

Clinical efficacy and safety of Shenqi Fuzheng injection for the treatment of chronic heart failure

Protocol for a meta-analysis and systematic review

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Abstract

Background: Chronic heart failure (CHF) is one of the most serious cardiovascular diseases. Shenqi Fuzheng injection (SQFZI), as a Chinese herbal injection, is usually used for the treatment of CHF. However, the clinical evidence of SQFZI for the treatment of CHF is unclear.

Methods: Two researchers will independently search literatures of SQFZI for CHF from Chinese National Knowledge Infrastructure database, VIP database, Chinese Biological and Medicine database, Wangfang database, MEDLINE, EMBASE, Cochrane Library and Web of Science. These inclusive data of included studies will be conducted by RevMan 5.3 software.

Results: This meta-analysis and systematic review will provide a series of outcome measures to verify clinical efficacy and safety of SQFZI for treating CHF, including New York Heart Association (NYHA) function classification, left ventricular ejection fraction, left ventricular end-diastolic dimension, cardiac output, stroke volume, brain natriuretic peptide, N-terminal pro-brain natriuretic peptide, and adverse events.

Conclusions: This meta-analysis and systematic review will provide up-to-date clinical evidence to assess SQFZI treatment efficacy for CHF patients.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, BNP = brain natriuretic peptide, CHF = chronic heart failure, CI = confidence interval, CO = cardiac output, hs-CRP = hypersensitive C-reactive protein, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, MD = mean difference, NT-proBNP = N-terminal pro-brain natriuretic peptide, NYHA = New York Heart Association, RCTs = randomized controlled trials, RR = rate ratio, SQFZI = Shenqi Fuzheng injection, SV = stroke volume, TCM = traditional Chinese medicine.

Keywords: chronic heart failure, meta-analysis, protocol, Shenqi Fuzheng injection, systematic review

1. Introduction

Chronic heart failure (CHF) is a heart disease which is caused by myocardial damage, heart overload and systolic dysfunction.^[1] The high incidence and mortality of CHF have brought enormous burden and challenge to social economy and medical resources.^[2]

CHF is a progressive disease, even if no new myocardial damage is produced from the onset.^[3] Patients show no obvious clinical signs and symptoms, but this does not mean the disease will not further develop. Currently, neurohormonal antagonists (ACEI, β -blockers, angiotensin receptor blockers and mineralocorticoid

This systematic review does not require formal ethical approval since no privacy health information will be included. The findings of this review will be disseminated through peer-reviewed publications or conference presentations.

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receptor antagonists) are recommended as cornerstone treatments for CHF.^[4,5] However, these are unsatisfactory in terms of clinical efficacy and safety.^[6] The Shenqi Fuzheng injection (SQFZI) is a Chinese herbal injection which is mainly composed of *Radix Codonopsis* (Dangshen) and *Radix Astragali* (Huangqi).^[7] SQFZI is approved by the China Food and Drug Administration (CFDA) and has already achieved positive results for the treatment of CHF in one clinical trial,^[8] although more evidence is needed for its efficacy to be approved in clinical guidelines.^[9,10] Recently, there have been more randomized controlled trials (RCTs) testing SQFZI's efficacy for treating CHF. We therefore conducted a systematic evaluation of the clinical efficacy and safety of SQFZI combined with Western medicine for treating CHF.

2. Methods

2.1. Inclusion criteria

2.1.1. Type of study. Studies will be included this meta-analysis, regardless of publication countries and language. These included studies of SQFZI for treating CHF.

2.1.2. Type of patients. According to "Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in China" or "American College of Cardiology/American Heart Association (ACC/AHA) guidelines 2016",^[11] patients only contains CHF, other diseases such as diabetes, hypothyroidism, gallbladder disease are excluded.

2.1.3. Type of intervention. For the treatment group, SQFZI will be intravenously instilled daily on the basis of conventional therapy with CHF patients, while in the control group, only conventional therapy for CHF treatment alone.

2.1.4. Type of outcome measures. Primary outcomes:

- NYHA function classification;
- Clinical total effective rate.

Secondary outcomes:

- Left ventricular ejection fraction (LVEF);
- Left ventricular end-diastolic dimension (LVEDD);
- Cardiac output (CO);
- Stroke volume (SV);
- Brain natriuretic peptide (BNP);
- N-terminal pro-brain natriuretic peptide (NT-proBNP);
- Hypersensitive C-reactive protein (hs-CRP);
- Adverse events.

2.2. Search strategy for the included studies

2.2.1. Database search. We will search for literatures on SQFZI treatment of CHF from the following 7 databases:

1. China National Knowledge Infrastructure (CNKI)
2. Wanfang Database
3. Chinese VIP Information (VIP)
4. Chinese Biomedical Literature Database (CBM)
5. MEDLINE
6. The Cochrane Library
7. Web of Science

2.2.2. Searching other resources. Meanwhile, we will also search Chinese Clinical Trials Registry (ChiCTR) (<http://www.chictr.org.cn/>) to collect data of included RCTs with SQFZI for treating CHF.

chictr.org.cn/) to collect data of included RCTs with SQFZI for treating CHF.

2.2.3. Search strategy in electronic database. These main keywords are: Shenqi Fuzheng Injection, CHF, randomized controlled trials. Details of search strategy in PubMed as follow:

#1 ("heart failure, chronic" [MeSH Terms]) OR ("heart failure*" [Title/Abstract]) OR ("chronic heart failure*" [Title/Abstract]) OR ("coronary heart disease*" [Title/Abstract]) OR ("coronary artery disease" [Title/Abstract])

#2 ("Shenqi Fuzheng, Injection" [MeSH Terms]) OR ("Shenqi Fuzheng Injection*" [Title/Abstract]) OR ("Shenqi Fuzheng Injectables*" [Title/Abstract]) OR ("SQFZ injection*" [Title/Abstract]) OR ("Dangshen and Huangqi, Injection" [Title/Abstract]) OR ("Radix Codonopsis and Radix Astragali, injection" [Title/Abstract])

#3 ("Randomized, controlled trial" [MeSH Terms]) OR ("Randomized controlled trial*" [Title/Abstract]) ("clinical study" [Title/Abstract]) OR ("Clinical Trial" [Title/Abstract]) OR ("Controlled study*" [Title/Abstract]) OR ("Controlled Trial*" [Title/Abstract])
#1 AND #2 AND #3

2.3. Data collection and analysis

2.3.1. Study selection. Through database searching, duplicate studies will be deleted and remaining eligible studies will be transferred to EndNote X9 software (Thomson Reuters, Inc, New York, NY). Two researchers will carefully scan the titles and abstracts of studies to exclude studies that is not related to the topic. Full-text studies will further screen studies that may meet the inclusion criteria. If necessary, the third researcher will discuss into disagreement of selection studies. Details of study selection will be shown as in a PRISMA flowchart (Fig. 1).

2.3.2. Data extraction. Two researchers independently screened the literature, following the inclusion and exclusion criteria. When there were differences, consensus was reached through discussion. If necessary, a third researcher joined the discussion. Extracted data included basic characteristics, including first author, publication year, country, patients' mean age, NYHA class, intervention methods, sample size, and outcomes.

2.3.3. Heterogeneity analysis. The risk ratio (RR) was results of dichotomous variables with 95% confidence intervals (CI 95%). The mean difference (MD) was the results of the continuous variables with CI 95%. A heterogeneity test was used. If $P > .1$, the fixed effect model was used for meta-analysis. Otherwise, the random effect model was used.

2.4. Risk of bias

The Cochrane Handbook suggests seven considerations for evaluating risk of bias as follow: random sequence generation method, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources. Each consideration was divided into three levels for the selected studies: "low risk", "high risk", or "unclear".

2.5. Publication bias

When more than ten RCTs are included, the symmetry of the funnel plot will be used to assess to evaluate whether the funnel

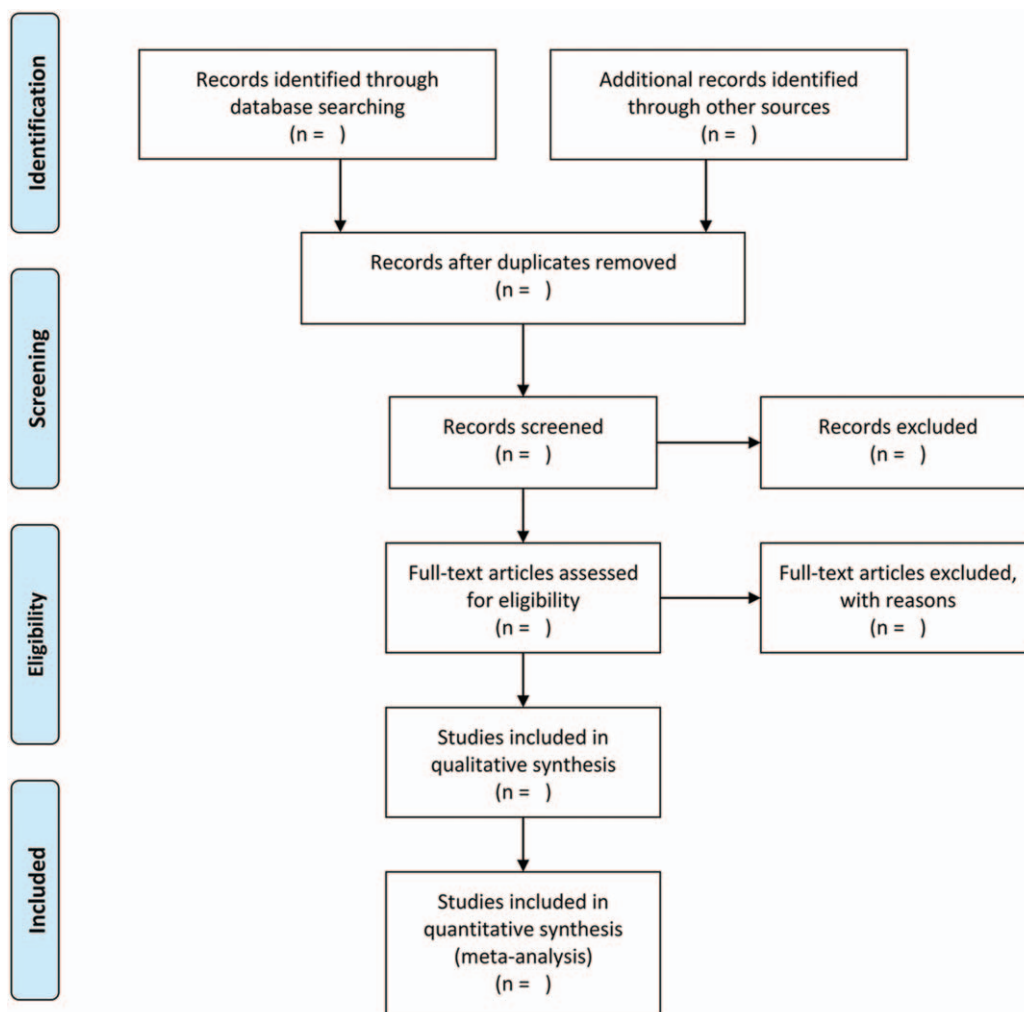


Figure 1. PRISMA flowchart of selection studies.

plot is symmetrical. If necessary, we will also use STATA 12.0 software to evaluate stability of included studies.

2.6. Subgroup analysis

Heterogeneity is one of the main factors affecting the results of meta-analysis. So, subgroup analysis will be used to analyze the source of heterogeneity. We will perform a subgroup analysis from the following points to determine the source of heterogeneity:

- Different treatment courses
- Different daily doses
- People of different skin colors
- Inclusion of differences in studies quality

2.7. Sensitivity analysis

Sensitivity analysis is an important method used in meta-analysis to assess the robustness and reliability of results. The commonly used method is to eliminate each of the included studies one by one and then combine the effect quantities, change the inclusion

of exclusion criteria or eliminate certain types of literature and then combine effect sizes.

3. Discussion

CHF is a global health problem.^[12] While medical technology has improved its treatment, disease incidence and mortality has increased year by year. Myocardial injury is the main pathogenesis of CHF, which can lead to the complex clinical syndrome of low ventricular pumping and filling function.^[13] In China, traditional Chinese medicine (TCM) has been widely used for treating heart failure.^[14,15] SQFZI is a new type of TCM injection and is mainly composed of Radix Codonopsis (Dangshen) and Radix Astragali (Huangqi), 2 herbal medicines which have been used in China for thousands of years.^[16] Hence, we will conduct a meta-analysis to evaluate efficacy and safety of SQFZI for treating CHF. However, due to methodological quality, different doses, and only included English and Chinese database, it is necessary to carry out large sample, high-quality RCTs in the future to verify the treatment's therapeutic effect and provide more convincing evidence for its use in the treatment of CHF.

Author contributions

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References

- [1] Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Rev Esp Cardiol (Engl Ed)* 2016;69:1167.
- [2] Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;63:1123–33.
- [3] Inamdar AA, Inamdar AC. Heart failure: diagnosis, management and utilization. *J Clin Med* 2016;5:E62.
- [4] Gheorghide M, Bonow RO. Introduction and overview: beta-blocker therapy in the management of chronic heart failure. *Am J Med* 2001;110 (Suppl 7A):1S–5S.
- [5] Butler J. An overview of chronic heart failure management. *Nurs Times* 2012;108:16–20.
- [6] Fu S, Zhang J, Menniti-Ippolito F, et al. Huangqi injection (a traditional Chinese patent medicine) for chronic heart failure: a systematic review. *PLoS One* 2011;6:e19604.
- [7] Cai YM, Zhang Y, Zhang PB, et al. Neuroprotective effect of Shenqi Fuzheng injection pretreatment in aged rats with cerebral ischemia/reperfusion injury. *Neural Regen Res* 2016;11:94–100.
- [8] Chen H, Yao X, Liu Z, et al. Efficacy and safety of Shenqi Fuzheng injection combined with platinum-based chemotherapy for stage III/IV non-small cell lung cancer: A protocol for systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2019;98: e17350.
- [9] Wang L, Qu H. Development and optimization of SPE-HPLC-UV/ELSD for simultaneous determination of nine bioactive components in Shenqi Fuzheng Injection based on Quality by Design principles. *Anal Bioanal Chem* 2016;408:2133–45.
- [10] Zhang SY, Fan CL, Huang XJ, et al. A new phenylpropanoid and a new isoflavone glycoside from Shenqi Fuzheng Injection. *J Asian Nat Prod Res* 2015;17:274–9.
- [11] Writing Committee M, Yancy CW, Jessup M, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2016;134:e282–93.
- [12] Neubauer S. The failing heart—an engine out of fuel. *N Engl J Med* 2007;356:1140–51.
- [13] Komajda M, Bohm M, Borer JS, et al. Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Eur J Heart Fail* 2018;20:1315–22.
- [14] Zhu MJ. [Experiences regarding clinical study on treatment of chronic heart failure with traditional Chinese medicine [in Chinese]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2008;28:1066–7.
- [15] Chen CX, Gao JP, Wu Q, et al. Progress in treatment of chronic heart failure in Western medicine and treatment strategies in traditional Chinese medicine [in Chinese]. *Zhong Xi Yi Jie He Xue Bao* 2010;8:7–14.
- [16] Yang Y, Ting W, Xiao L, et al. Immunoregulation of Shenqi Fuzheng injection combined with chemotherapy in cancer patients: a systematic review and meta-analysis. *Evid Based Complement Alternat Med* 2017;2017:5121538.