

A Chinese Patent Medicine for the Secondary Prevention of Myocardial Infarction

China

Boli Zhang and Junhua Zhang.

Tianjin University of Traditional Chinese Medicine,

312 Anshanxi Str.,

Nankai District, Tianjin,

China 300193

Tel.: +86 22 59596123

URL: iec.tjutcm.edu.cn/english2015/HOME.htm

Email: zjhtcm@foxmail.com

Duration: 2004-2009

Total cost: USD 1,000,000 (Ministry of Science and Technology, State Administration of Traditional Chinese Medicine of PR China)

Summary

Survivors from acute myocardial infarction (MI) remain at greatly increased risk of serious vascular events. Thus, secondary prevention aimed to decrease mortality and morbidity in survivors after acute MI is of great, and increasing, significance around the world. Several types of chemical drugs have been recommended for the secondary prevention of MI. However, these conventional strategies have several limitations, such as low adherence, high cost, and side effects during long-term use. Novel approaches to this problem are still needed. Our study aimed to evaluate the effectiveness and safety of Qi-Shen-Yi-Qi Dripping Pills (QSYQ), a multi-ingredient Chinese patent medicine, for the secondary prevention of MI.

A total of 3,505 eligible patients were randomly assigned to a QSYQ group (1,746 patients) and an aspirin group (1,759). Patients took their treatments for 12 months. The final follow-up visit took place 6 months later. The 12-month and 18-month estimated incidences of the primary outcome were 2.98% and 3.67%, respectively, in the QSYQ group. The figures were 2.96% and 3.81% in the aspirin group. These data did not show significant difference of primary and secondary outcomes between aspirin and QSYQ in patients who have had an MI. The result suggested that QSYQ has similar effects to aspirin in the secondary prevention of MI.

Background and Justification

Acute myocardial infarction is a leading cause of death worldwide. More than 7 million people a year have a myocardial infarction (MI). Over the past three decades, MI has emerged from an illness seen predominantly in developed countries to becoming more common also in developing countries. Progress in emergency management led to substantial reductions in the mortality rate of acute MI. However, survivors from acute MI remain at greatly increased risk of serious vascular events. Thus, secondary prevention aimed at decreasing mortality and morbidity in survivors of acute MI is of great, and increasing, significance around the world.

Platelets play a key role in the development of thrombotic and ischaemic diseases. Anti-platelet therapy is a major strategy for treating and preventing MI. Anti-platelet drugs have been shown to have definite and substantial net benefits for people who have occlusive vascular disease. Aspirin is a safe and cost-effective anti-platelet drug and current guidelines recommend low-dose aspirin (75-150 mg daily) for the secondary prevention of MI in many countries. However, there are several limitations related to this drug. Long-term therapy with aspirin is associated with an increase in the incidence of symptomatic

peptic ulcer, duodenal ulcers, and gastrointestinal and intracranial haemorrhage, even when used at low doses or in buffered or enteric-coated formulations. In a population-based cohort with 4.1 million citizens in Italy, for example, aspirin increased the risk of major gastrointestinal or cerebral bleeding episodes, and patients with diabetes had a high rate of bleeding. Furthermore, aspirin resistance has become a notable problem. Several studies have found that about 1 in 4 individuals may express biochemically defined aspirin resistance. Patients who are resistant to aspirin are at greater risk of recurrent serious vascular events than those who are sensitive to aspirin.

Current anti-platelet therapies are generally based on a specific signaling pathway in platelet activation, that is a single agent acting on a single target. Hence, the limitations associated with aspirin also exist for other anti-platelet agents, such as clopidogrel. Agents with multiple ingredients acting on multiple targets may be more effective and less harmful.

In Traditional Chinese Medicine (TCM), the key pathogenesis of MI is mainly “Qixu” (vital energy deficiency) and “Xueyu” (blood stagnation), that is, degradation of body function and thrombosis. Qi-Shen-Yi-Qi Dripping Pills (QSYQ), a Chinese patent medicine for adding “qi” and resolving stasis, was approved for clinical use for coronary heart disease and MI rehabilitation by the State Food and Drug Administration of China in 2003. QSYQ is made of extractions from Danshen (*Radix Salviae Miltiorrhizae*), Sanqi (*Radix Notoginseng*), Jiangxiang (*Lignum Dalbergiae Odoriferae*), and Huangqi (*Radix Astragali*). The quality control of QSYQ is good. Herbal materials were cultivated according to the good agriculture practices (GAP), and manufacturing processes strictly followed the standard of good manufacturing practices (GMP). Mass spectroscopy was used to analyse seven quality control markers of QSYQ and showed good consistency of the active markers among different batches. Pharmacological studies revealed that constituents of QSYQ could inhibit the platelet aggregation and the over release of β -TG (a platelet protein). Clinical studies have suggested that QSYQ had similar effect to aspirin in inhibiting platelet aggregation.

QSYQ is widely used for the secondary prevention of MI in China. However, there is insufficient evidence to know whether QSYQ can be used as an alternative to aspirin. This multi-centre randomized clinical trial aimed to test whether the regular administration of QSYQ would result in a significant reduction in total serious vascular events in patients who had experienced at least one documented MI.

Description

A randomised, double-blind, parallel controlled study was carried out. With such a large scale clinical trial, the quality control of process management was key for the validity and reliability of the results.

The study protocol was reviewed and approved by the Ethics Committee of Tianjin University of Traditional Chinese Medicine and the trial registered with the World Health Organization Clinical Trial Registering Platform. Patients with a definite diagnosis of ST-elevation or non-ST-elevation MI (ST is a diagnostic section of an ECG readout) were potentially eligible for this study if they met the following criteria: (1) the last documented MI was 4 weeks to 24 months earlier; (2) Traditional Chinese Medicine symptoms were “Qixu-Xueyu” (vital energy deficiency combining with blood stagnation); (3) aged from 18 to 75 years (the maximum age was adjusted from 65 years to 75 years in July 2006 because of inadequate recruitment).

Patients were required to be free of other life-threatening diseases or problems which might have limited the ability to obtain long-term follow up and to be free of any condition which would mean that regular use of the trial drugs was contraindicated. Patients with any of the following conditions were excluded: (1) a history of percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG); (2) pregnant women or those who were breast feeding; (3) contraindication to aspirin (e.g., asthma, active phase peptic ulcer, and haemorrhagic disease); (4) heart function of grade IV (NYHA grade); (5) uncontrolled systemic hypertension (contractive pressure ≥ 180 mmHg or diastolic pressure ≥ 110 mmHg); (6) uncontrolled serious cardiac arrhythmias (e.g., atrial fibrillation and supraventricular tachycardia); (7) serious primary disease of liver, kidney, and hemopoietic system, or psychosis, or malignant tumor; (8) allergic history to study drugs; (9) participation in other clinical trials during the previous three months.

After a comprehensive medical evaluation, patients were given a full explanation of the study by investigators. Each patient was asked for their written informed consent before joining the study. Recruitment took place in 88 hospitals across China. Patients were randomly assigned to two groups (ratio 1:1): QSYQ group and aspirin group. In the QSYQ group, patients took 0.5 g (one package) QSYQ three times per day and 100 mg (in four tablets) simulated enteric-coated aspirin once a day. Patients in the aspirin group took 0.5 g (one package) simulated QSYQ three times per day and 100 mg (in four tablets) enteric-coated aspirin daily. Placebos for QSYQ and aspirin were developed which had the same appearance, colour, and taste as the relevant drug. Patients were prohibited from taking other anti-platelet drugs or “Yiqi-Huoxue” Chinese medicines during the treatment period. Concomitant medications, such as antihypertensive (e.g., beta-blockers and ACE

inhibitors), hypoglycaemic agents, and lipid-lowering drugs, could be prescribed at the discretion of the attending physicians and had to be recorded in detail (including drug name, period taken, dosage, and purpose). The treatment period for the trial drugs was 12 months. After this time (or if the trial drugs were stopped for some other reason), patients could be prescribed treatments by their physicians without any limitation.

The primary endpoint was a composite of cardiovascular death, non-fatal re-infarction (documented by ECG and enzyme changes), and non-fatal stroke (diagnosed by CT or MRI). After a first visit for collecting baseline data after randomization, enrolled patients, their dependents, or both, were asked to visit clinical centres monthly. If no primary endpoints occurred, there were 12 visits during the treatment period and a final visit (6 months after the termination of the trial drugs). When a patient had one of the primary endpoints, the case was considered completed and there was no further follow-up visit.

The number of patients for each group at each stage of the trail are shown in Fig. 1. At the end of the trial period, statistical analyses were carried out on the date from 1,456 patients in the QSYQ cohort and 1,500 in the aspirin group.

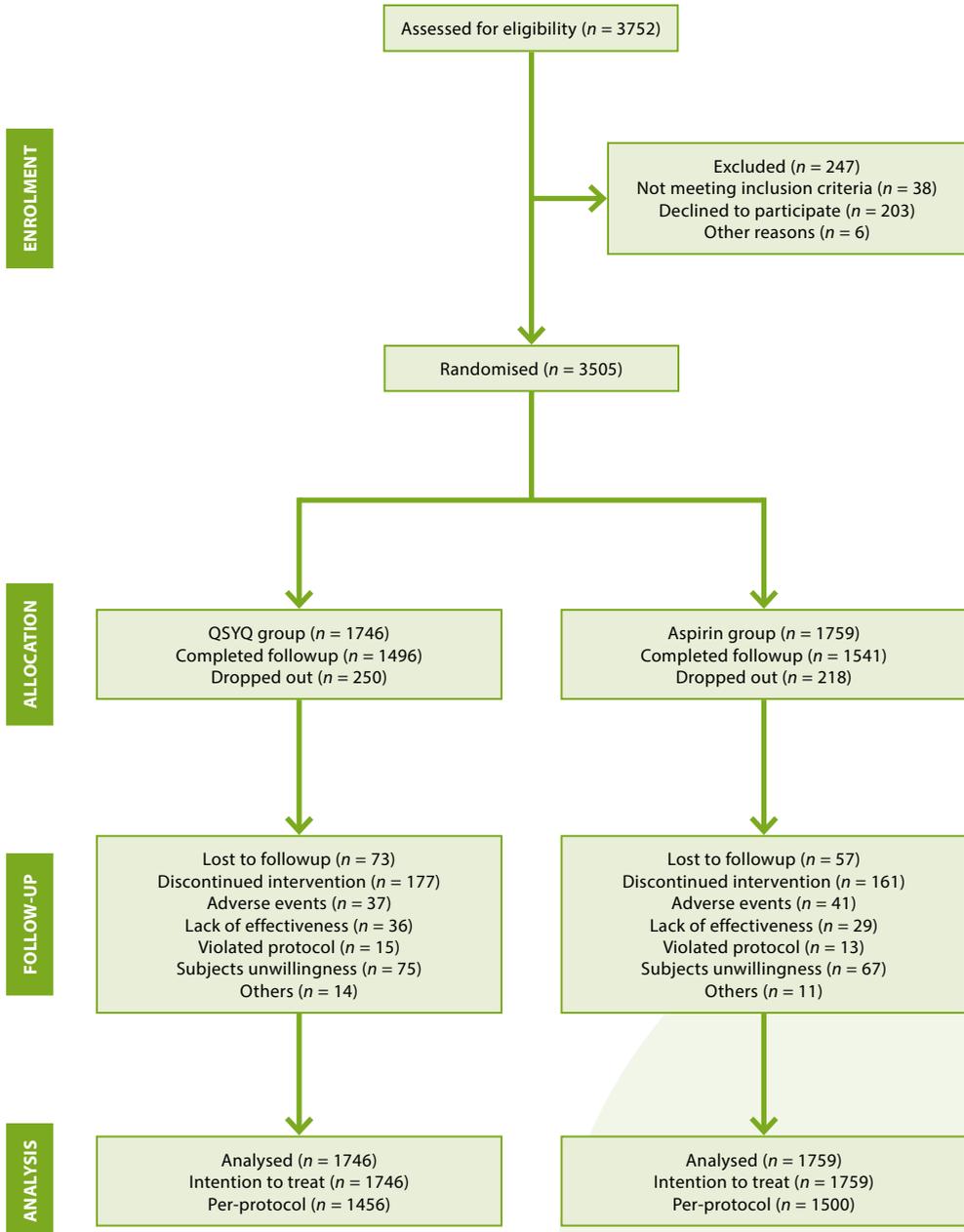


Figure 1: Flow diagram of participants through each stage of the trial.

Results

In the trial, QSYQ showed similar effects to aspirin for the prevention of recurrent vascular events in patient with a previous MI (Figure 2). The rate of composite endpoints (cardiovascular death, non-fatal MI, and non-fatal stroke) after 12 months of treatment was 2.98% in the QSYQ group and 2.96% in the aspirin group. The incidence of serious vascular events of this trial was lower than previous studies of secondary prevention for MI, which may be due to several factors.

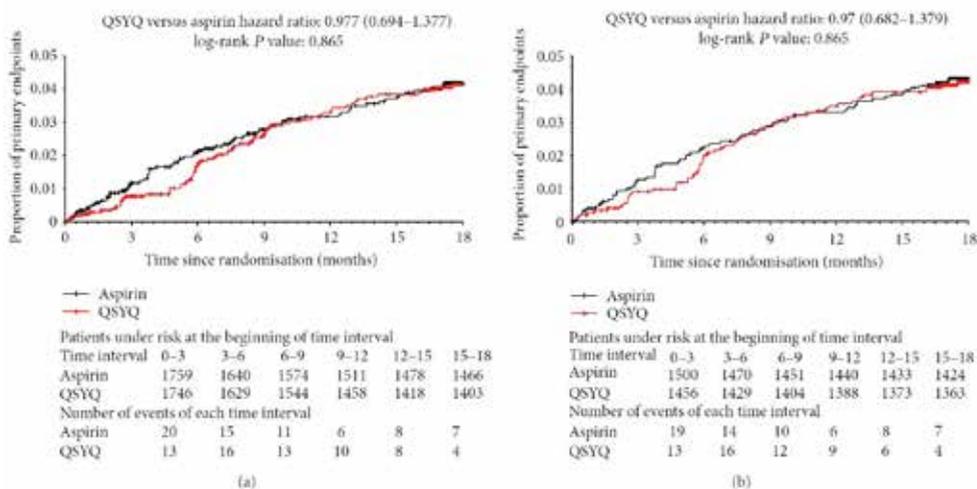


Figure 2: Cumulative incidence curves of the primary outcome composed of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke: (left) intention-to-treat analysis; (right) per-protocol analysis.

Partnerships

Among the main partners of this trial were Peking University First Hospital, the Chinese Academy of Traditional Chinese Medicine and Xiyuan Hospital, Beijing.

The protocol of the trial was revised more than ten times after consulting with multi-discipline experts from clinical epidemiology, evidence-based medicine, statistics and cardiology, etc. Before patients were recruited, the protocol of this trial was evaluated by Italian and US experts. The trial was designed, executed and analysed by a steering committee, a clinical monitoring centre, an endpoints committee, a drug management centre, a data management centre, and a biostatistics centre. Investigators in each clinical centre were trained before beginning the study.

Impact

- After completing this trial, we established a series of criteria and methods for completing large scale clinical trial. This trial won a National Award of Science and Technology.
- The methods and experience of this trial have been widely used in post-marketing evaluation of traditional Chinese medicines. After rigorous clinical evaluation, sales of Chinese patent medicines have developed greatly.
- The trial was successful mainly because it received support from the Ministry of Science and Technology and the State Administration of Traditional Chinese Medicine of China.

Replicability

The experience, especially the efforts taken to ensure a robust design and analysis of the trial, will be valuable for clinical trials of other traditional medicines.

Lessons Learned

How to manage the process of randomisation, drug allocation, timely data collection and audit were the main obstacles for the trial. We used a Clinical Research Interactive Voice Respond System (CRIVRS) for dynamic management of this trial. Investigators connected to the CRIVRS by telephone when a patient was ready to be randomised and the CRIVRS then provided a subject number, randomisation code, and drug number to the investigator by voice, email, and SMS.

Because of the care taken to develop the trial's randomized control design, the results have been widely accepted by clinical practitioners and researchers worldwide.

Future Plans

We intend to evaluate more Chinese patent medicines. For future clinical trials, we will design the protocols with international collaboration.

Publications

- Hongcai Shang, Junhua Zhang, Chen Yao, Baoyan Liu, Xiumei Gao, Ming Ren, Hongbao Cao, Guohua Dai, Weiliang Weng, Sainan Zhu, HuiWang, Hongjuan Xu and Boli Zhang. Qi-Shen-Yi-Qi Dripping Pills for the Secondary Prevention of Myocardial Infarction: A Randomised Clinical Trial. Evidence-Based Complementary and Alternative Medicine 2013. Article ID 738391, <http://dx.doi.org/10.1155/2013/738391>.