

The effects of the wenyang huoxue method on coronary heart disease heart failure

A protocol for systematic review

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Abstract

Background: Coronary heart disease (CHD) has become the primary cause of heart failure (HF). Wenyang Huoxue method can significantly improve cardiac function in patients with CHD complicated with HF, but it has not been systematically evaluated for efficacy and safety.

Methods: We will search China National Knowledge Infrastructure Database, Wanfang database, China Biomedical Literature Database, China Science Journal Database PubMed, Excerpt Medica Database, and Cochrane library. Clinical trial registrations, potential grey literature, related conference abstracts, and reference lists of identified studies will also be retrieved. The electronic database will be searched for literatures published from January 2000 to September 2019. Based on the heterogeneity test, data integration is performed using a fixed effect model or a random effects model. Changes in total effective rate in cardiac function will be assessed as primary outcome. 6-minute walk test, left ventricular ejection fraction, and plasma brain natriuretic peptide will be assessed as secondary outcomes. RevMan 5.3.5 will be used for meta-analysis.

Results: This study will provide a high-quality comprehensive evaluation of the efficacy and safety of Wenyang Huoxue method for treating patients with CHD complicated with HF.

Conclusions: This systematic review will determine whether Wenyang Huoxue method provides evidence for effective intervention in patients with CHD complicated with HF.

Ethics and dissemination: This systematic review and meta-analysis of randomized controlled trials does not require ethical recognition, and the results of this paper will be published in an open access, internationally influential academic journal.

Trial registration number: CRD42016025957

Abbreviations: CHD = coronary heart disease, HF = heart failure, TCM = traditional Chinese medicine.

Keywords: Coronary heart disease, heart failure, protocol, systematic review, wenyang huoxue method

1. Introduction

Heart failure (HF) is the main presentation of the terminal stage of different cardiovascular diseases, defined as the inability of the

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WH and YZ have contributed equally to this work.

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heart to supply the peripheral tissues with the required amount of blood and oxygen to meet their metabolic demands.^[1] The growing burden of HF has been 1 of the most serious health problems facing society today, affecting an estimated 50 million people worldwide.^[2] While advances have been made in the treatment of HF, patients still have high morbidity.^[3] As we know, the most common cause of HF is ischemic heart disease due to impaired myocardial perfusion, mostly caused by an acute or chronic myocardial ischemia.^[4] Recent research also suggests that coronary events might be an important driver of death in HF with preserved ejection fraction.^[5] Coronary heart disease (CHD) complicated with HF has been a global problem. In China, the mortality rate of hospitalized HF patients is about 5.3%, and CHD has become 1 of the major complications of HF, accounting for 49.4%.^[6] The large number of patients with CHD and HF has brought great economic burden both to the country and its people.

The treatment of CHD complicated with HF has been constantly standardized. The application of medication such as angiotensin-converting enzyme inhibitors, β -blockers, aldosterone receptor antagonists and angiotensin-receptor neprilysin inhibitors have improved the clinical outcome of HF.^[7] Recently study shows that sodium glucose co-transporter 2 inhibitors reduce the risk of HF or death from cardiovascular disease, which

was hailed a major victory in the fight against HF.^[8,9] However, the risks associated with sodium glucose co-transporter 2 inhibitors, such as amputation, limb ischemia and diabetic ketoacidosis, need to be taken seriously.^[10,11] On the other hand, although the CANTOS study has brought new hope for CHD, the risk of infection, high treatment costs and other aspects are not satisfactory, which will limit its clinical application.^[12,13] Patients with CHD and HF still face high mortality rate, low quality of life, and multiple side effects.^[3,14]

Under the circumstance, traditional Chinese medicine (TCM), plays an irreplaceable role in the treatment of CHD complicated with HF. TCM treatment is widely used in the world for its good efficacy, safety, low cost and sustainable improvement of patients' symptoms and prognosis. TCM believes that Yang deficiency and blood stasis is the common pathogenesis of CHD and HF, while wenyang huoxue method can be used to treat CHD complicated with HF, benefits from its functions of activating blood circulation, accelerating the clearance of blood oxygen free radicals and anti-inflammation.^[15–18] Although previous systematic reviews had shown good effects of TCM for treating HF patients, the quality of the studies has become a common concern. And there is still a lack of high-quality evidence for treating CHD complicated with HF patients with Wenyang Huoxue method. This present study was designed to perform a comprehensive systematic review and evaluation of the efficacy and safety of Wenyang Huoxue treatment for CHD complicated with HF.

2. Methods and analysis

2.1. Design and registration of the review

The protocol of this review has been registered with the international Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42016025957) and has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.^[19]

2.2. Inclusion criteria

2.2.1. Type of study. Randomized controlled trials that using Wenyang Huoxue method combined with western medicine to treat CHD complicated with chronic HF patients, regardless of blinding, will be included in this study. Studies with a sample size smaller than 30 in the intervention group will be excluded.

2.2.2. Types of participants. Patients with a confirmed clinical diagnosis of CHD complicated with HF using New York cardiology society's classification criteria for heart function will be included. There are no limitation in age, sex, nation, ethnicity, and disease stage.

2.2.3. Types of interventions. The control group was treated with conventional treatments such as antiplatelet aggregation, statins, angiotensin-converting enzyme inhibitors, β -blockers, and aldosterone receptor antagonists. Patients in the treatment group were treated with the Wenyang Huoxue method and conventional treatments.

2.2.4. Types of outcomes. The primary outcome will be the total effective rate in cardiac function, total effective rate = (total effective number)/total number \times 100%. The secondary outcomes included the 6-minute walk test, left ventricular ejection fraction, and plasma brain natriuretic peptide.

2.3. Data sources and search methods

2.3.1. Electronic searches. To identify all relevant studies, we systematically searched China National Knowledge Infrastructure Database, Wanfang database, China Biomedical Literature Database, China Science Journal Database, PubMed, Excerpt Medica Database, and Cochrane library, which was concluded from Jan 2000 to Sep 2019. The following search terms were used individually or in combination: "coronary heart disease", "heart failure", "Wenyang Huoxue", and "randomized controlled trial". The search strategy for Medline will be searched via PubMed and is shown in Table 1.

2.3.2. Searching other resources. A reference list of research and systematic reviews will be reviewed and retrieved for additional testing. Potential gray literature will be searched in OpenGrey.eu. We will search for relevant conference abstracts to find eligible trials. In addition, we will search the World Health Organization International Clinical Trial Registration Platform and the clinical trial website ClinicalTrials.gov for all new comments related to this topic.

2.4. Data collection and management

Based on the research criteria and search strategies identified above, 2 reviewers will review the topics and abstracts independently and use standardized data sheets to extract data including basic information such as patients, interventions, and outcomes. If the reviewers encountered inconsistencies, they would be resolved in a consultation with a third reviewer. See the PRISMA flow chart for the research selection (Fig. 1).

2.5. Data extraction and analysis

The RevMan 5.3.5 software provided by the Cochrane Collaboration was used for data analysis. Dichotomous data

Table 1
Search strategy used in Pubmed.

Number	Search terms
1	Coronary heart disease.Mesh
2	Stable angina pectoris.ti,ab
3	Unstable angina pectoris.ti,ab
4	Acute myocardial infarction.ti,ab
5	Acute coronary syndrome.ti,ab
6	1 or 2 or 3 or 4 or 5
7	Heart failure.Mesh
8	Cardiac Failure.ti,ab
9	Cardiac insufficiency.ti,ab
10	7 or 8 or 9
11	Wenyang Huoxue.Mesh
12	Wenyang.all
13	Warming yang.all
14	Tonifying yang.all
15	Huoxue.all
16	Activating blood circulation.all
17	Promoting blood circulation.all
18	Invigorate circulation of blood.all
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	Randomized controlled trial.all
21	Controlled clinical trial.all
22	Randomized.all
23	Randomly.all
24	20 or 21 or 22 or 23
25	6 and 10 and 19 and 24

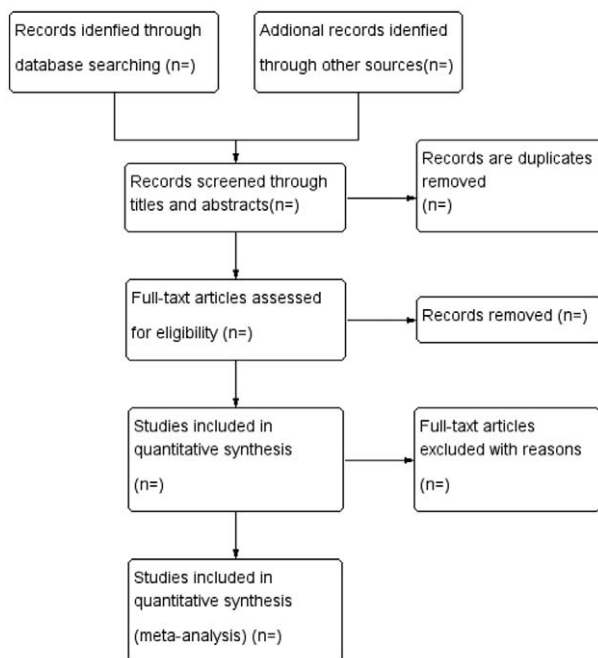


Figure 1. Flow diagram of the literature searching and study selection.

are expressed as relative risk, continuous outcomes are presented as weighted mean difference or standard mean difference, and the 95% confidence intervals were calculated for both. The meta-analysis was performed in the intervention and control groups.

2.6. Assessment of risk of bias in the included studies

To ensure that the selected literature was of high quality, we used the RevMan 5.3.5 to assess the studies systematically and comprehensively, according to the 7-parameter set. These were sequence generation, allocation concealment, blinding of participants, and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Each item will be rated as high risk bias, low risk bias, and uncertain bias. When there is any disagreement, it will be resolved through discussion or consultation with the third reviewer.

2.7. Assessment of heterogeneity

The statistical heterogeneity was considered significant if the I^2 index exceeded 50% or $P < .1$. In the absence of significant heterogeneity, we pooled the data using fixed ($I^2 < 50\%$) or random ($I^2 > 50\%$) effects models.

2.8. Assessment of reporting biases

When more than 10 studies are included, a funnel plot will be used to detect report bias.

2.9. Subgroup analysis and sensitivity analysis

We will select subgroup analysis and sensitivity analysis to detect sources of possible clinical or methodologic heterogeneity.

2.10. Grading the quality of evidence

The GRADE profiler software (Version 3.6, The GRADE Working Group) will be used to analyze the quality level of evidence.

3. Discussion

HF has been a global problem, which is associated with high mortality and is estimated to have cost about US\$100 billion in 2012.^[20,21] The main risk factors of HF is coronary artery disease (CAD).^[4] Although the incidence of acute myocardial infarction has decreased worldwide, the prevalence of ischaemic HF has increased.^[22] The treatment of CHD complicated with HF has important clinical significance to reduce the economic burden and improve the quality of life. However, we are unable to do much more than reduce congestion with diuretics in HF patients.^[23,24] Now TCM gives us a new option. Researchers have developed a large number of clinical studies in Wenyang Huoxue method of CHD complicated with HF patients. Nevertheless, no systematic review related to Wenyang Huoxue method for CHD complicated with HF has been published in English so far. In this paper, we present a protocol for a systematic review of Wenyang Huoxue method for CHD complicated with HF patients. We hope this review will facilitate clinicians when making decisions.

Author contributions

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References

- [1] Dharmarajan K, Rich MW. Epidemiology, pathophysiology, and prognosis of heart failure in older adults. *Heart Fail Clin* 2017; 13:417–26.
- [2] Braunwald E. The war against heart failure: the Lancet lecture. *Lancet* 2015;385:812–24.
- [3] O'Connor CM, deFilippi C. PARAGON-HF — Why we do randomized, controlled clinical trials. *N Engl J Med* 2019;381:1675–6.
- [4] Tanai E, Frantz S. Pathophysiology of heart failure. *Compr Physiol* 2015;6:187–214.
- [5] Cleland JGF, Lyon AR, McDonagh T, et al. The year in cardiology: heart failure: The year in cardiology 2019. *Eur Heart J* 2020;pii: ehz949. doi: 10.1093/eurheartj/ehz949. [Epub ahead of print].
- [6] Chen WW, Gao RL, Liu LS, et al. The summary of “ Report on cardiovascular diseases in China 2016”. *Chin Cir J* 2017;32:521–30.
- [7] Wang YW, Zhou R, Lu C, et al. Effects of the angiotensin-receptor neprilysin inhibitor on cardiac reverse remodeling: meta-analysis. *J Am Heart Assoc* 2019;8:e012272.
- [8] John JV, McMurray MD, Scott D, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; 381:1995–2008.
- [9] Bhatt DL, Verma S, Braunwald E. The DAPA-HF trial: a momentous victory in the war against heart failure. *Cell Metab* 2019;30:847–9.
- [10] Fralick M, Schneeweiss S, Paterno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. *N Engl J Med* 2017;376:2300–2.
- [11] Fitchett D. A safety update on sodium glucose co-transporter 2 inhibitors. *Diabetes Obes Metab* 2019;21:34–42.
- [12] Baylis RA, Gomez D, Mallat Z, et al. The CANTOS trial: One important step for clinical cardiology but a giant leap for vascular biology. *Arterioscler Thromb Vasc Biol* 2017;37:e174–7.

- [13] Harrington , Robert A. Targeting inflammation in coronary artery disease. *N Engl J Med* 2017;377:1197–8.
- [14] Chen J, Normand SL, Wang Y, et al. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries 1998–2008. *Jama-J Am Med Assoc* 2011;306:1669–78.
- [15] Li X, Zhang J, Huang J, et al. A multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the effects of qili qiangxin capsules in patients with chronic heart failure. *J Am Coll Cardiol* 2013;62:1065–72.
- [16] Jiang T, Wang WW, Mei Y, et al. Meta analysis of the efficacy of Qili Qiangxin capsule combined with western medicine to treat chronic heart failure. *J Clin Cardiol* 2015;31:868–74.
- [17] Tian Y, Gu JX. A meta-analysis of Qishenyiqi Drop Pill in treating heart failure with coronary heart disease. *J Emer TCM* 2016;25:1725–7. +1742.
- [18] Deng ZY, Wang MJ, Fan YH, et al. A systematic review of randomized controlled trials of the Wenyang Huoxue method in treating diabetic peripheral neuropathy. *Medicine* 2019;98:e17618.
- [19] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- [20] Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2095–128.
- [21] Cook C, Cole G, Asaria P, et al. The annual global economic burden of heart failure. *Int J Cardiol* 2014;171:368–76.
- [22] Moran AE, Forouzanfar MH, Roth GA, et al. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. *Circulation* 2014;129:1493–501.
- [23] McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;33:1787–847.
- [24] Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147–239.