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Protocol

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Abstract

Background

Angina pectoris (AP) is the primary symptom of coronary heart disease. Evidence has shown Chinese herbal medicines can bring benefits to patients suffering from AP. There are many kinds of herbal medicines. However, the difference between them has not been systematically analysed. It is uncertain which one is better. For comparison and ranking, a systematic review and network meta-analysis is needed.

Methods

We will search for the following 6 electronic databases: China Biological Medicine DataBase (CBM), China National Knowledge Infrastructure (CNKI), WanFang Database, PubMed, Embase and the Cochrane Library, from inception to May 2021. Randomized controlled trials, which aim to assess the efficacy and safety of 5 kinds of Chinese herbal medicine for AP will be included. The outcomes include reduction of AP, improvement of the electrocardiogram and adverse events. The study screening and data extraction will be presented by 2 researchers. The risk of bias will be assessed according to the Cochrane handbook. A Bayesian network meta-analysis will be performed to compare the efficacy of 5 Chinese herbal medicines. Surface under the cumulative rank curve value will be calculated to rank the efficacy of each herbal medicine.

Discussion

Our protocol will be expected that the results of this study will provide evidence for Clinical Practice Guideline, clinical decisions, and development of proprietary Chinese medicines.

Systematic review registration

PROSPERO registration number: CRD42019146185.

Introduction

Angina pectoris (AP) is a clinical syndrome with chest pain which is caused by transient myocardial ischemia [1]. AP is the primary symptom of coronary heart disease (CHD) [2]. It is generally found in patients with major branch lumen diameter stenosis of the coronary artery. When under physical or mental stress, coronary blood flow can not match the need for myocardial metabolism, people may suffer from AP caused by myocardial ischemia [3]. It can be relieved by having a rest or taking nitroglycerin [4].

AP often occurs in middle-aged or elderly people, affecting men more than women, and mostly found in mental workers [5]. The incidence of CHD in a group of over 65 years old both in Britain and America is more than 10% [6,7]. The incidence of CHD in China has significantly elevated over the last 10 years. Until
2018, there were 11 million patients suffering from CHD. Ap has been becoming the major public health issue in the world [8].

At present, western medicines (WMs) for AP mainly include organic nitrates, beta-blockers and calcium channel blockers [9]. The benefits of WM are definite therapeutic mechanism and high pertinency. It can improve the symptoms of AP and quality of life. However, side effects, (such as abdominal pain, diarrhea, nausea and vomiting et al.),[10] drug resistance, and other adverse reactions cannot be ignored[11]. Chinese herbal medicine (CHM) has the superiority of multiple targets and mild effects, which can be regarded as an excellent complementary therapy [12]. Besides, according to several researches, using additional CHM based on WM can effectively reduce the dose of WM, taking nitroglycerin as an example [13–15]. And can improve the response rate [16].

According to the traditional Chinese medicine (TCM) theory, AP belongs to the TCM domain of “chest stuffiness” and “heartache”. Han Dynasty physician Zhang Zhong-jing thought the reason for “chest stuffiness” and “heartache” is “insufficiency of heart Yang”, “phlegm turbidity”, “blood stasis” or “cold coagulation” and so on, and he set up the theory of “weak pulse of YANG and stringy pulse of YIN” [17]. Thus we selected five Warming Yang CHMs for “chest stuffiness” and “heartache” from the Catalogue of famous ancient classics (first batch). Several systematic reviews and clinical trials have been conducted to examine the comparative efficacy and safety of the five CHMs based on WM [18–22]. However, the evidence of ranking the efficacy of each CHM is still insufficient. The five CHMs including Gualou xiebai banxia decoction (GLXBBXD) (contains: Trichosanthes kirilowii Maxim, Allium macrostemon, Pinellia ternate, white spirits), Zhishi xiebai guizhi decoction (ZSXBGZD) (contains: Immature Bitter Orange, Magnolia officinalis, Allium macrostemon, Cassia Twig, Trichosanthes kirilowii Maxim), Huangqi guizhi wuwu decoction (HQGZWWD) (contains: Astragalus, Radix Paeoniae Alba, Cassia Twig, Ginger, Jujube), Linggui zhugan decoction (LGZGD) (contains: Poria cocos, cassia twig, atractylodes, licorice roo), Danggui sini decoction (DGSN) (contains: Angelica, cassia twig, peony, asarum, licorice, tongcao, jujube).

We will try to compare the efficacy and safety of these five different CHMs by network meta-analysis to provide evidence for clinical guidelines, clinical decision making, and Chinese patent medicine development.

**Objective**

Aiming to conduct a protocol for Bayesian network meta-analysis of randomized controlled trials aiming to make sure which of the five Chinese herbal medicines works better.

**Methods And Analysis**

This systematic review and NMA protocol has been registered on PROSPERO (CRD42019146185). This protocol is written according to the standard of Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols[23] (PRISMA-P). See S1 Table for the checklist. Network Meta-analysis will be
designed according to the standard of Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses (PRISMA-NMA) [24].

**Ethics and dissemination**

No ethics clearance is required as this is a literature review. The findings from this study will tell us which of the five traditional Chinese herbal medicines works better, and evidence-based recommendations to improve treatment will be offered. The results will be published in a peer-reviewed journal.

**Criteria for included studies**

**Language.** Published in English or Chinese

**Type of study.** Randomized controlled trials (RCTs). Narrative reviews, meeting abstracts, letters, and any papers lacking primary data or description of methods will not be included in this study.

**Participants.** patients diagnosed with AP according to relevant diagnostic criteria. (2013 ESC guidelines on the management of stable coronary artery disease: The task force on the management of stable coronary artery disease of the European Society of Cardiology[25]. 2012 ACCF/ AHA/ ACP/ AATS/ PCNA/ SCAI/ STS guideline for the diagnosis and management of patients with stable ischemic heart disease[26]. Expert consensus on the diagnosis and treatment of coronary heart disease stable AP [27].) Patients diagnosed as chest pain caused by acute myocardial infarction of coronary heart disease and other heart diseases, severe neurosis, climacteric syndrome, hyperthyroidism, cervical spondylosis, gallbladder heart disease, gastric and esophageal reflux will be excluded. Patients with severe hypertension, severe cardiopulmonary insufficiency, severe arrhythmia, liver, kidney, hematopoietic system, and other serious primary diseases and mental disorders will not be included in our study. No limitations to age, gender, nationality, birthplace and ethnicity. Intervention and Comparators: Chinese herbal medicine and western medicine will be involved. Chinese herbal medicines include five kinds of herbal decoction: GLXBBXD, ZSXBGZD, HQGZWWD, LGZGD, DGSND. The comparisons will be set as: (1) CMD or CMD + WM compared with WM. (2) CMD or CMD + WM compared with placebo. (3) CMD or CMD + WM compared with another kind of CHM, except five CMD in this study, alone or with WM, the WM used in both groups should be comparable in type, dose, and treatment duration.

**Outcome**

**Reduction of AP:** Reduction of AP will be calculated by formula: (number of recovery patients/ total number of patients) *100%, recovery means the time of AP decreased by more than 50% or the dosage of nitroglycerine decreased by more than 50%[28,29]. **Improvement of Electrocardiogram:** Improvement of Electrocardiogram (ECG) will be calculated by formula: (number of recovery patients/ total number of patient) *100%, recovery means S-T segment returned above 0.05mV or inverted T waves recover more
than 25%, or flat T waves turn to inverted, or ECG back to normal[28,29]. **Adverse event:** (1) Allergy, digestive tract dysfunction. (2) Blood, urine, and stool tests abnormalities. (3) dysfunction of heart, liver, and kidney.

**Criteria for excluded studies**

1. The RCTs have incorrect or incomplete data.
2. The intervention contains other Chinese traditional therapies (Acupuncture, moxibustion, massage, scraping, electroacupuncture, acupoint injection, etc.)
3. Repeated publications, only the first will be included.

**Information source and search strategy**

**Information source.** Sinomed, CNKI, WanFang Database, PubMed, Embase, and the Cochrane Library will be searched for RCTs about 5 CHMs in the treatment of AP, from the inception to May 2021. And we will date to the references of the included literature aiming to get the related literature.

**Search strategy.** Main search terms include: Coronary Disease, Angina Pectoris, Gualou xiebai banxia decoction, Zhishi xiebai guizhi decoction, Huangqi guizhi wuwu decoction, Linggui zhugan decoction, Danggui sini decoction, Randomized Controlled Trial, Systematic Review, Meta-Analysis. Taking Pubmed as an example, we use the combination of MeSH terms and free words for search. The search strategy of Pubmed is shown in Table 1.
Table 1.
Search Terms

<table>
<thead>
<tr>
<th>Number</th>
<th>Search Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>“Coronary Disease”[MeSH Terms] OR (“Coronary Disease*”[Title/Abstract] OR “Coronary Heart Disease*”[Title/Abstract])</td>
</tr>
<tr>
<td>#2</td>
<td>“Angina Pectoris”[MeSH Terms] OR (“Stenocardia*”[Title/Abstract] OR “Angor Pectoris”[Title/Abstract] OR “Angina Pectoris”[Title/Abstract])</td>
</tr>
<tr>
<td>#3</td>
<td>#1 OR #2</td>
</tr>
<tr>
<td>#5</td>
<td>“Huangqi Guizhi Wuwu”[Title/Abstract] OR “Huangqiguizhiwuwu” [Title/Abstract] OR “Huangqiguizhiwuwutang”[Title/Abstract] OR “Astragalus and Cinnamon Twig Decoction with Five Ingredients”[Title/Abstract]</td>
</tr>
<tr>
<td>#6</td>
<td>“Gualou Xiebai Banxia”[Title/Abstract] OR “Gualouxiebaibanxia” [Title/Abstract] OR “Trichosanthes Fruit Fistular Onion Stalk and Pinellia Decoction”[Title/Abstract]</td>
</tr>
<tr>
<td>#7</td>
<td>“Lingguizhugan”[Title/Abstract] OR “Lingguizhugantang”[Title/Abstract] OR “Linggui Zhugan”[Title/Abstract] OR “Poria Cinnamon Twig Ovate Atractylodes and Licorice Decoction”[Title/Abstract]</td>
</tr>
<tr>
<td>#8</td>
<td>“Zhishixiebaiguizhi”[Title/Abstract] OR “Zhishi xiebai guizhi”[Title/Abstract] OR “Zhishixiebaiguizhitang”[Title/Abstract]</td>
</tr>
<tr>
<td>#9</td>
<td>#4 OR #5 OR #6 OR #7 OR #8</td>
</tr>
<tr>
<td>#10</td>
<td>“Randomized Controlled Trial”[Publication Type] OR “Randomized Controlled Trial”[Title/Abstract]</td>
</tr>
<tr>
<td>#11</td>
<td>“Systematic Review”[Publication Type]] OR “Systematic Review”[Title/ Abstract]</td>
</tr>
<tr>
<td>#12</td>
<td>“Meta-Analysis”[Publication Type]] OR “Meta-Analysis”[Title/Abstract]</td>
</tr>
<tr>
<td>#13</td>
<td>#10 OR #11 OR #12</td>
</tr>
<tr>
<td>#14</td>
<td>#3 AND #9 AND #13</td>
</tr>
</tbody>
</table>

Study screening and Data extraction

Study screening. The procedures of the study screening will be as follows: (1) Importing the included literature into the document management software NoteExpress V3.2.0. duplication will be removed by the combination of manual and software. (2) Reading the title and the abstract of the literature, eliminating the study that can't meet the inclusion and exclusion criteria. (3) If it can not be determined by the title and the abstract, the full text should be downloaded to make the judge. This process will be made
by two researchers independently and then cross-check, and the discrepancies will be solved by 
consulting a third researcher. (see Figure 1)

**Data extraction.** We will design a standardized data extraction sheet and use Epidata software 3.1 for 
data extraction. The extract content will be included with the following: (1) Basic information of literature: 
title, author, published magazine and publishing year. (2) Basic information of the research subjects, 
grouping situation, age and gender of participants, duration of disease, diagnosis, inclusive and exclusive 
criteria, and the information of random and blind methods. (3) Intervention measures, course of 
treatment, and follow-up. (4) Outcomes include effectiveness indicators and safety indicators. If the 
complete information isn’t obtained, we will attempt to contact the author of the literature by email. If the 
complete information still can not be got by that way, the literature will be eliminated. This process also 
will be made by two researchers independently and then made cross-check, and the discrepancies will be 
solved by consulting a third researcher.

**Risk of bias assessment**

The Risk of Bias 2 (RoB 2) tool will be used to assess the risk of bias of included RCTs [30], it includes 
five domains: Randomisation process, Deviations from intended interventions, Missing outcome data, 
measurement of the outcome, selection of the reported result. And overall bias. The assessment result 
will be presented with “low risk”, “high risk” and “unclear risk”. The bias risk assessment will be made by 
two researchers independently and then made cross-check, and the discrepancies will be solved by 
consulting a third researcher. The result of the assessment will be shown in “risk of bias graph” drawn by 
Review Manager 5.3.

**Heterogeneity and transitivity assessment**

We will draw a comparison-adjusted funnel plot for examination of heterogeneity, selective reporting, and 
publication and funding biases. Egger tests will be used to test the asymmetry of the funnel plot. The 
asymmetrical appearance of the plot indicates the meaning that publication bias will be suspected. 
Transitivity assumptions across different treatment methods will be assessed by possible confounding 
factors in pairwise comparisons [31]. And boxplots or percentages also will be used in the assumption of 
transitivity [32-34]. Only when these factors are appropriated will data synthesis and analysis be 
performed.

**GRADE assessment**

According to the GRADE Working Group approach for rating the quality of treatment effect estimates 
from NMA, the evidence will be interpreted. The approach is based on four steps to assess the quality of
treatment effect estimates from direct, indirect, and NMA (combined direct + indirect) evidence, as well as quality ratings for direct and indirect comparisons [35].

**Statistical analysis**

**Pairwise Meta-analysis.** The Pairwise Meta-analysis of direct comparative evidence will be performed by a random-effects model with Stata V.13 software. Dichotomous data will be presented as odds ratio (OR), continuous data will be calculated as the mean difference (MD), both of them will correspond with 95% confidence intervals (CIs). The statistical heterogeneity of each pairwise comparison will be assessed by the $I^2$ test and $\chi^2$ test.

**Network diagram.** The Network diagram will be drawn by Stata V.13 software. It will show the relationship of direct comparison between different interventions by nodes and line. The node represents a kind of intervention, the size of the node means the sample size of its respective intervention. The line represents the direct comparison, the width of the line means the number of study.

**Network Meta-analysis.** The Network Meta-analysis based on random-effects model under a Bayesian framework and using Markov Chain Monte Carlo algorithm will be performed by WinBUGs V. 1.4.3 software [36]. Dichotomous data will be presented as odds ratio (OR), continuous data will be calculated as the mean difference (MD), both of them will correspond 95% credible intervals (CrI). Then we will accumulate the surface under the cumulative ranking curve (SUCRA) value to rank the effect of each intervention [37]. The range of SUCRA value is from 0 to 1. If the value of the SUCRA is higher, the effect will be better.

**Subgroup analysis and sensitivity analysis.** If we find considerable heterogeneity, subgroup analysis will be performed to investigate the possible source of heterogeneity. It will be performed in the following aspects: age, type of AP (like stable AP and unstable AP), and treatment duration. To explore the stability of the conclusion, we will perform the sensitivity analysis to compare studies with a low risk of bias to those with high or unclear risk of bias. If low-quality studies bring significant heterogeneity, they will be excluded, evaluate the sensitivity again to ensure the homogeneity of studies. and the quality of each study depends on the result of the risk of bias assessment.

**Assessment of inconsistency.** The most direct and best way to evaluate consistency is to compare the results of direct and indirect comparisons. The Hypothesis test is to obtain the difference between direct comparison and indirect comparison results and then verify whether it is statistically significant according to the statistical Z Test. Thus we will perform the assessment of inconsistency by Z-test with Stata V.13 software [38].

**Publication bias.** The publication bias of the included studies will be appraised by comparison-adjusted funnel plot which is drawn by Stata V.13 software. Studies with small sample size and low accuracy will
distribute at the bottom symmetrically, while those with large sample size and high accuracy will distribute at the top and gather to the location with the effect size as its center.

**Discussion**

Our protocol will be the first Bayesian network meta-analysis of randomized controlled trials about Chinese herbal medicines for AP: It will be expected that the results of this study will provide evidence for Clinical Practice Guideline, clinical decisions, and development of proprietary Chinese medicines.

**Abbreviations**

AP= angina pectoris

CHD= coronary heart disease

CHM= Chinese herbal medicine

WM= western medicine

GLXBBXD= Gualou xiebai banxia decoction

ZSXBGZD= Zhishi xiebai guizhi decoction

HQGZWWD= Huangqi guizhi wuwu decoction

LGZGD= Linggui zhugan decoction

DGSND= Danggui sini decoction

RCTs= Randomized controlled trials

ECG= Electrocardiogram.

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable
Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

NL, WP, and JZ* conceived the study and drafted the protocol. NL, WP wrote the first draft of the manuscript. FY, BP, XJ assisted in protocol design and revision. KW participated in the design of the search strategy. WZ participated in the design of data synthesis and analysis. All authors have read and approved the final manuscript.

Conceptualization: Nan Li, Wentai Pang.

Data curation: Nan Li, Wentai Pang.

Formal analysis: Nan Li, Wentai Pang, Junhua Zhang.

Methodology: Nan Li, Wentai Pang, Fengwen Yang , Bo Pang and Xinyao Jin.

Project administration: Junhua Zhang.


Supervision: Junhua Zhang.

Writing – original draft: Nan Li, Wentai Pang.

Writing – review & editing: Junhua Zhang and Fengwen Yang.

Acknowledgements

Not applicable

References


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Figures

Figure 1
Flow chart of study selection
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2020checklist.docx