

Chinese herbal injections for heart failure

A protocol for systematic review and network meta-analyses

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Abstract

Background: Chinese herbal injections (CHIs) are commonly used for the treatment of heart failure in China. Due to the variety of CHIs used in clinic, selecting a suitable CHI for patients with heart failure is vital. This study aims to assess and compare the effect of different CHIs for heart failure using network meta-analysis (NMA).

Methods: Six electronic databases, including PubMed, the Cochrane Central Register of Controlled Trials, Embase, China National Knowledge Infrastructure, Wanfang, and Chinese Biomedical Literature Database will be searched from inception to January 2018. Randomized controlled trial (RCT) comparing CHI with another CHI will be included. The primary outcome will be changes in heart function classification and left ventricular ejection fraction. Risk of bias assessment of the included RCTs will be conducted according to the Cochrane Handbook 5.1.0. A Bayesian NMA will be performed using WinBUGS 14 software and the result figures will be generated using Stata 13 software. GRADE will be used to explore the quality of evidence.

Results: The results of this NMA will be published in a peer-reviewed journal.

Conclusion: Our study will generate evidence of CHIs for patients with heart failure and provide suggestions for Chinese medicine clinical practice or guideline.

Ethics and dissemination: Ethics approval and patient consent are not required because this study is an NMA based solely on the published literature. The results of this NMA will be submitted to a peer-reviewed journal.

Protocol registration number: PROSPERO CRD 42018086740

Abbreviations: CHI = Chinese herbal injection, NMA = network meta-analysis, RCT = randomized controlled trial, ROB = risk of bias.

Keywords: Chinese herbal injection, heart failure, network meta-analysis

1. Introduction

Heart failure is a chronic disease exhibiting an unpredictable trajectory and an escalating symptom profile along with time.^[1] Almost 26 million people suffered from heart failure around the world.^[2] It is one of the most primary causes of hospitalization in people over 65 years,^[3] about 9.6% of patients with heart failure died and 19.4% rehospitalized for cardiovascular causes within 90 days of admission.^[4]

Authorship: FY, JZ, and JZ conceived the study, developed the criteria, and wrote the protocol. LG and JT will search the literature and assess the risk of bias. JHJ and MSL advised on protocol design and revised the manuscript. All authors read and approved the final manuscript.

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According to the World Bank Development Indicators, the cost of heart failure in China during 2012 was up to \$5.42 billion, ranking as the greatest healthcare burden among middle and low-income nations, and taking up 5.01% of total healthcare costs.^[5] Although Chinese herbal injections (CHIs) are not the mainstream for the treatment of heart failure in the world, they are widely used as a complementary and alternative therapy for patients with heart failure in China due to its rapid action, high bioavailability, and no digestive tract absorption.^[6]

It is difficult to determine the superiority of CHIs using pairwise meta-analysis, network meta-analysis (NMA) has become increasingly popular in assessing different therapies through direct or indirect comparisons.^[7] It allows a comprehensive analysis of all studies that compared different kinds of interventions and rank them one by one.^[8,9] This study aims to evaluate the effect of different AHIs in the treatment of heart failure and to provide evidence for clinicians in the selection of AHIs.

2. Methods

2.1. Study registration

The study protocol has been registered on PROSPERO CRD 42018086740.

2.2. Eligibility criteria

2.2.1. Type of study. Randomized controlled trials (RCTs) that investigated the effect of CHI for the treatment of heart failure will be included. No language limitation exists.

2.2.2. Participants. Patients with heart failure, which should be confirmed according to the diagnostic standard.^[10–13] There are no limitations in age, gender, race, or nationality.

2.2.3. Interventions. Interventions of CHI compare with another CHI are eligible, conventional pharmacotherapy (eg, cardiotoxic, diuretic, vasodilators, ACEI, β -blocker, and so on) could be used in both groups or not. As the following 2 forms: CHI a versus CHI b; CHI a+conventional pharmacotherapy versus CHI b+conventional pharmacotherapy. Conventional pharmacotherapy in the 2 groups should be same.

2.2.4. Outcomes. The primary outcomes include changes of heart function classification according to NYHA standard and left ventricular ejection fraction, the secondary outcome was adverse event. RCTs reporting on at least one primary outcome will be included.

2.3. Data source

Six electronic databases, including PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, and Wanfang Database will be searched from inception to January 2018. There was no language restriction in this study. Search strategy of PubMed was as follows:

#1 (((((((((((("Heart Failure"[MeSH Terms]) OR "Heart Failure"[Title/Abstract]) OR "Cardiac Failure"[Title/Abstract]) OR "Heart Decompensation"[Title/Abstract]) OR "Decompensation, Heart"[Title/Abstract]) OR "Right-Sided Heart Failure"[Title/Abstract]) OR "Right Sided Heart Failure"[Title/Abstract]) OR "Myocardial Failure"[Title/Abstract]) OR "Congestive Heart Failure"[Title/Abstract]) OR "Left-Sided Heart Failure"[Title/Abstract]) OR "Left Sided Heart Failure"[Title/Abstract])

#2 (((((Injections[MeSH Terms]) OR Injection[Title/Abstract]) OR Injectables[Title/Abstract]) OR Injectable[Title/Abstract]) OR Injections[Title/Abstract]))

#3 (((("Medicine, Chinese Traditional"[MeSH Terms]) OR "Traditional Chinese Medicine"[Title/Abstract]) OR "Chinese Traditional Medicine"[Title/Abstract]) OR zhongyi[Title/Abstract]) OR zhongyao[Title/Abstract])

#4 #2 AND #3

#5 #1 AND #4

2.4. Study selection

Records from database searches will be managed by EndNote X7 software. The titles and abstracts of each record retrieved will be checked by 2 independent authors (FY and JZ) according to eligibility criteria. The full texts of potentially relevant studies will be retrieved for further assessment. Disagreements will be resolved by discussion or consultation of a 3rd author (JZ). A data spreadsheet will be created using Microsoft Excel 2007 to collect relevant information and data. The information, including author, year of publication, sample size, intervention, and outcome will be extracted from each study and entered into the spreadsheet.

2.5. Risk of bias (ROB) assessment

ROB assessment will be conducted by 2 independent authors (LG and JT). Disagreement will be resolved by discussion or consultation of Junhua Zhang. The ROB Tool in Cochrane

Handbook 5.1.0 will be used to assess the potential ROB of included RCTs.^[14] Seven items are included in ROB: random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete data, selective reporting, and other biases. Every item in ROB will be graded as low risk, high risk, or unclear risk.

2.6. Statistical analysis

2.6.1. Pairwise meta-analyses. Pairwise meta-analyses will be carried out using random-effects model by Stata 13 software. Odds ratio with 95% confidence interval (95% CI) will be presented for dichotomous data (heart function classification and adverse event) and continuous data (left ventricular ejection fraction) will be reported as mean difference with 95% CI. The χ^2 test and I^2 test will be conducted to assess the potential heterogeneity across the included studies. Sensitivity analyses, which was mainly according to the methodological qualities and sample size, will be carried out to investigate the source for potential heterogeneity if $I^2 > 50\%$ and $P < 0.1$. Subgroup analysis will also be performed if the heterogeneity was detected.

Begg and Egger funnel plot method through Stata 13 will be used to examine the publication bias when applicable.^[15,16]

2.6.2. Network meta-analyses. A Bayesian NMA will be performed by WinBUGS 14 (MRC Biostatistics Unit, Cambridge University, UK).^[17] We will use node splitting method to examine the inconsistency between direct and indirect comparisons if a loop connecting 3 or more arms exist.^[18] Surface under the cumulative ranking will be used to rank the CHIs,^[19] a larger surface under the cumulative ranking means a more effective intervention. Comparison-adjusted funnel plots will be conducted to assess the effects of the sample size on the results. All the result figures will be generated using Stata 13 software.

2.7. Quality of evidence

The quality of evidence for the main outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation,^[20] which contains 4 levels: high level, moderate level, low level, and very low level. Flaws in study design, inconsistency, imprecision, indirectness, and publication bias will be investigated.

3. Discussion

This NMA will summarize the direct and indirect evidence through providing a ranking of the CHIs for heart failure. To the best of our knowledge, this is the first NMA to comprehensively evaluate and compare the effect of different CHIs for heart failure, although a few studies have assessed the effect of the individual CHI.^[6,21,22] We hope the results of this NMA will provide the clinical recommendation for patients with heart failure in Chinese medicine clinical practice or guideline.

This protocol is designed in adherence to guideline for NMA protocols^[23] and will be conducted and reported strictly according to the PRISMA extension statement for NMAs.^[24]

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