Journal of Ethnopharmacology 186 (2016) 136–142

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

A randomized, double-blind, multicenter, placebo-controlled clinical study on the efficacy and safety of Shenmai injection in patients with chronic heart failure

Shaoxiang Xian [a,*,1], Zhongqi Yang [a,1], Jun Lee [b], Zhiping Jiang [c], Xiaohan Ye [d], Luyi Luo [e], Lili Jin [f], Tianlun Yang [g], Suilin Ye [h], Dongfeng Lu [i]

[a] The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China
[b] The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China
[c] Yuebei People's Hospital, Shaoguan, China
[d] Dongguan Hospital of Traditional Chinese Medicine, Dongguan, China
[e] Shenzhen Hospital of Traditional Chinese Medicine, Shenzhen, China
[f] Guangdong second Traditional Chinese Medicine Hospital, Guangzhou, China
[g] Xiangya Hospital, Central South University, Changsha, China
[h] Guangzhou Hospital of Traditional Chinese Medicine, Guangzhou, China
[i] The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

ARTICLE INFO

Article history:
Received 19 November 2015
Received in revised form
4 February 2016
Accepted 31 March 2016
Available online 1 April 2016

Keywords:
Heart failure
Shenmai injection
Randomized controlled trial
Traditional Chinese medicines
Panax ginseng
Ophiopogon japonicas

ABSTRACT

Ethnopharmacological relevance: Shenmai injection (SMI) is a traditional Chinese herbal medicine extracted from *Panax ginseng* (*Panax ginseng* C.A. Mey, steamed and dry) and *Ophiopogon japonicus* (*Ophiopogon japonicus* (L.f.) Ker-Gawl, root). It has been widely used for the treatment of chronic heart failure (CHF) in China. However, the evidence supporting its effects remains unclear due to lack of high quality trials. The aim of this study was to investigate the efficacy and safety of SMI in CHF patients with coronary artery disease (CAD).

Materials and methods: This double-blind, multicenter study randomized 240 eligible patients equally to receive SMI or placebo (100 ml/day) in addition to standard medicines for the treatment of CHF. The primary endpoint was the New York Heart Association (NYHA) functional classification. The secondary endpoints were 6-min walking distance (6MWD), short-form 36 (SF-36) hearth survey score, traditional Chinese medicines (TCM) syndrome score, left ventricular ejection fractions (LVEF) and B-type natriuretic peptide (BNP) level.

Results: During treatment of 1 week, the NYHA functional classification was gradually improved in both groups, but the SMI group demonstrated a significantly greater improvement compared with the placebo group ($p=0.001$). Moreover, the improvement in patients received SMI was superior to those in control group with respect to 6MWD, SF-36 score and TCM syndrome score. Treatment with SMI within 1 week was well tolerated with no apparent safety concerns.

Conclusions: The integrative treatment with standard medicines plus SMI can further improve NYHA functional classification for patients with CHF and CAD. Therefore, SMI could be recommended in the combination therapy for CHF accompanied with CAD.

1. Introduction

Chronic heart failure (CHF) is a major public health problem and has been singled out as an epidemic (Roger et al., 2004), associated with significant mortality and heavy healthcare expenditures (Go et al., 2014; Roger, 2013). Evidence from epidemiology confirmed that coronary artery disease (CAD) have the largest population attributable risk for HF (Owan et al., 2006; Roger, 2013) and is correlated with poor prognosis for patients with CHF (Murdoch et al., 1998). Treatment strategies have been

* Correspondence to: The First Affiliated Hospital of Guangzhou University of Chinese Medicine, No. 16 Airport Road, Guangzhou 510000, China.
E-mail addresses: zhongfyy@126.com (S. Xian), zqyang66@163.com (Z. Yang), junlee008@126.com (J. Lee), jzp7448@163.com (Z. Jiang), xiaohanye666@126.com (X. Ye), luoluyi8@126.com (L. Luo), wondergirl2@yeah.net (L. Jin), yangtl44@yeah.net (T. Yang), suilinye52@163.com (S. Ye), ludf123@126.com (D. Lu).
[1] Dr. Shaoxiang Xian and Dr. Zhongqi Yang are the co-first authors and contributed equally to this work.

http://dx.doi.org/10.1016/j.jep.2016.03.066
0378-8741/

developed based upon the understanding of the pathophysiological mechanisms in HF (Kemp and Conte, 2012). According to the latest guidelines for HF (McMurray et al., 2012; Yancy et al., 2013), standard medicines include diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, aldosterone antagonist and digitalis. Despite advances in the drug and surgical treatment, the survival estimates remain 50% and 10% at 5 and 10 years, and rates of readmissions continue to rise (Roger, 2013). Therefore, improved treatments are imperative.

In the theory of traditional Chinese medicine (TCM), Qi usually refers to life energy that manifests simultaneously on the physical and mental-spiritual level (Maciocia, 2005). Yin and Yang are terms used to describe relative opposite qualities or manifestations of Qi. From the perspective of TCM, the principal problems of CHF are deficiency of Qi and inadequacy of either Yin or Yang, which impair the circulation of blood (Li et al., 2013b; Mao et al., 2009; Tang and Huang, 2013), leading to retention of body fluid and stasis of blood. Shenmai injection (SMI) is a traditional Chinese herbal medicine extracted from *Panax ginseng* (*Panax ginseng* C. A. Mey, steamed and dry) and *Ophiopogon japonicus* (*Ophiopogon japonicus* (L.f.) Ker-Gawl, root), with effects of tonifying Qi, nourishing Yin and replenishing bodily fluids (Chen et al., 2012; Ma et al., 2010; Yu et al., 2014). Therefore, SMI has long been used as a complement to the standardized treatments for CHF in China. Although its efficacy against heart failure has been demonstrated in several studies, the poor quality of these trials compromised the reliability of the evidence (Chen et al., 2012). This clinical trial was aimed to further evaluate whether CHF patients with CAD can benefit from the integrative treatments with standard medicines plus SMI.

2. Material and methods

2.1. Study design

This study was designed as a multicenter, randomized, double-blind, placebo-controlled study based on standard therapy and parallel groups. The trial was conducted in eight A-level hospitals and enrolled 240 patients with CHF and CAD based on the inclusion and exclusion criteria. The study conforms to the Declaration of Helsinki and was performed in accordance with the *Good Clinical Practice* and national regulations. The trial protocol and its informed consent form were approved by appropriate independent ethics committees. All participants submitted informed consent before the start of the study. The clinical trial has been registered at Chinese Clinical Trial Registry with the registration number: ChiCTR-TRC-12003063.

Block randomization with stratification was used to assign eligible patients to either SMI group or placebo group in the ratio of 1:1. The corresponding randomization code was generated by SAS software (SAS Institute, Cary, North Carolina) according to the number of enrolled patients in each center and was held centrally by the first affiliated hospital of Guangzhou University of Chinese Medicine. All patients and investigators were kept unaware of the treatment allocation.

Prior to this trial, patients had received standard medicines for at least 1 month with reference to the Chinese Society of Cardiology guidelines for the treatment and diagnosis of CHF. Besides standard medicines, eligible patients were randomized to receive 100 ml/day SMI or 100 ml/day 5% glucose injection (placebo) intravenously at the rate of 20–40 drops per minute, for consecutive 7 days. The baseline of patients was tested before intervention. After treatment for 4 and 7 days, patients were evaluated for the effects from the intervention. Except for SMI, any other TCM that could confuse the outcome of SMI was forbidden. In the case of comorbidities, only the medicine that fulfilled the corresponding guidelines was enabled.

2.2. Study products

SMI, prepared from *Panax ginseng* and *Ophiopogon japonicus*, has been mass-produced as a patented drug based on the national standards approved by CFDA (China Food and Drug Administration). Briefly, *Panax ginseng* (100 g) and dried tuber roots of *Ophiopogon japonicus* (100 g) were respectively extracted by refluxing with 90% ethanol for 2 h each time (*Panax ginseng*, six times; *Ophiopogon japonicus*, two times). The extract was condensed to the concentration of 0.3–0.4 g crude drug weight/ml solution. The solution was then stirred with 1% acticarbon for 1 h, followed by filtration and dilution with water for injection. This process was repeated twice. Finally, polysorbate 80 was added and the solution was diluted to 1000 ml with water for injection. SMI (batch number: 1105079) used in our research was manufactured in accordance with applicable GMP by Qingchunbao Pharmaceutical Co., Ltd (Hangzhou, China). The batch sample analyses and characteristic records of SMI were maintained. As reported previously (Wu et al., 2013), high-performance liquid chromatography (HPLC) analysis was performed to identify the phytochemical characteristics of SMI. The HPLC chromatogram of SMI including ginsenosides as standard was showed in Fig. 1. The components conformed to the national standards of Shenmai injection approved by CFDA.

The placebo (5% glucose injection) was proprietary preparations produced by Dongguan Lifeline Pharmaceutical Co., Ltd with the batch number of 11070603. In order to avoid the exposure of study drugs from the brown color of SMI, light-resistant containers and infusion apparatus were used during treatment.

2.3. Study participants

Inclusion criteria include male and female patients with 40–80 years of age; history of CHF combined with CAD; New York Heart Association (NYHA) functional classification II–IV; diagnosis of Qi-Yin deficiency (Wang et al., 2013); subjects received standard medicines for at least 1 month, whose condition remained unstable and required further treatment in hospital; submission of informed consent. Exclusion criteria include the patients with acute cardiac dysfunction; exacerbation of CHF induced by the adverse effects of digitalis; comorbidities of cardiac shock, malignant cardiac arrhythmia, degree II type II or severer atrioventricular block, obstructive myocardiopathy, unrepaired valvular heart disease, constrictive pericarditis, cardiac tamponade, pulmonary embolism, acute myocardial infarction, or uncontrolled

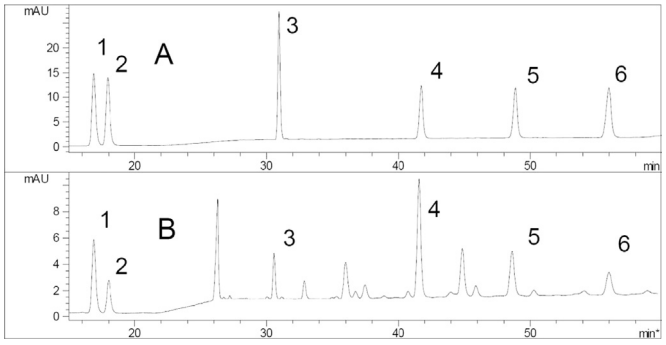

Fig.1. The HPLC chromatogram of SMI (Shenmai injection). (A) The HPLC chromatogram of control solution that contains six main compounds of SMI (ginsenoside Rg1, Re, Rf, Rb1, Rb2 and Rd); (B) The HPLC chromatogram of SMI. In both (A) and (B), chromatographic peaks from 1 to 6 represented Rg1, Re, Rf, Rb1, Rb2 and Rd respectively.