INPLASY PROTOCOL

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The authors declare that they have no competing interests.

Chinese herbal medicine injections (CHMIs) for chronic pulmonary heart disease: protocol for a Bayesian network meta-analysis

Lei, YP[1]; Wang, ML[2]; Sun, GQ[3]; Liu, Y[4]; Yang, YP[5]; Hao, D[6].

Review question / Objective: **Which Chinese herbal medicine injection (CHMI) is more effective for the treatment of patients with chronic pulmonary heart disease (CPHD)?**
Condition being studied: **Chinese herbal medicine injection, chronic pulmonary heart disease, efficacy and safety.**
Information sources: **Relevant RCTs, quasi-RCTs and high-quality prospective cohort studies will be systematically searched from PubMed, Google Scholar, Excerpt Medica Database, Medline, Cochrane Library, Web of Science, China Scientific Journal Database, China National Knowledge Infrastructure, Chinese Biomedical Literature Database and Wanfang Database from their inception to December 2020. Language is limited with English and Chinese.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 December 2020 and was last updated on 01 December 2020 (registration number INPLASY2020120004).

INTRODUCTION

Review question / Objective: **Which Chinese herbal medicine injection (CHMI) is more effective for the treatment of patients with chronic pulmonary heart disease (CPHD)?**

Rationale: **Chinese herbal medicine injections (CHMIs) are frequently used for various refractory diseases including chronic pulmonary heart disease (CPHD). However, due to the diversity of CHMIs treatments, its relative effectiveness and safety remain unclear. In our study, Bayesian network meta-analysis will be**

used to identify differences in efficacy and safety between diverse CHMI for CPHD.

Condition being studied: Chinese herbal medicine injection, chronic pulmonary heart disease, efficacy and safety.

METHODS

Search strategy: To perform a comprehensive and focused search, experienced systematic review investigators will be invited to develop a search strategy. The plan searched terms are as follows: "pulmonary heart disease" or "chronic pulmonary heart disease" or "cor pulmonale" or "chronic cor pulmonale" or "fei yuan xing xin zang bing" or "fei xin bing" and "Chinese herbal medicine" or "Chinese herbal medicine preparation" or "Chinese herbal medicine injection" or "Chinese herbal injection" or "traditional Chinese medicine" or "traditional Chinese drug" or "Chinese herbal preparation" or "traditional Chinese preparation" or Chinese patent medicine" or "zhongcaoyao" or "CHMIs" or "TCM" et al. The preliminary retrieval strategy for PubMed is provided in Table 1, which will be adjusted in accordance with specific databases.

Participant or population: Patients diagnosed with CPHD will be included in this study. No restrictions regarding age, gender, racial, region, education and economic status.

Intervention: In the experimental group, CPHD patients must be treated with CHMI alone or in combination with other pharmacological interventions. One or more outcome measures, including the therapeutic effect, or hemorheology or blood gas indexes, or adverse events must be included in each study. There will be no restrictions with respect to dosage, duration, frequency, or follow-up time of treatment.

Comparator: There will be no restrictions with respect to the type of comparator. The comparators are likely to include placebo, western medical therapies, supportive care, and other therapeutic methods.

Study designs to be included: All available comparative clinical trials that investigated the efficacy and safety of CHMIs for patients diagnosed with CPHD will be included in this systematic review.

Eligibility criteria: This study will include randomized controlled trials (RCTs) and quasi-RCTs or prospective controlled clinical trials that investigated the efficacy and safety of CHMIs for patients diagnosed with CPHD. Duplicated studies, papers without sufficient available data, non-comparative clinical trials, case reports and series, meta-analysis, literature reviews, meeting abstracts, and other unrelated studies will be excluded from analysis.

Information sources: Relevant RCTs, quasi-RCTs and high-quality prospective cohort studies will be systematically searched from PubMed, Google Scholar, Excerpt Medica Database, Medline, Cochrane Library, Web of Science, China Scientific Journal Database, China National Knowledge Infrastructure, Chinese Biomedical Literature Database and Wanfang Database from their inception to December 2020. Language is limited with English and Chinese.

Main outcome(s): The primary outcomes will include: i) Markedly effective rate (MER) and the total effective rate (TER); ii) Quality of life (QoL) obtained from the corresponding scale; iii) Adverse events.

Additional outcome(s): Secondary outcomes will include: i) New York Heart Association (NYHA) classification; ii) Left ventricular ejection fraction (LVEF); iii) Mean pulmonary artery pressure (mPAP); iv) B-type natriuretic peptide (BNP); v) Hemorrheology assessment, the hemorrheology index includes whole blood viscosity (WBV), plasma viscosity (PV), hematocrit, erythrocyte aggregation index (EAI) and content of fibrinogen (FBG); vi) Blood gas analysis, the blood gas indicator contains partial pressure of oxygen (PaO2), partial pressure of carbon dioxide (PaCO2),

saturation of hemoglobin with oxygen (SaO2) and pH value.

Data management: After screening the literature, the two authors (Yuping Lei and Meili Wang) will independently extract the information contained in the eligible literature to form a document feature table. The extracted data are as follows: i) Study characteristics and methodology: country of study, the first author's name, year of publication, randomization, sample size, periods of data collection, follow-up duration, outcome measures, inclusion and exclusion criteria, et al. ii) Participant characteristics: age, gender, NYHA heart function classification, diagnostic criteria, et al. iii) Interventions: therapeutic means, dose, administration route, course of treatment, and duration of treatment, et al. iv) Outcome and other data: MER, TER, QoL, NYHA classification, LVEF, mPAP, BNP, hemorrheology indexes (WBV, PV, hematocrit, EAI and FBG), blood gas indicators (PaO2, PaCO2, SaO2 and pH value), and adverse effects, et al.

Quality assessment / Risk of bias analysis: Two authors (Yuping Lei and Meili Wang) will independently assess risk of bias for each selected study in accordance with the Cochrane "Risk of bias" assessment tool which includes seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each item will be evaluated at three levels: low risk, unclear, and high risk. Effective Practice and Organisation of Care (EPOC) guidelines will be used to assess the risks of non-RCTs. Any disagreements will be resolved via discussion with a third researcher (Guiqiang Sun).

Strategy of data synthesis: We will conduct a conventional pairwise meta-analysis of the direct comparison results obtained from the literature. Continuous data will be presented as mean difference (MD) or standardized mean difference (SMD) with their confidence intervals (CIs). Dichotomous data will be recorded as odds ratio with 95% CIs. Stata 14.2 (StataCorp., College Station, TX, USA) and WinBUGS1.4.3 (MRC Biostatistics Unit, Cambridge, UK) through the GeMTC package will be used to perform network meta-analysis to synthesize direct and indirect evidence. The network meta-analysis will be undertaken primarily in WinBUGS using the Markov chain Monte Carlo method. Convergence of the simulations will be evaluated with potential scale reduction factor and Gelman-Rubin-Brooks plots. The selection of the final model will depend on the deviance information criterion value. Generally, a model with a smaller deviance information criterion value is better. we will calculate the ranking probabilities for all treatments of being at each possible rank for each intervention, using the surface under the cumulative ranking curve (SUCRA), where the SUCRA values can range from zero to one. The evidence relationship of included studies will be figured out by Stata software. If there is a "closed loop," the node splitting method will be used to evaluate the inconsistency of each loop. The heterogeneity of each pairwise comparison will be tested by $\chi 2$ statistics and the I2 statistics. When the P value was > 0.1, and I2 was $< 50\%$, it suggested that there was no statistical heterogeneity and the Mantel-Haenszel fixed-effects model was used for meta-analysis. Otherwise, a random-effects mode will be used to calculate the outcomes.

Subgroup analysis: If the $\chi 2$ and I2 test detect obvious heterogeneity between studies, we will explore sources of heterogeneity with respect to age, region, treatment duration and types of CHMI by subgroup analysis and meta-regression.

Sensibility analysis: Sensitivity analysis will be conducted to assess the reliability and robustness of the aggregation results via eliminating trials with low-quality. A summary table will report the results of the sensitivity analyses.

Language: Language is limited with English and Chinese.

Country(ies) involved: China.

Other relevant information: i) Publication bias. Funnel plot will be performed to analyze the existence of publication bias if the included studies are sufficient (n ≥ 10). If the funnel chart has poor symmetry, it indicates publication bias. ii) Assess the quality of evidence. The evidence grade will be assessed by using the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE, https://gradepro.org/). The quality of all evidence will be assessed at four levels: high, moderate, low, and very low.

Keywords: chronic pulmonary heart disease; Bayesian network meta-analysis; Chinese herbal medicine injections; efficacy.

Dissemination plans: The results of this study will be published in a peer-reviewed journal, and provide reliable evidence for different CHMIs on CPHD.

Contributions of each author:
Author 1 - Yuping Lei - Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing-original draft.
Author 2 - Meili Wang - Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft.
Author 3 - Guiqiang Sun - Data curation, Investigation, Visualization, Writing-original draft.
Author 4 - Yong Liu - Formal analysis, Investigation, Validation, Writing-original draft.
Author 5 - Yapei Yang - Funding acquisition, Methodology, Validation, Writing-review & editing.
Author 6 - Dong Hao - Conceptualization, Project administration, Resources, Software, Supervision, Validation, Writing-review & editing.