cardiovascular death, reinfarction, and revascularization (interventional therapy and coronary artery bypass graft).

Secondary endpoints including:
- Scoring of angina.
- Symptom scoring according to TCM
- Quality of Life-Seattle Angina Questionnaire (SAQ)

Data management and analysis

Data collection
Each centre will be provided with a Protocol, Manual of Operations, questionnaires and patient CRFs. Data will be recorded onto two part NCR CRFs and the top copy sent to the CTEU at the times specified. Specific adverse event forms for
death, myocardial infarction, major bleed, cerebrovascular accident, revascularisation and other serious adverse events (ie. other events that require or prolong hospitalisation) are provided. Centres are required to complete these adverse event forms and fax to the CTEU within 72 hours of their knowledge of the event.

**Sample Size**

The trial will be powered to test the hypothesis that QSYQDP will reduce the incidence of MACE at least as effective as aspirin. The sample size calculation is based on the estimate of the incidences of the primary outcomes in our study population. To detect a reduction of MACE incidence by about 30% (equal to that may be achieved by the use of aspirin) with 90% power and 5% alpha requires about 3600 cases (1800 in each of the QSYQDP group and control group).

**Statistics**

Continuous data will be compared between the two groups using two-sided Student’s t tests, two-sample Wilcoxon rank-sum tests, or ANOVA as appropriate, and a Fisher’s exact test will be used for categorical data. In order to assess possible interactions between patient characteristics (such as diabetes) and treatment outcomes, an exploratory analysis using multivariate linear regression will be performed.

**Discussion**

MISPS is the first and currently the largest randomized double blinded clinical trial to evaluate the efficacy of TCM for patients with old myocardial infarction. Specifically, it will answer the questions of whether QSYQDP, a TCM formulation appears to be effective for the treatment of CAD patients from large number of clinical observations, will reduce the incidence of major adverse cardiac events or all-cause mortality in patients with a history of myocardial infarction. We tried to design the trial as good as possible. But all trials, especially TCM clinical trials have their problems. For examples, factors such as the choice of target population, the compliance of the patients, and the aptitude of the evaluators should always be considered carefully.

Aspirin is effective in the short- and long-term prevention of adverse vascular events in high-risk patient groups, including those with ACS, stroke and peripheral arterial disease. Aspirin also has been shown to reduce the frequency of ischemic complications after PCI. Despite the impressive and consistent effects of aspirin in reducing adverse events in a variety of ischemic heart disease states, a significant rate of such events persists. Furthermore, there has been an increasing concern about aspirin resistance (AR) in recent years. To improve the care of patients, therapies must be found that can overcome the resistance to platelet aggregation inhibition, and TCM appears to be one of the promising approach, based on our previous clinical observations and laboratory studies. Should the QSYQDP show the similar efficacy in reducing MACE in patients with history of MI, the MISPS trial has the potential to redefine modern antiplatelet management of coronary artery disease patients.

We believe that the strengths of this study are its randomized and blinded design. Patients will be randomized into two treatment groups, and blinding will occur for all patients and health care providers.

The results of this randomized trial will be generalizable to all patients with coronary artery disease. Although the trial enrolment is limited to patients with a history of myocardial infarction who are under 65 years old, it is anticipated that the results will also be applicable to all patients with CAD.

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**References**

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