Effect of Jiawei Shenfu decoction on tumor necrosis factor-alpha and nuclear factor-kappa B in patients who have chronic heart failure with syndromes of deficiency of heart Yang

Yu Mei, Guo Hangyuan, Ye Lingling, Bian Jiaping, Ma Lijuan, Zheng Chunli

Abstract

OBJECTIVE: To examine the clinical efficacy of Jiawei Shenfu decoction on tumor necrosis factor-alpha (TNF-α) and nuclear factor-kappa B (NF-κB) levels in patients who have chronic heart failure with syndromes of deficiency of heart Yang.

METHODS: A total of 63 patients with syndromes of deficiency of heart Yang (chronic heart failure) were enrolled. Patients were randomly divided into the control group and Jiawei Shenfu group. All patients received standard medications for treatment of chronic heart failure. Patients in the Jiawei Shenfu group were additionally provided Jiawei Shenfu decoction one dose daily. Treatments continued for 4 consecutive weeks. The primary endpoint was the change in plasma B-type natriuretic peptide (BNP), NF-κB, and TNF-α levels during 4 weeks of treatment.

RESULTS: At the 4-week follow-up, a significant reduction in BNP levels compared with baseline was observed in both groups, but the Jiawei Shenfu decoction group showed a significantly greater reduction than did the control group. The Jiawei Shenfu group also showed superior performance regarding the Minnesota Living with Heart Failure Questionnaire score, the Chinese medicine syndrome score, heart rate, left ventricular ejection fraction, and 6-min walking distance compared with the control group. The degree of changes in NF-κB and TNF-α levels in the Jiawei Shenfu group was more significant than that in the control group.

CONCLUSION: Routine medicine combined with Jiawei Shenfu decoction for patients with heart Yang deficiency syndrome in chronic heart failure can improve the left ventricular ejection fraction and cardiac function, and reduce BNP levels. The mechanism may be related to inhibition of pro-inflammatory cytokines and the NF-κB-induced kinase pathway, leading to amelioration of the inflammatory response.

Keywords: Heart failure; Natriuretic peptide, brain; Tumor necrosis factor-alpha; NF-kappa B; Heart-Yang deficiency; Jiawei Shenfu decoction

INTRODUCTION

Heart failure is a devastating disease, and one possible cure for this condition is to replace lost cardiomyocytes.
through regeneration. Failing hearts are characterized by progressive myocyte loss and replacement fibrosis, ultimately leading to susceptibility to fatal arrhythmia and pump dysfunction. Besides symptomatic treatment to relieve these symptoms, several classes of drugs improve the prognosis of patients with chronic heart failure (CHF). These agents target the so-called neurohumoral activation process that is involved with evolution of heart failure syndrome, irrespective of the underlying pathophysiology. Inhibition of activity of the renin-angiotensin-aldosterone system and beta-adrenergic signaling are well-established treatment principles, which are incorporated in current guidelines. However, morbidity and mortality remain substantial in patients with CHF, despite optimal medical and device therapy. The indication for these therapies has recently been broadened.

Chinese medicine has accumulated experience in treating heart failure. According to the principle of Traditional Chinese Medicine (TCM) based on syndrome differentiation, the combination of some TCMs and Western medicines has a synergistic effect and reduces adverse reactions. This combination has a good clinical effect. However, the specific mechanism of Chinese medicine is unclear. An inflammatory activation in patients with CHF has been recognized. There is a large variety of potential therapeutic targets in the field of pro-inflammatory signaling in heart failure. Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that promotes ischemic myocardial injury and cardiac dysfunction. Sustained TNF-α expression can contribute to development of heart failure. Therefore, we aimed to investigate the effect of Jiawei Shenfu decoction on cardiac function and inflammatory cytokines in patients with CHF.

MATERIALS AND METHODS

Study design
This randomized, double-blind clinical study was conducted in our hospital from March 2013 to September 2015. A total of 63 participants were recruited from inpatients at two hospitals located in China. These hospitals included The Affiliated Shaoxing Hospital of Zhejiang Chinese Medical University and Shaoxing People’s Hospital. The study was performed in accordance with good clinical practices and ethical principles from the Declaration of Helsinki. The study was approved by the Ethics Board of The Affiliated Shaoxing Hospital of Zhejiang Chinese Medical University. Each participating center also obtained local Institutional Review Board approval. All enrolled participants were observed and followed up during their disease course. Participants were recruited through invitation letters, information pamphlets, and posters in Shaoxing Hospital of TCM, affiliated with Zhejiang Chinese Medical University, and Shaoxing People’s Hospital, Shaoxing Hospital, Zhejiang University School of Medicine. During the participants’ first visit, informed consent and baseline assessments were obtained. Participants were randomly assigned with equal allocation to either the Jiawei Shenfu group or the control group using computer-generated simple randomization. The computer-generated random sequence was produced by an investigator not involved in running the trial. The random sequence was kept by him, and the other researchers were unaware of the assignments. All participants and the data collector in study were blinded regarding the group assignment (the Jiawei Shenfu group or the control group). However, the therapist (first author), who provided the treatment for all of the participants, was not blinded regarding group assignment.

Criteria for inclusion
Criteria for participation in the trial included the following. (a) patients with CHF had a Framingham diagnosis in 1971 (New York Classification of Heart Failure class II or III) and were aged between 15 and 90 years. (b) The echocardiographically measured left ventricle ejection fraction (LVEF) was < 40%. (c) Patients had deficiency of heart Yang with CHF. Main symptoms included the following: chest tightness, heart palpitations, shortness of breath, cold body and limbs, and a pale complexion. Secondary symptoms included the following: fatigue, oliguria, abdominal distension, limb edema, cough, frothy sputum, sweating, irritability; and a pale red or dark purple tongue, thin, white, tongue coating that was slippery, plump tongue that was slippery and had dental indentations on the margin, and a forceless deep pulse. (d) Patients voluntarily participated in the study and provided signed informed consent.

Criteria for exclusion
Criteria for exclusion in the trial included the following: (a) an ongoing primary Electrocardiographic QRS wave width of > 130 ms, with complete left bundle branch block and atrioventricular dissociation; (b) patients with a malignant tumor; (c) patients who were pregnant or breast-feeding; (d) patients with mental disorders and an allergic constitution; (e) patients with serious liver or renal diseases; (f) patients with cardiogenic shock or fatal arrhythmia, such as a high degree of atrioventricular block; (g) patients with acute heart failure or pericardial tamponade; (h) patients with acute myocardial infarction or pulmonary embolism; (i) patients with uncontrolled blood pressure(> 160/90 mm Hg, 1 mm Hg = 0.133 kPa); (j) patients with acute inflammatory disease; (k) patients with digestive tract hemorrhage and other hemorrhagic disease; (l) patients who had other drugs in clinical trials; and (m) patients presenting with complex TCM syndrome.

Patients’ conditions
Sixty-three patients were admitted to the Department
of Cardiology with a diagnosis of CHF with syndromes of deficiency of heart Yang. There were 29 women and 34 men, aged 41-86 years [mean age: (69 ± 9) years], and the course of disease was 1.2-26.8 years [mean: (7 ± 4) years]. Thirty-one patients were diagnosed with heart failure due to ischemic heart disease and 12 patients suffered from dilated cardiomyopathy. Six patients suffered from pulmonary heart disease, four patients suffered from rheumatic heart disease, seven patients suffered from hypertension, and three patients suffered from hypertrophic cardiomyopathy. Complications included 39 cases of dyslipidemia, 26 cases of atrial fibrillation, 24 cases of type 2 diabetes, 13 patients with a history of a cerebrovascular accident, 29 cases of high uric acid levels, 15 cases of renal insufficiency, and 19 cases of high homocysteine levels.

To determine the levels of the studied factors, blood samples were collected from a vein the next morning after admission of the patients. The samples for TNF-α were then centrifuged for 15 min at 1000 x g and serum was stored at ≤ −20 °C. The samples for NF-κB were centrifuged for 10 min at 1000 x g and the serum was stored at ≤ −70 °C. TNF-α levels were determined using a double antibody sandwich ELISA assay (Catalog Number: DHG00; Shanghai Ruipin Biotechnology Co., Ltd., Shanghai, China), according to the kit instructions.

BNP concentrations were determined using immune luminescence (RIA) (I2000 immunity analyzer; Yapei Systems, Abbott Laboratories, Illinois, America). Serum levels of NF-κB were measured using the double antibody sandwich ABC-ELISA method and NF-κB was detected at a 450-nm wavelength. A standard curve was created to calculate NF-κB concentrations (Hangzhou ADICON Co., kits for BD Biosciences, Hangzhou, China).

Transthoracic echocardiography was performed in all of the patients using Philip IU22 color Doppler ultrasound. General Electric device, equipped with an S5-1 MHz probe. The left ventricular ejection fraction (LVEF) was determined using the standard formula: LVEF = (LVEDV − LVESV) / LVEDV × 100%, where LVEDV is left ventricular end-diastolic volume and LVESV is left ventricular end-systolic volume. LVEDV and LVESV were calculated using the Teichholz method. A computer was used to determine left ventricular volume using approximately perpendicular cross-sectional areas of the left ventricle in apical two- and four-chamber views, as determined by an investigator.

Therapy method

All patients were asked about their medical history and completed the Minnesota Living with Heart Failure Questionnaire (MLHFQ) score test. These scores range from 0 to 105 points. The Chinese medicine syndrome integral score was also recorded. Patients then underwent a clinical examination, a 12-lead electrocardiogram, plasma measurement of BNP, TNF-α, and NF-κB levels, the 6-min walking distance (6MWD) test, a transthoracic echocardiogram, and a chest X-ray. According to the 2012 European Society of Cardiology guidelines for treatment of CHF, diuretics, angiotensin-converting enzyme (ACE) inhibitors (or when not tolerated, angiotensin receptor blockers were used), beta-blockers, aldosterone receptor antagonists, digitalis, and vasodilating agents should be used as standard treatments for heart failure. ACE inhibitors or angiotensin receptor blockers and beta-blockers needed to be up-titrated, “starting low, going slow”, with targeting for recommended doses. Antiplatelet drugs, such as aspirin or clopidogrel, were selected as appropriate, or anticoagulation with low molecular weight heparin or warfarin was used. All of the enrolled patients continued with their medicinal treatment.

All patients were randomly divided into the control group or Jiawei Shenfu decoction group. Patients in the Jiawei Shenfu decoction group were additionally provided Jiawei Shenfu decoction (Renshen (Radix Ginseng) 9 g, Fuzi (Radix Aconiti Lateralis Preparata) 9 g, Huangqi (Radix Astragali Mongolici) 30 g, Baizhu (Rhizoma Atractylodis Macrophalae) 10 g, Danshen (Radix Salviae Miltiorrhizae) 15 g, stir-frying with liquid adjuvant Gancao (Radix Glycyrrhizae) 6 g). All of these ingredients were immersed in water and cooked until boiling for a 30 min. One dose was orally taken daily, and the therapeutic course was 4 weeks in the two groups. The decoction of TCM was prepared in a manufacturing laboratory.

Statistical analysis

Statistical analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). All analyses were performed on a per-protocol basis. Data are presented as mean ± standard deviation ( x ± s). The assumed level of statistical significance was P < 0.05.

RESULTS

From March 2013 to September 2015, we screened 356 participants for eligibility. Of these 356 patients, 276 patients not meeting inclusion criteria or refused to participate were excluded. 80 patients were information standardization, medical records heart failure establishment and information entry. 4 patients withdrew due to their busy schedule in the follow-up stage. 76 patients were randomly assigned to receive either the Jiawei Shenfu group (n = 39) or the Control group (n = 37). In Jiawei Shenfu group, 6 patients were lost to follow-up because of reduced interest in the study. In the control group, 7 patients were lost to follow-up because of their busy schedule or a job change (Figure 1). Finally, 63 patients completed all trial procedures. Among these patients, no differences were observed in the baseline characteristics between groups. The baseline characteristics of all participants are shown in Table 1.
Comparison of heart syndrome scores, heart rate, 6MWD, and LVEF between the groups

At baseline and the 4-week follow-up, echocardiography and the 6MWD test were performed. The parameters of the echocardiographic measurements and the 6MWD test were not different between the two groups at baseline (Table 2). These parameters showed a large improvement after treatment in the two groups. Patients in the Jiawei Shenfu decoction group showed greater improvement in LVEF (%) (45.9 ± 3.9 vs 35.3 ± 2.9) and 6MWD (393.0 ± 7.9 vs 206.3 ± 5.7) compared with the control group. The MLHFQ was completed at each visit, and the two groups showed similar mean MLHFQ scores at baseline (Table 1). Overall, there was a gradual improvement in the mean MLHFQ score during the treatment period, with a significant effect of Jiawei Shenfu decoction treatment compared with controls at the 4-week visit (P < 0.05, Table 2).

Comparison of cytokines between the groups

A favorable effect of Jiawei Shenfu decoction was observed on plasma BNP levels (Table 3). After 4 weeks of treatment, both groups showed a significant decrease in BNP levels from baseline. BNP levels in the Jiawei Shenfu decoction group were significantly more reduced than those in the control group. Plasma NF-κB and TNF-α levels in the Jiawei Shenfu decoction group were significantly lower than those in the control group (P < 0.05, Table 3). These results indicated that Jiawei Shenfu decoction lowered plasma NF-κB and TNF-α levels in patients who had CHF with the syndrome of deficiency of heart Yang.

DISCUSSION

CHF is clinically associated with a high mortality, high morbidity, decrease in quality of life, and substantial burden on health care systems. The goals of treatment in patients with heart failure are to improve their clinical status, functional capacity, and quality of life, prevent hospital admission, and reduce mortality. Several drugs for CHF have shown detrimental effects on
Table 1 Baseline characteristics of the patients (±s)

<table>
<thead>
<tr>
<th>Item</th>
<th>Jiawei Shenfu group (n = 33)</th>
<th>Control group (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>18/15</td>
<td>16/14</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.0±21.0</td>
<td>50.1±20.2</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Heart Rate (Bpm)</td>
<td>113.9±8.7</td>
<td>112.3±6.5</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Minn LwHFQ (Points)</td>
<td>38.1±18.0</td>
<td>37.3±20.1</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Chinese Medicine Syndrome Integral Score</td>
<td>13.6±6.1</td>
<td>13.0±8.7</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>206.3±5.7</td>
<td>209.4±5.7</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>35.3±2.9</td>
<td>35.8±2.6</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Notes: all patients received standard medications for treatment of CHF for 4 weeks. Patients in the Jiawei Shenfu group were additionally provided Jiawei Shenfu decoction one dose daily for 4 weeks. Values are mean ± standard deviation. MLHFQ: Minnesota Living with Heart Failure Questionnaire; 6MWD: 6-min walking distance; LVEF: left ventricular ejection fraction.

Table 2 Changes in symptom scores, heart rate, 6MWD, and LVEF in the two groups from baseline to after the 4-week follow-up (±s)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Jiawei Shenfu group (n = 33)</th>
<th>Control group (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>Minn LwHFQ (points)</td>
<td>38.1±18.0</td>
<td>29.3±12.4*</td>
<td>37.3±20.1</td>
</tr>
<tr>
<td>Chinese medicine syndrome score</td>
<td>13.6±6.1</td>
<td>5.3±3.24*</td>
<td>13.0±8.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>113.9±8.7</td>
<td>72.5±3.0*</td>
<td>112.3±6.5</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>206.3±5.7</td>
<td>393.0±7.9*</td>
<td>209.4±5.7</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>35.3±2.9</td>
<td>45.9±3.9*</td>
<td>35.8±2.6</td>
</tr>
</tbody>
</table>

Notes: all patients received standard medications for treatment of CHF for 4 weeks. Patients in the Jiawei Shenfu group were additionally provided Jiawei Shenfu decoction one dose daily for 4 weeks. MLHFQ: Minnesota Living with Heart Failure Questionnaire; 6MWD: 6-min walking distance; LVEF: left ventricular ejection fraction. Statistically significant at *P < 0.05 (4 weeks of follow-up vs before treatment); †P < 0.05 (Jiawei Shenfu decoction group vs control group).

Table 3 Changes in BNP, TNF-α, and NF-κB levels in the two groups from baseline to after 4 weeks of follow-up

<table>
<thead>
<tr>
<th>Item</th>
<th>BNP (pg/mL)</th>
<th>NF-κB (pg/mL)</th>
<th>TNF-α (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiawei Shenfu group (n = 33)</td>
<td>Before treatment 1165.4±252.6</td>
<td>72.8±3.4</td>
<td>20.5±7.6</td>
</tr>
<tr>
<td></td>
<td>After treatment 413.68±189.2*</td>
<td>39.2±3.0*</td>
<td>10.1±3.3*</td>
</tr>
<tr>
<td>Control group (n = 30)</td>
<td>Before treatment 1028.7±413.4</td>
<td>69.9±3.7</td>
<td>19.9±5.3</td>
</tr>
<tr>
<td></td>
<td>After treatment 543.3±203.9*</td>
<td>50.3±3.6*</td>
<td>14.2±2.3</td>
</tr>
</tbody>
</table>

Notes: all patients received standard medications for treatment of CHF for 4 weeks. Patients in the Jiawei Shenfu group were additionally provided Jiawei Shenfu decoction one dose daily for 4 weeks. BNP: B-type natriuretic peptide; TNF-α: tumor necrosis factor-alpha; NF-κB: nuclear factor-kappa B. Statistically significant at *P < 0.05 (4 weeks of follow-up vs before treatment); †P < 0.05 (Jiawei Shenfu decoction group vs control group).

long-term outcomes, despite showing beneficial effects on shorter-term surrogate markers. This has led to regulatory bodies and clinical practice guidelines seeking mortality morbidity data for approving recommending therapeutic interventions for CHF. Preventing hospitalization for CHF and improving functional capacity are important benefits to be considered if a mortality excess is ruled out.**

Shenfu decoction has been a widely used in TCM since the Song dynasty in China. Shenfu decoction is a water extract of dried root or root stalk of Panax ginseng C. A. Mey (Asian ginseng) and radix aconiti lateralis preparata. The efficacy of Shenfu decoction against cardiac hypertrophy and remodeling has already been shown in several studies as follows. Yang et al.** investigated the effects of Shenfu decoction in rats with CHF by restoring disturbed metabolic pathways, especially those related to energy metabolism. These authors offered new methodologies for increasing the understanding of CHF and systematically characterizing the efficacies and mechanisms of Shenfu decoction in treating CHF. Wei et al.** showed that oral Shenfu decoction as an adjuvant therapy in patients with CHF significantly improved MLHFQ scores, the grading of cardiac function and LVEF were increased, and TNF-α levels were decreased. Kang et al.** showed that total ginseng saponins significantly reduced the increase in 5-hydroxy tryptamine and tryptophan levels induced by lipopolysaccharide, and also decreased mRNA levels for interleukin (IL)-1β, interleukin-6 (IL-6), TNF-α, and indoleamine 2, 3-dioxygenase in the hippocampus. These authors believe that the anti-depressive efficacy of total ginseng saponins can be largely attributed to its peripheral anti-inflammatory
activity. We use Jiawei Shenfu decoction in patients with CHF and syndromes of deficiency of heart Yang. In our study, we found that BNP levels and syndromes of deficiency of heart Yang were more decreased in the Jiawei Shenfu decoction group than in the control group. These findings suggest another mechanism to explain the anti-emotional distress effect of Jiawei Shenfu decoction in patients with CHF. Radix aconiti lateralis preparata and Astragalus mongholicus have positive inotropic, chronotropic, and diuretic effects, and positive effects on vasodilation. Furthermore, these ingredients have an anti-inflammatory response, block Ca²⁺ channels, and downregulate chymase-mediated angiotensin. Astragalus mongholicus regulates gene expression of components of the renin-angiotensin system, including renin, ACE, angiotensin II, and the angiotensin II type 1 receptor. In view of the effects of Astragalus mongholicus on ACE and other renin - angiotensin system-related activities, we speculate that Jiawei Shenfu decoction might affect the activity of cardiac chymase, and thus elicit beneficial effects in cardiac remodeling.

NF-κB is a major factor in regulating gene transcription, especially early response genes associated with immune and inflammatory reactions that play an important role in the pathogenesis of CHF. Inflammatory cardiomyopathy is associated with increased TNF-α signaling via its downstream target NF-κB. Similarly, TNF-α signaling is critically required for induction and progression of experimental autoimmune myocarditis. Several previous studies have shown that inflammatory reactions play an important role in the pathogenesis of CHF and inflammation mainly involves innate immunity mechanisms. Animal experiments and modern clinical trials had shown that red ginseng and Astragalus mongholicus are immunologically active stimulated macrophages, they promote antibody formation and activate complement, and they increase T lymphocyte proliferation. In our study, we also found that TNF-α and NF-κB levels were significantly lower in the Jiawei Shenfu decoction group compared with the control group. According to TCM, a deficiency of heart Yang results in dysfunction of Yang Qi transformation, retention of fluid in the heart, weak blood transportation, and retention of blood stasis. Furthermore, heart failure is a syndrome of root deficiency and branch excess in which heart Yang Qi deficiency is root deficiency, and phlegm and blood stasis is branch excess. Jiawei Shenfu decoction has warming heart Yang and tonifying Qi effects, and it promotes blood transportation, enhances immune function, and inhibits inflammatory responses. Jiawei Shenfu decoction has multi-channel and multiple targets, in line with the new direction in recent years for the treatment of heart failure.

In conclusion, our study suggests that Jiawei Shenfu decoction can markedly reduce BNP and inflammatory cytokine levels, which suggests that these patients may have an improved prognosis with long-term treatment. However, there are several limitations of our study. The small sample size of the study might have reduced the statistical power. Furthermore, Chinese medicine decoction is not convenient enough.

ACKNOWLEDGMENT

We are very grateful to Ms. Li Quiping and Ms Chen Xiaowen for the help in preparing the manuscript. We also thank Mr. Shen Jiancheng for the collection and detection of the blood samples. We also thank Mr. Huang, Weigang for the collection of the echocardiographically measurement. We also thank Mr Lü Zheng for his participation in drawing charts.

REFERENCES

1. McMurray J, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European society of cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012; 14(8): 803-869.


