INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Danshen decoction in the treatment of heart failure: a systematic review and meta-analysis protocol of randomized controlled trials

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Review question / Objective: **HF (heart failure) is considered to be the clinical endpoint and the leading cause of death of CVD (cardiovascular diseases). With people's growing desire for a healthy and better life, TCM (traditional Chinese medicine) as an alternative in the prevention and treatment of HF is becoming more popular. The basic and clinical research related to TCM has also been widely concerned by the cardiovascular community of scientists/clinicians. In recent years, a large number of preclinical (in vivo/in vitro) experiments and clinical observation studies have proved the therapeutic efficacy of Danshen decoction in the treatment of HF. However, systematic evaluation and review of the clinical treatment of Danshen decoction is insufficient, leaving objective and quantitative evaluation indicators of Danshen decoction to be inadequate. Therefore, evidence-based studies are urgently needed to demonstrate its efficacy and safety.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 July 2022 and was last updated on 25 July 2022 (registration number INPLASY202270107).

INTRODUCTION

Review question / Objective: **HF (heart failure) is considered to be the clinical endpoint and the leading cause of death of CVD (cardiovascular diseases). With people's growing desire for a healthy and better life, TCM (traditional Chinese medicine) as an alternative in the prevention and treatment of HF is becoming more popular. The basic and clinical research related to TCM has also**

been widely concerned by the cardiovascular community of scientists/clinicians. In recent years, a large number of preclinical (in vivo/in vitro) experiments and clinical observation studies have proved the therapeutic efficacy of Danshen decoction in the treatment of HF. However, systematic evaluation and review of the clinical treatment of Danshen decoction is insufficient, leaving objective and quantitative evaluation indicators of Danshen decoction to be inadequate. Therefore, evidence-based studies are urgently needed to demonstrate its efficacy and safety.

Rationale: This meta-analysis will search all the studies related to Danshen decoction, formulate inclusion-exclusion criteria, and screen out all the eligible clinical studies. Afterwards, the Revman V.5.4 software will be used for systematic reviews, summaries and meta-analysis of clinical studies. The ability to improve CF and the effect of reducing serum diagnostic indicators such as BNP (brain natriuretic peptide), NT-proBNP (N-terminal pro-B type natriuretic peptide), hs-CRP (hypersensitive C-reactive protein), etc were used as indicators to evaluate the therapeutic effect of Danshen decoction. Finally, the credibility of the article will be improved by reasonable statistics and correct meta-analysis results, using the chi-square test. The results of this study will provide more updated and comprehensive evidence for clinical decision-making, providing a reference for the follow-up study of Danshen decoction in the treatment of HF.

Condition being studied: Heart failure (HF) is considered the clinical endpoint of all CVDs (cardiovascular diseases). Although a large number of HF drugs and therapies have been developed, it is still to find therapies with better clinical efficacy and fewer side effects. The purpose of this systematic evaluation is to assess the efficacy and safety of Danshen decoction on HF and the improvement of cardiac function (CF).

METHODS

Search strategy: We will search PubMed (1946 present), EMBASE (1974 present), Cochrane Central Registry of controlled trials (all years), Web of Science (1900 present), China biomedical literature database (1978 present), China National Knowledge Infrastructure (1979 present) and Wanfang Data (1998 present) to identify any eligible studies. There are no restrictions set for on the language, publication date, or status of the study. The CER of HF treatment is considered to be the main result. CF, various serum inflammatory factors, and adverse events were defined as secondary outcomes. When more than one article is used to study the changes and results of the same index, we will conduct a meta-analysis. If the heterogeneity is not statistically significant ($P > 0.10$ or $I2 < 50\%$), a fixed-effect model will be established to estimate the overall intervention effect. Otherwise, random effect models will be used to provide more conservative results.

Participant or population: The meta-analysis of this study will be completely based on the existing RCTs. Patients and the public will not participate in the research of problems and the formulation of outcomes. At the same time, the experimental design, research process, and research results of this study will not be disclosed to patients.

Intervention: Control interventions included no treatment, placebo, or routine treatment. The drugs, dosage, frequency, and duration of routine treatment will not be limited.If available, the following comparisons will be considered:(a) Comparison of Danshen decoction alone with no treatment.(b) Use Danshen decoction and placebo alone.(c) Comparison between Danshen decoction alone and routine treatment.(d) Comparison between Danshen decoction combined with CT and CT.(e) Comparison between Danshen decoction combined with CT and placebo plus CT.Not applicable.

Comparator: Not applicable.

Study designs to be included: This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) 2020This study used the preferred reporting item of the guidelines for systematic reviews and meta-analyses (PRISMA) and all research procedures were completed in accordance with PRISMA requirements. Parallel group RCTs will be included. There are no restrictions on the language, publication date, or status of the study.

Eligibility criteria: Relevant documents will be selected according to the following inclusion and exclusion criteria.Inclusion criteria:(a) Clinical studies related to Danshen decoction.(b) It must be related to various CVDs.(c) The patients either have first diagnosis of HF or the clinical manifestations of HF.(d) It must include but not be limited to CER (clinical effective rate) and any of the following indicators: cardiac color Doppler ultrasound, BNP, etc. (e) HF classification or quantitative indicators of HF must be included. Exclusion criteria:(a) The first diagnosis has nothing to do with CVDs. (b) It is not a clinical control experiment or the control group of the experimental group is not clear. (c) The experimental data is not clearly stated or the results are wrong.

Information sources: Four databases, PubMed (https://pubmed.ncbi.nlm.nih.gov/), CNKI (https://www.cnki.net/), VIP (http://www.cqvip.com/) and Wanfang (https://www.wanfangdata.com.cn/) were used for retrieval. The following keywords were used for individual or joint searches: randomized controlled trial, clinical controlled experiment, clinical observation, Danshen decoction, cardiovascular System, coronary heart disease, heart failure, ischemia-reperfusion injury, angina pectoris, heart valve disease, hypertension, pericardial disease, endocarditis, cardiac arrest and sudden cardiac death. According to the above search method, RCTs related to the treatment of HF with Danshen decoction were manually screened and included in this study.

Main outcome(s): CER is defined as the main result of this meta-analysis. The objective evaluation of the effectiveness of a treatment for the disease after treatment includes five grades: clinical cure, significant improvement, mild/moderate improvement, ineffectiveness, and deterioration. It can be evaluated by different types of clinical symptom scales. The nimodipine method is usually used to calculate CER. CER = (basic cure + significant improvement + improvement) number of cases / total number of cases × 100%, CER is the simplest, most intuitive, and most comprehensive evaluation index to measure a treatment method. We will judge whether Danshen decoction has a good curative effect according to the actual situation of CER in the control group and the experimental group.

Additional outcome(s): CF, BNP, etc were identified as secondary outcomes. CF includes but is not limited to LVEF, LVEDD, LVESD etc. The improvement of CF is a significant sign that all CVDs are controlled and the treatment have good curative effect, and it is also an important turning point for the recovery of HF. Other inflammatory factor indicators that have a therapeutic effect on HF, such as BNP, NT-proBNP, hs-CRP, etc will be a better choice if they can be included in the secondary indicators. According to the detailed reading and screening of the included clinical research literature, no adverse reactions related to the treatment of Danshen decoction were found.

Data management: Two investigators (Mengnan Liu and Ziyi Li) will independently extract the following information: (a) General information (title, first author, year of publication). (b) Experimental design characteristics (experimental design scheme, experimental grouping, randomization principle, blind method, sample size). If possible, we will contact the original author to request to check the data. Only reasonable and correct data can be used in the primary analysis. When the data are correct, in the case of extreme worst and best cases, sensitivity analysis will be used to evaluate the impact of

abnormal data on the final results. (c) Patient characteristics (age, nationality, first diagnosis, basic diseases, complications). (d) Clinical observation characteristics (control group intervention, experimental group intervention, drug name, drug dose, frequency of use, treatment course). (e) Outcomes (primary and secondary outcome indicators, outcome indicator units, outcome evaluation methods, blind outcome evaluation methods, adverse reactions). If necessary, we will contact the authors of the included studies to provide further details or clarifications.

Quality assessment / Risk of bias analysis: Jadad scale tool will be used to check the methodological quality of each reference included in the trial by two investigators (Mengnan Liu and Ziyi Li).[31] Four aspects were included: random sequence generation, randomized hiding, blind method, and withdrawal. Three levels will be used to evaluate the quality of the method: "high compliance" (2 points), general compliance (1 point), and "non-compliance" (0 points). If necessary, differences will be discussed with other researchers to reach consistent conclusions. For each included study, the risk of bias in each field will be classified as low, high, or unclear. If a study describes it as an RCT but does not report the randomization method, we will try to contact the author to provide further details or clarification. If the information about the sequence generation process is insufficient to judge "low risk" or "high risk", the risk of bias will be rated as "unclear". The overall risk of bias in the study is estimated to be low only when all four aspects are rated as low risk of bias. When there are differences in the risk of bias between studies, we will try to analyze the influencing factors of the risk of bias. The deviation risk map and deviation risk summary will be generated by Revman v.5.4. Any differences will be resolved through discussion and analysis with the third investigator.

Strategy of data synthesis: The Revman V.5.4 software will be used to measure and evaluate the treatment effect. The dichotomy data are expressed as risk ratio (RR), risk difference (RD), or odds ratio (OR). We express the continuous result data as mean difference (MD), with a confidence interval of 95%. A Chi-square test will be performed for heterogeneity. When I2 < 50%, there is no substantial heterogeneity between studies, and a random effect model will be used for meta-analysis. When studies are homogeneous, the fixed-effect model will be used to estimate RR (OR, RD), WMD (or SMD), and 95% confidence interval. Statistical heterogeneity across the studies included will be tested using Chi-square test. When the P-value of chi-square is less than 0.05, the heterogeneity will be considered statistically significant. When I2 > 50%, exploratory sensitivity or subgroup analysis will be carried out to determine the possible cause. When an indicator has more than one clinical study and has comparable primary and secondary indicators, we will conduct a meta-analysis of this indicator. If there is no heterogeneity, a fixed-effect model will be established to estimate the overall intervention effect. If there is heterogeneity in various clinical studies in the indicators, the random effect model will be used to analyze the results. When multiple intervention groups are used in the study, we will group them according to the characteristics of each intervention group and conduct a subgroup analysis. All statistical analyses will be performed by Revman V.5.4 software. Statistical significance was defined as P<0.05. If the meta-analysis is not feasible, we will provide a narrative description of the results.

Subgroup analysis: If possible, subgroup analysis will be performed based on the following variables: (a) The first diagnosis of the patient. (b) Non-acute and acute diseases of patients. A Chi-square test will be carried out for the difference in intervention effect in each subgroup. For example, P<0.05 indicates statistical significance.

Sensitivity analysis: If necessary, the sensitivity analysis will be used to assess the effect of each study on the random effects model. The sensitivity of the general combined effect of all outcome indicators will be analyzed by the exclusion method. In short, each study will be excluded and the rest will be re-analyzed to determine the stability of the results, which will be considered stable if the combined effects shown have not changed qualitatively.

Language restriction: Not limited.

Country(ies) involved: The Affiliated TCM Hospital of Southwest Medical University, China.

Other relevant information: None.

Keywords: Danshen decoction; heart failure; meta-analysis; clinical research; traditional Chinese medicine.

Contributions of each author:

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