Efficiency and Safety of Ling-Gui-Zhu-Gan Decoction in the Treatment of Chronic Heart Failure: A Systemic Review and Meta-Analysis Study

Song, Y1; Wang, HY2; Qin, LL3; Wu, LL4; Liu TH5.

Review question / Objective: The aim of this study was to review existing evidence on the effectiveness of Ling-Gui-Zhu-Gan Decoction for the treatment of chronic heart failure.

Condition being studied: Chronic heart failure (CHF) is a complex clinical syndrome characterized by reduced cardiac output, inadequate perfusion of tissues and organs, venous system congestion, etc. It is a serious manifestation and end stage of various heart diseases. The prevalence of CHF continues to increase due to an aging population, increased risk factors for cardiovascular disease, and prolonged survival of patients with disease. According to traditional Chinese medicine, heart failure is a disease characterized by palpitation, asthma and limb edema. Traditional Chinese medicine treatment for CHF can effectively improve the main clinical symptoms of patients, and also has a good effect on accompanying symptoms such as abdominal distension, anorexia and fatigue. Ling-Gui-Zhu-Gan decoction is a famous prescription in Treatise on Febrile Diseases. The prescription has the characteristics of warming Yang and invigorating the spleen, invigorating heart Yang. Modern studies have confirmed that Linggui Zhugan decoction can improve cardiac function, regulate hemodynamics, improve ventricular remodeling, slow down myocardial ischemic injury, and inhibit neuroendocrine and cytokines. Traditional Chinese medicine treatment for CHF can effectively improve the main clinical symptoms of patients, and also has a good effect on accompanying symptoms such as abdominal distension, anorexia and fatigue.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 July 2020 and was last updated on 17 July 2020 (registration number INPLASY202070077).
inadequate perfusion of tissues and organs, venous system congestion, etc. It is a serious manifestation and end stage of various heart diseases. The prevalence of CHF continues to increase due to an aging population, increased risk factors for cardiovascular disease, and prolonged survival of patients with disease. According to traditional Chinese medicine, heart failure is a disease characterized by palpitation, asthma and limb edema. Traditional Chinese medicine treatment for CHF can effectively improve the main clinical symptoms of patients, and also has a good effect on accompanying symptoms such as abdominal distension, anorexia and fatigue. Ling-Gui-Zhu-Gan decoction is a famous prescription in Treatise on Febrile Diseases. The prescription has the characteristics of warming Yang and invigorating the spleen, invigorating heart Yang. Modern studies have confirmed that Linggui Zhugan decoction can improve cardiac function, regulate hemodynamics, improve ventricular remodeling, slow down myocardial ischemic injury, and inhibit neuroendocrine and cytokines. Traditional Chinese medicine treatment for CHF can effectively improve the main clinical symptoms of patients, and also has a good effect on accompanying symptoms such as abdominal distension, anorexia and fatigue.

METHODS

Search strategy: In addition, trial registers would be also searched: World Health Organization International Clinical Trials Registry (www.who.int/ictrp/en/); and US National Institutes of Health Ongoing Trials Register (www.ClinicalTrials.gov). No language restriction was used. We further scanned the references of all included studies and relevant reviews to identify any trials that met our inclusion criteria.

Participant or population: We included participants of any age or sex with CHF clearly diagnosed by internationally recognized criteria.

Intervention: The Treatment Group was treated with Ling-Gui-Zhu-Gan decoction combined with conventional western medicine, and the intervention course was ≥14d.

Comparator: The control group was treated with simple conventional Western medicine or conventional Western medicine combined with placebo.

Study designs to be included: Randomised controlled trials (RCTs) with a correct description of randomisation procedure would be included irrespective of blinding or language.

Eligibility criteria: All included trials met the following selection criteria: (1) the study was a randomized controlled trial (RCT); (2) the study examined CHF participants who received Ling-Gui-Zhu-Gan as intervention; (3) the study included participants irrespective of gender, age, or ethnicity, and CHF was diagnosed by clearly defined or internationally recognized criteria.

Information sources: The following seven electronic databases would be searched to identify eligible trials published from inception to June 26, 2020. The English electronic databases included Pubmed, Embase, and the Cochrane Central Register of Controlled Trials. The Chinese electronic databases would be CNKI, CBM Wangfan and VIP. The reference lists of relevant retrieved articles would be searched manually to identify any additional eligible studies. In addition, trial registers would be also searched: World Health Organization International Clinical Trials Registry (www.who.int/ictrp/en/); and US National Institutes of Health Ongoing Trials Register (www.ClinicalTrials.gov). No language restriction was used. We further scanned the references of all included studies and relevant reviews to identify any trials that met our inclusion criteria.

Main outcome(s): 1. Clinical efficacy of chronic heart failure; 2. BNP; 3. LVEF; 4. 6MWT; 5. LVEDD; 6. LVESD; etc.

Data management: Two review authors independently extracted data concerning details of study population, intervention, and outcomes using a pre-designed data...
extraction form. The following data would be extracted: general trial characteristics (title, authors, year); baseline patient and disease data (sample size, age, gender); interventions (dose and the details of control interventions); and outcomes (follow-up length, outcome measures, adverse events). We resolved differences in data extraction by consensus or a third party. One author entered data into the Cochrane software Review Manager 5 (RevMan 5) and another checked the data to reduce the possibility of data entry errors.

Quality assessment / Risk of bias analysis: Two authors independently assessed the "risk of bias" according to guidance in the Cochrane Handbook for Systematic Reviews of Interventions. This involved the following domains: random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. We completed a 'Risk of bias' table according to Cochrane guidelines. We made judgement on each of these criteria relating to the risk of bias: low, high or unclear (indicating unclear or unknown risk of bias). Discrepancies in this interpretation would be resolved by consensus or after discussion with a third party.

Strategy of data synthesis: The data would be analyzed using Review Manager 5.3 software. Publication bias was examined using funnel plots. For outcomes, data regarding incidence would be dichotomous, and others would be continuous. Risk ratios (RRs) would be calculated using the Mantel-Haenszel method for dichotomous outcomes, and weighted mean differences (MDs) would be calculated using the inverse variance method for continuous variables. I² statistics would be used to assess heterogeneity. A fixed-effects (FE) model was used if there was no significant heterogeneity in the data (I²50%). Sensitivity analysis was performed to assess the stability of conclusions. Where heterogeneity was detected, accepted methods would be used to explore the statistical heterogeneity using clinical parameters such as treatment duration, sample size, publication year, diagnostic criteria, publication language, and TCM syndrome. Publication bias was assessed using funnel plots.

Subgroup analysis: Subgroup analyses would be performed if one of the primary outcome parameters demonstrated statistically significant differences between treatment groups. The following subgroup analyses would be planned: age (subdivided into groups, based on data); gender; duration of intervention (subdivided into groups, based on data).

Sensibility analysis: If we had identified a sufficient number of RCTs, we plan to undertake sensitivity analyses to explore the influence of risk of bias on effect estimates. The following aspects of quality will be considered for this sensitivity analysis: inadequate blinding, non-comparable groups (because they had different baseline characteristics), and no intention-to-treat analysis.

Language: No language limits.

Country(ies) involved: China.

Keywords: Chronic Heart Failure; Ling-Gui-Zhu-Gan Decoction; Systemic Review; Meta-Analysis.

Contributions of each author:
Author 1 - Yanan Song.
Author 2 - Haiyan Wang.
Author 3 - Lingling Qin.
Author 4 - Lili Wu.
Author 5 - Tonghua Liu.