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Chinese herbal medicine for chronic heart failure: a multicenter, randomized, double-blind, placebo-controlled trial

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KEYWORDS
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Abstract *Objective:* The purpose of this study was to assess the efficacy and safety of Chinese herbal medicine (CHM) in the treatment of chronic heart failure (CHF) patients according to syndrome differentiation.
Methods: In this multicenter, randomized, double-blind, placebo-controlled clinical trial, a total of 220 CHF patients were assigned to receive CHM or placebo granules without decoction according to syndrome differentiation in addition to their standard western treatment for 4 weeks. The change in the left ventricular ejection fraction (LVEF) was the primary outcome, and the changes in the TCM syndrome scores (TCM-SS) and New York Heart Association functional classification (NYHA-FC) were the secondary outcomes.

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; AE, adverse event; AMI, acute myocardial infarction; ARB, angiotensin receptor antagonist; CHD, coronary heart disease; CHF, chronic heart failure; CHM, Chinese herbal medicine; CI, confidence interval; CM, Chinese Medicine; CONSORT, Consolidated Standards of Reporting Trials; CRF, case report form; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiogram; HF, heart failure; HBP, hypertension; ITT, Intention-To-Treat; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA-FC, New York Heart Association functional classification; PPS, per-protocol set; SAE, serious adverse event; SAS, Statistics Analysis System; SBP, systolic blood pressure; SD, standard deviation; TCM, Traditional Chinese Medicine; W, weeks; WM, western medicine.

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Results: After 4 weeks of treatment, the mean changes in the LVEF (13.1 ± 9.78 vs. 7.34 ± 7.40, $P < 0.001$) and the TCM syndrome scores (−34.2 ± 24.6 vs. −23.5 ± 25.2, $P = 0.002$) were better in the CHM group than in the placebo group. After two weeks of treatment, the mean changes in the LVEF (9.26 ± 7.83 vs. 4.72 ± 5.60, $P < 0.001$) and the TCM syndrome scores (−23.5 ± 18.6 vs. −14.0 ± 15.9, $P < 0.001$) were better in the CHM group than in the placebo group. In addition, repeated-measures analysis of variance (ANOVA) indicated significant time course effects of CHM versus placebo in the LVEF and TCM syndrome cores ($P < 0.001$ for all). The distention of the jugular vein ($P = 0.021$), expectoration ($P = 0.044$), abdominal distention ($P = 0.004$), and rib pain ($P = 0.005$) were significantly less in the CHM group than in the placebo group after two weeks of treatment. Fatigue ($P = 0.001$), less gas and lazy words ($P = 0.001$), dizziness ($P = 0.003$), gasping for breath ($P = 0.027$), abdominal distention ($P = 0.011$), nausea ($P = 0.001$) and emesis ($P = 0.012$) were significantly less in the CHM group than in the placebo group after treatment for four weeks. After four weeks of treatment, the change in the NYHA functional classification in the CHM group was better than that in the placebo group ($P < 0.001$). There was one death in the placebo group, and one patient in the CHM group experienced atrial fibrillation.

Conclusion: CHM treatment according to syndrome differentiation effectively improved the LVEF, TCM-SS, and NYHA-FC in patients with CHF and also appeared to be safe. Thus, CHM treatment could be used as an adjuvant therapy in the treatment of CHF (Clinical trial registration: NCT01939236).

Introduction

Heart failure (HF) can be defined as an abnormality of cardiac structure or function leading to the failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues despite normal filling pressures (or only at the expense of increased filling pressures).[1] In addition, according to the nature of the clinical presentation, HF is divided into acute and chronic HF.[1]

Despite major improvements in the treatment of virtually all cardiac disorders, heart failure (HF) is an exception because its prevalence is rising and only small prolongations in survival have been achieved.[2] The diagnosis and treatment of cardiovascular disease (CVD) have developed rapidly in the past several decades. The mortality of many CVDs, with the exception of HF, has decreased. The annual hospital discharge of subjects with a primary diagnosis of HF has increased steadily since 1975, and the discharge rate now exceeds 1 million per year, although it may be leveling off in the United States.[3,4]

In 2003, a random sample survey of 15,518 urban or rural residents between 35 and 74 years of age in China indicated that the prevalence rate of heart failure was 0.9%. According to the result, there were approximately 4,000,000 HF subjects in China.[5] Another retrospective investigation of 10,714 HF subjects in the full-year segments of 1980, 1990, and 2000 was conducted in 42 hospitals in China, and this study revealed that the underlying cause of HF in 45.6% of HF subjects was coronary heart disease (CHD).[6]

The mortality of CHD has been reduced due to the wide application of percutaneous coronary intervention and coronary artery bypass grafting. The early mortality in subjects with acute myocardial infarction may have declined by 75% during the past half-century;[7] however, the survivors still have CHD and remain at risk for subsequent episodes of ischemic myocardial damage with further loss of myocardium and possibly HF.

The western medicine (WM) treatment for HF is standardized around the world.[8,9] The conventional therapeutic approaches in HF management are angiotensin-converting enzyme inhibitors (ACEI), β-adrenergic blockers, and diuretics. In China, the integrative treatment of western and traditional Chinese medicine for HF is usually applied and has been developed as a treatment model.[8] CHM has been used in China for thousands of years. Syndrome differentiation and treatment variation are the basic principles of TCM in the understanding and treatment of diseases. Syndrome differentiation is the comprehensive analysis of the clinical information gained by the four main diagnostic TCM procedures, namely, observation, listening, questioning, and pulse analysis, and it is used to guide the choice of treatment by CHM. We would like to test the hypothesis that it is efficacious and safe for patients to take CHM granules according to syndrome differentiation.

In this study, a multicenter, randomized, double-blind, placebo-controlled trial was conducted. The aim was to evaluate the efficacy and safety of CHM on CHF according to syndrome differentiation.

Materials and methods

Study design

This multicenter, randomized, double-blind, placebo-controlled study was conducted in seven centers of four