Improvement of Shen’ge formula on heart function in diastolic heart failure

A protocol for randomized, double-blind, placebo-controlled clinical study

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Abstract

Introduction: Diastolic heart failure (DHF) is an important pathological type of heart failure, that involves multiple organ dysfunction and multiple complications. The prevalence of DHF is high, and effective treatments are lacking. Chinese herbs are an alternative therapy for DHF. Shen’ge formula (SGF) is a classical formula from which patients can benefit, but convincing evidence of its efficacy is lacking. Therefore, we designed this randomized controlled trial protocol.

Methods/design: This randomized, double-blind, placebo-controlled clinical trial will evaluate the efficacy and safety of SGF in the treatment of DHF. A total of 130 patients with DHF will be enrolled in the trial and treated with SGF granules or placebo for 12 weeks and followed up for 12 weeks. The primary outcome measurement will be to changes in plasma N-terminal brain natriuretic peptide precursor before versus after treatment, while the second primary outcome measurement will be changes in heart function before versus after treatment and the 12-week follow-up period. It will also include echocardiography, a cardiopulmonary exercise test, cardiac function grading, traditional Chinese medicine syndrome score, and the Minnesota Heart Failure Quality of Life Scale. Adverse events will be evaluated throughout the trial.

Discussion: The results of this trial will demonstrate whether SGF could alleviate symptoms, improve cardiac function, reduce readmission rates, and improve quality of life of patients with DHF.

Trial registration: Chinese Clinical Trial Register, ChiCTR200036533, registered on August 24, 2020.

Abbreviations: AE = adverse event, CHM = Chinese herbal medicines, CRF = case report form, DHF = Diastolic heart failure, HFPEF = ejection fraction retention heart failure, NT-proBNP = N-terminal brain natriuretic peptide precursor, NYHA = New York Heart Association, SGF = Shen’ge formula, TCM = traditional Chinese medicine.

Keywords: diastolic heart failure, randomized controlled trial, Shen’ge formula, traditional Chinese medicine

1. Introduction

Diastolic heart failure (DHF) is also known as heart failure (HF) with preserved ejection fraction (HFpEF). The prevalence of DHF has been increasing at a rate of 1% per year, increasing from 38% to 54% over the past 20 years.[1] The data collected from the American College of Cardiology’s National Cardiovascular Data Registry Practice Innovation and Clinical Excellence showed that 56.5% (n=622 866) of 1 103 386 patients had HFpEF.[2] A study also showed that more than 90% of patients had HF with diastolic dysfunction independent of ejection fraction.[3]
However, as a current major public health problem, there is no effective treatment for DHF,[4] and the interventions mainly include smoking cessation, moderate exercise, weight control, and the treatment of basic diseases.[5] Moreover, DHF will be a major cause of HF in the next 10 years and involves multiple organ dysfunction with multiple complications.[6]

Traditional Chinese medicine (TCM), a verified complementary or alternative treatment for patients with HF,[7–11] has been used to treat various heart diseases in China for thousands of years. In our study, Shen’ge formula (SGF), a representative TCM formula, consisting of ginseng and gecko (Table 1) in a 3:1 proportion by weight will be used as a therapeutic drug to treat patients with DHF. A previous study showed that SGF could improve cardiac function and myocardial contractility in HF patients.[12] Gu Ben Pei Yuan San, another TCM formula containing ginseng, gecko, and other herbs, was suggested to improve cardiac function and repair the myocardium in adult mice after apical resection or myocardial infarction.[13] To promote the use of SGF for the treatment of DHF worldwide, randomized, double-blind, placebo-controlled clinical trials are still needed to prove its effectiveness. All of the information for this study was obtained from the Chinese Clinical Trial Registry (registration number: ChiCTR2000036533; http://www.chictr.org.cn).

This randomized double-blind placebo-controlled clinical trial of DHF will include 12 weeks of clinical intervention and 12 weeks of follow-up. Changes in plasma N-terminal brain natriuretic peptide precursor (NT-proBNP) before versus after treatment will be the primary outcome measure. Changes in cardiac ultrasound, cardiopulmonary exercise test, cardiac function grade, TCM syndrome score and Minnesota Heart Failure Quality of Life Scale will be the secondary outcome measure. We will also assess its safety aspects by thoroughly documenting any adverse events (AEs) that occur.

2. Methods

2.1. Study design

This randomized double-blind placebo-controlled clinical trial will investigate the efficacy and safety of SGF in DHF patients. We will recruit 130 patients with DHF from LongHua Hospital affiliated with the Shanghai University of TCM. A total of 130 participants will be equally randomized into the SGF or placebo group. Patients in the SGF group will take 4g SGF per day for 12 weeks, while patients in the placebo group will take SGF placebo for the same duration. The trial process is summarized in Figure 1.

2.2. Ethical issues

The clinical trial will follow the Declaration of Helsinki and the Ethical Guidelines for Clinical Research. The trial protocol was approved by the Institutional Review Board of Longhua Hospital affiliated with Shanghai University of Traditional Chinese Medicine (approval number: 2020LHSB053). Additionally, the protocol has been registered in the Chinese Clinical Trial Registry.

| Table 1 Components of SGF. |
|-----------------------------|
| **Latin scientific name**   | **English name** | **Chinese name** |
| Panax ginseng C.A.Mey.      | Ginseng         | Renshen         |
| Gekko gecko Linnaeus        | Geckos          | Gejie           |

SGF = Shen’ge formula.

Figure 1. Study flowchart. The entire trial will last 24 weeks including 12 weeks for oral drugs and another 12 weeks for follow-up. DHF = diastolic heart failure, SGF = Shen’ge formula.
2. Shock, acute myocardial infarction, pulmonary embolism,

2.5. Main exclusion criteria
(5) Patients who participate in this clinical trial voluntarily,
(3) Patients aged 18 to 80 years;
(2) Patients with New York Heart Association (NYHA) grade II

2.4. Main inclusion criteria
will be retained as clinical trial documents for future reference.
Before entering the trial, patients and their families must provide
written informed consent, and patients and their families have the
right to withdraw from the study at any time. Informed consent
will be retained as clinical trial documents for future reference.
The planned enrollment period is 24 months.

2.3. Study participants
Participants will be recruited from LongHua Hospital affiliated
with Shanghai University of Traditional Chinese Medicine.
Recruitment posters and social application advertisements will be
distributed. The objective, approaches, and potential side effects
and advantages of this study will be fully explained in writing to
the patient and his or her family or designated representative.
Before entering the trial, patients and their families must provide
written informed consent, and patients and their families have the
right to withdraw from the study at any time. Informed consent
will be retained as clinical trial documents for future reference.
The planned enrollment period is 24 months.

2.4. Main inclusion criteria
(1) Patients who meet the diagnostic criteria of Western medicine
and TCM;
(2) Patients with New York Heart Association (NYHA) grade II–
IV cardiac function;
(3) Patients aged 18 to 80 years;
(4) Patients who are not taking forbidden medicine and are able
to complete the trial; and
(5) Patients who participate in this clinical trial voluntarily,
understand its objectives, and provide written informed
consent.

2.5. Main exclusion criteria
1. Shock, acute myocardial infarction, pulmonary embolism,
   infectious endocarditis, severe hepatic, or renal insufficiency;
2. Currently pregnant or lactating or current mental disorder;
3. Seriously ill patients with a life expectancy of less than 6
   months; or
4. Patients who are taking other TCM and unwilling to stop.

2.6. Randomization and allocation
Using the random number method in Excel software, the random
arrangement of treatment (therapeutic versus control drug)
received by 130 subjects will be generated by the given seed
number of 2020, and the corresponding treatment allocation for
the serial number of 1 to 130 will be listed. According to the order
in which the subjects are enrolled, the researchers will fill in a
random number on the medical record sheet and distribute the
experimental drugs matching the random number.

2.7. Blinding
TCM granules (SGF) and placebo will be packaged identically.
The label on each package includes the drug number, quantity,
method of administration, storage conditions, the label “for
clinical research only,” and the drug supply unit. The 2 drugs will
be randomly cataloged, and the doctors in charge of the general
manager plan will issue medical advice for drug distribution, the
nurses will issue the drugs, and the doctors in charge of the
patients will register the drug distribution. The doctors and
nurses in charge of the patients will be blinded to the patients’
drug allocations.

2.8. Interventions
2.8.1. TCM intervention. In the SGF group, patients will be
instructed to dissolve SGF (4g) in 50 mL of hot water and take
the solution orally once a day for 12 weeks, while patients in the
placebo group will take SGF placebo in the same way. The SGF
and SGF placebo will be manufactured, packaged, and labeled by
the Department of Pharmacy, Longhua Hospital Affiliated to
Shanghai University of Chinese Medicine. SGF consists of
ginseng (Renshen, 3g) and gecko (Gejie 1g). All herbs will be
crushed into a powder using a pulverizer and collected after being
subjected to No. 10 sifter-mediated selection. Finally, the SGF
will be packed in individual bags (4g each). For the control
group, SGF placebo will also be prepared by the above
department to achieve a similar color, smell, taste, and texture
as the SGF. The research drugs will be stored in cool and dark
places, placed in dry places away from light, managed and
distributed by special personnel, and tracked carefully.

2.8.2. Conventional Western medicine intervention. All
enrolled patients will be administered basic drug therapy
according to the Chinese Guidelines for the Diagnosis and
Treatment of Heart Failure, Chinese Society of Cardiology
(2018). Angiotensin-converting enzyme inhibitors or angiotensin
receptor blockers, β-receptor blockers, diuretics, digitalis drugs,
and nitrate drugs will be selected for specific situations.

2.8.3. Forbidden treatments and drugs.
(1) Any other TCM methods are not allowed (herbs except for
SGF or SGF placebo, acupuncture, cupping, etc).
(2) Medications outside of the guidelines are not allowed.
(3) The dosage, duration, and name of any intervention must be
recorded thoroughly in the case report form.

2.9. Outcomes
2.9.1. Primary outcomes. NT-proBNP levels will be deter-
dined using an enzyme-linked immunosorbent assay kit before
and after drug administration (week 0 and week 12).

2.9.2. Secondary outcomes
2.9.2.1. Echocardiography. Echocardiography includes left
ventricular mass index, E/E’ ratio, pulmonary systolic pressure,
and right ventricular end-diastolic volume.

2.9.2.2. Cardiopulmonary exercise test. Peak oxygen uptake,
aerobic threshold, and other indicators will be detected at
weeks 0 and 12.

2.9.2.3. NYHA cardiac function classification. NYHA cardiac
function classification: Cardiac function I, patients with heart
disease but unrestricted activity in whom normal physical activity
does not cause fatigue, palpitations, shortness of breath, or
angina. Cardiac function II, heart function and physical activity
are limited by mild heart attack, no discomfort when resting but
normal activity can lead to fatigue, heart palpitations, shortness
of breath, or angina. Cardiac function III, heart disease, limited
physical activity, less than the usual general activity causes
symptoms. Cardiac function IV, heart patients cannot perform
any physical activity, and in the resting state can experience
symptoms of HF or angina pectoris plus aggravating discomfort after physical activity.

Significant effect: Cardiac function was restored to level I or improved by 2 levels.

Effective: Cardiac function improves by 1 but not 2 levels.

Null: No change in cardiac function; deterioration; cardiac function decreased by 1 or more levels.

2.10. TCM syndrome score

This score form is constitutive of 2 parts: symptoms and signs. There are a total of nine appraisable items including palpitation, shortness of breath, lassitude, asthma, falling cold, chest distress, edema, oliguria, and abdominal distention. Each item consists of 4 levels. The minimum score is 0, and the maximum score is 54. Higher scores indicate more severe conditions. The scores and details of TCM syndromes are presented in Table 2. The scores are determined using the semi-quantitative integral method (0–6 points) according to the severity of clinical symptoms.

2.11. Minnesota Heart Failure Quality of Life Scale

The Minnesota Heart Failure Quality of Life Scale is widely used to measure the impact of HF on life.[14] This scale involves the impact of HF on patient lifestyle within the last 1 month (Table 3).

2.12. Safety assessments

AE time, severity, duration, action taken, and outcomes will be recorded truthfully on the designated case report forms (CRFs) during the study. Mild, moderate, and severe labels will be used
to describe the intensity of each AE and assess possible associations between each AE and the study or control drug. If a severe AE occurs during the trial, the patients will be suspended from the trial and treated as a lost case. For the safety assessment, the patients’ blood, urine, and kidney and liver function will be tested before and after treatment. To protect privacy, all participants will be visited in a closed room and given the option to withdraw at any time.

2.13. Sample size

One study\textsuperscript{[15]} showed that HF patients whose NT-proBNP levels decreased by more than 30% had better clinical prognosis. In this study, it was estimated that the decrease in plasma NT-proBNP in the treatment group after treatment would reach 42%. Formula $n = \frac{(α + β)\cdot u_0}{d^2}\cdot\frac{1}{u_0^2}$ was calculated according to the sample size, where standard deviation (instead of $σ$) is set to 30%, $α = 0.05$, $u_0 = 1.645$, $β = 0.1$, $uβ = 1.282$, and $δ = 42 – 30 = 12$.

The sample size was calculated as 54 cases, considering a withdrawal rate of no more than 20%, the sample size of this study was determined to be 130 people with a ratio of the experimental and control groups of 1:1 for 65 people in each group.

2.14. Data collection and monitoring

In this 24-week trial, all participants will be treated with SGF or SGF placebo for 12 weeks and followed up for another 12 weeks. All data will be entered into the designated database that will be exclusively managed by the research team members. Electronic data files, including databases, analysis programs, analysis results, and explanatory files, will be classified and stored in multiple backups on different recording media and properly stored to prevent damage. All of the original files shall be kept in accordance with the unified requirements of scientific research management, and the management data shall be transmitted in time.

2.15. Quality control

Longhua Hospital affiliated with Shanghai University of Traditional Chinese Medicine (http://www.longhua.net/ywsy/gzlc/287.jhtml) is responsible for quality control and training for all investigators. All team members of the trial will receive systematic training to completely apprehend the study procedures. The person in charge will regularly inspect the subjects, systematically train to completely apprehend the study procedures, and regularly monitor the study and discuss with the investigator its progress, the CRF and the original records, and the accuracy of the data records.

2.16. Statistical analysis

The statistical analysis will be performed using SPSS 20.0. If the measurement data are normally distributed with homogeneous variance, the mean $±$ standard ($±$ s) will be used for the statistical analysis and the t-test will be used for the intergroup comparisons. If the data do not follow a normal distribution, the rank sum test will be used to make statistical inferences. Enumeration data will be statistically described as frequency, constituent ratio, and rate. Comparison of indicators with dichotomous or multi-classification disorders will be performed using the $χ^2$ test. The rank sum test will be used to compare groups of ordered classification analysis indicators. Statistical significance will be set at $P < 0.05$.

3. Discussion

HF, the final stage of many heart diseases, is a worldwide problem. The report mentioned that mortality, hospitalization, and rehospitalization rates remained high in HF patients.\textsuperscript{[17]} The 2016 ESC Guideline\textsuperscript{[18]} highlighted the ejection fraction preservation in the diagnosis of HF, suggesting that we must pay more attention to the status of patients with DHF. There is currently no clear and effective drug for the treatment of DHF, and high-quality clinical trials on this disease treated by TCM are lacking. SGF is a TCM that has been used for hundreds of years owing to its unique theoretical connotation and practical effect, but its clinical efficacy and safety have not been systematically evaluated in randomized controlled trials. A query of PubMed, Web of Science, Embase, the Cochrane Library, Wan Fang Database, and Clinical Trials for publications through February 2021 revealed no data about the efficacy or safety of SGF for treating DHF patients. Therefore, this study will be the first randomized double-blind placebo-controlled study to evaluate the efficacy and safety of the SGF in the treatment of patients with DHF.

The results of this study will not only prove the exact efficacy of SGF on DHF, also it will document changes in SGF on quality of life through follow-up. This clinical trial will provide powerful evidence to provide a safe and effective reference for future research.

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References

[1] Singh A, Mehta Y. Heart failure with preserved ejection fraction (HFpEF): implications for the anesthesiologists. J Anaesthesiol Clin Pharmacol 2018;34:161–5.

[2] Ibrahim NE, Song Y, Cannon CP, et al. Heart failure with mid-range ejection fraction: characterization of patients from the Pinnacle Registry. ESC Heart Failure 2019;6:784–92.

[3] Brucks S, Little WC, Chao T, et al. Contribution of left ventricular diastolic dysfunction to heart failure regardless of ejection fraction. Am J Cardiol 2005;95:603–6.

[4] Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of
Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:e240–327.
[5] Pagel PS, Tawil JN, Boerntcher ET, et al. Heart failure with preserved ejection fraction: a comprehensive review and update of diagnosis, pathophysiology, treatment, and perioperative implications. J Cardiothorac Vasc Anesth 2020.
[6] Parikh KS, Sharma K, Faizat M, et al. Heart failure with preserved ejection fraction expert panel report: current controversies and implications for clinical trials. JACC Heart Fail 2018;6:619–32.
[7] Bai HY, Li YF, Han K, et al. Effectiveness of Chinese herbal medicine as an adjunctive treatment for dilated cardiomyopathy in patients with heart failure. J Altern Complement Med 2013;19:811–9.
[8] Hao P, Jiang F, Cheng J, et al. Traditional Chinese medicine for cardiovascular disease: evidence and potential mechanisms. J Am Coll Cardiol 2017;69:2952–66.
[9] Chang M, Cheng L, Shen Y, et al. Qishenyiqi dripping pill improves ventricular remodeling and function in patients with chronic heart failure: a pooled analysis. Medicine 2019;98:e13906.
[10] Zheng H, Chen Y, Chen J, et al. Shengmai (a traditional Chinese herbal medicine) for heart failure. Cochrane Database Syst Rev 2011; Cd005052.
[11] Holubarsch CJK, Colucci WS, Eha J. Benefit-risk assessment of crataegus extract WS 1442: an evidence-based review. American journal of cardiovascular drugs: drugs, devices, and other interventions 2018; 18:25–36.
[12] Qiao S, Li G, Ding L, et al. Clinical observation on the adjuvant treatment of 36 cases of chronic heart failure with Shen’ge formula. Journal of Traditional Chinese Medicine 2020;61:1536–9.
[13] Cui BP, Zheng YF, Zhou XY, et al. Repair of adult mammalian heart after damages by oral intake of Gu Ben Pei Yuan San. Front Physiol 2019;10.
[14] Austin J, Williams WR, Hutchison S. Patterns of fatigue in elderly heart failure patients measured by a quality of life scale (Minnesota living with heart failure). Eur J Cardiovasc Nurs 2012;11:439–44.
[15] Bettencourt P, Azevedo A, Pimenta J, et al. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004;110:2168–74.
[16] Li X, Zhang J, Huang J, et al. A multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the effects of qil qiangxin capsules in patients with chronic heart failure. J Am Coll Cardiol 2013;62:1065–72.
[17] Dharmarajan K, Rich MW. Epidemiology, pathophysiology, and prognosis of heart failure in older adults. Heart Fail Clin 2017; 13:417–26.
[18] Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart J 2016;37:2129–200.