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Evidence-Based Integrative Medicine

Oral Chinese Herbal Medicine for Heart Failure with Preserved Ejection Fraction: A Meta-Analysis*

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ABSTRACT **Objective**: To evaluate the effectiveness and safety of oral Chinese herbal medicine (OCHM) for heart failure with preserved ejection fraction (HFpEF). **Methods**: PubMed, Excerpta Medica Database (EMBASE), Cochrane Library, Chinese Biological Medicine Database (CBM), Wanfang Database, Chongqing VIP Information (VIP) and China National Knowledge Infrastructure (CNKI) were searched for appropriate articles from respective inceptions until June 3, 2018. Randomized controlled trials (RCTs) investigating the effectiveness of OCHM for the patients with HFpEF were eligible. Quality assessment was performed by employing the Cochrane Risk of Bias assessment tool. Papers were independently reviewed by two reviewers and analyzed using Cochrane software Revman 5.3. Dichotomous data were analyzed by relative risk (RR) with a 95% confidence interval (CI), while continuous variables were analyzed by using mean difference (MD) with 95% CI for effect size. **Results**: A total of 16 RCTs involving 1,320 participants were identified. Fourteen of the trials used conventional Western medicine (CWM) as the control, the control of 1 trial was no treatment, and another was placebo. Three of the trials served Chinese patent medicine (CPM) as interventions, and other OCHM were Chinese medicine decoctions (CMDs). Only limited evidence showed experimental group with OCHM may get better effect on brain natriuretic peptide (BNP: MD –37.29, 95% CI –53.08 to –21.50, P<0.00001) or N terminal pro B type natriuretic peptide (NT-proBNP: MD –236.04, 95% CI –356.83 to –115.25, P=0.0001), Minnesota Living with Heart Failure questionnaire (MLHFQ, MD –9.94, 95% CI –16.77 to –3.11, P=0.004), but the results had high heterogeneities. With concerns on 12 of 16 trials, the meta-analysis found that the adjuvant therapy of OCHM might be more effective in increasing overall response rate (RR 1.17, 95% CI 1.11 to 1.24, P<0.00001), when compared with CWM alone. Subgroup meta-analysis between CPMs and CMDs showed that the two CPMs may have more therapeutic effect on MLHFQ, but not on NT-proBNP, and CMD came to the opposite conclusion. No significant differences were found between experimental groups and control groups on 6-min walk test (6MWT). Adverse events, such as more defecation, weakness, cardiopalmus, edema, cough and hypotension, were mild in all groups and disappeared after the easement of pharmacological intervention. **Conclusions**: Due to the insufficient quality of trials that were analyzed, it is not appropriate to confirm or deny the potency of OCHMs in treating HFpEF at the present time. More rigorously designed RCTs focusing on primary endpoints with long-term follow-up are warranted to validate the effect of OCHMs for patients with HFpEF.

KEYWORDS oral Chinese herbal medicine, heart failure with preserved ejection fraction, meta-analysis, systematic review

The current description of heart failure (HF) is based on measurement of the left ventricular ejection fraction (LVEF), and HF comprises a wide range of patients, from those who have HF with preserved ejection fraction (HFpEF) to those who have HF with reduced EF (HFrEF). Over the past 30 years, improvements in treatments which consist of some effective medicines, such as diuretics, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and β-blockers, have improved survival and reduced the hospitalization rate in patients with HFrEF. However, there are many

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differences between HFpEF and HFrEF in underlying aetiologies, demographics, comorbidities and response to therapies.[1] The proportion of patients with HFpEF increased over a 15-year period and was significantly higher among community patients than among referral patients (55% *vs*. 45%), while the rate of death from this disorder remained unchanged.[2] To date, there are no approved therapies to reduce hospitalization or mortality for HFpEF. No specific treatment for HFpEF is established and management is limited to diuretics and treatment of comorbidities. ACEI, ARB, digoxin, β-blockers were not effective in reducing mortality.[3] There remains a lack of consensus on the therapeutic targets, and goals for therapy for this syndrome.

Oral Chinese herbal medicine (OCHM) has been used to treat HFpEF-like symptoms (such as breathlessness, ankle swelling and fatigue) for centuries in China. In recent decades, a number of clinical trials have been conducted to evaluate the efficacy of OCHM for HFpEF. Results from previous studies[4-20] showed that OCHM, as a complementary treatment, may improve the ventricular function and the quality of life of HFpEF patients. However, systematic clinical research evidence for the effectiveness of OCHM for HFpEF is still insufficient.

METHODS

Database and Search Strategy

Randomized controlled trials (RCTs) assessing the administration of OCHM in the treatment for HFpEF were located by searching the databases of PubMed, Excerpta Medica Database (EMBASE), Cochrane Library, Chinese Biological Medicine Database (CBM), Wanfang Database, Chongqing VIP Information (VIP) and China National Knowledge Infrastructure (CNKI) and assisted by manual retrieval. There is no restriction for publication language. The last search was run on June 3, 2018, and case reports and small case series were excluded. The detailed search strategy used for PubMed is shown in Appendix 1. In addition, the reference lists of articles identified as eligible were reviewed.

Inclusion Criteria

Search results were screened for trials by two reviewers (Mei J and Ju JQ). Two reviewers worked independently when using the following items as essential inclusion criteria: (a) type of studies: Randomized controlled trials (RCTs) were included regardless of blinding, language, publication status; (b) the inclusion of cases in line with national or international standards for the diagnosis of HFpEF[1] and the average age of 18 years or older; (c) trials containing patients with HFpEF, irrespective of the etiology, and HFpEF was diagnosed by the following criteria: HFpEF diagnostic criteria established by European Society of Cardiology or American Heart Association/American College of Cardiology Foundation or Chinese Society of Cardiology,[21,22] and Chinese Consensus on the Diagnosis and Treatment of Heart Failure with Normal Ejection Fraction;[23] (d) the treatment groups received OCHM alone or in combination with other treatments; the control groups received conventional Western medicine (CWM) only; (e) the primary outcomes included levels of brain natriuretic peptide (BNP) or N terminal pro B type natriuretic peptide (NT-proBNP); secondary outcomes included overall response rate (ORR) by referring to the evaluation criteria of Guidelines for Clinical Research on Chinese New Herbal Medicines,[24] Minnesota Living with Heart Failure questionnaire (MLHFQ), 6-minute walk test (6MWT). Therefore, "markedly effective and effective" was classified as an effective result and "invalid and pejorative" as an ineffective result. The ORR is the ratio of effective cases to total cases which was shown in Appendix 2.

Exclusion Criteria

Exclusion criteria included the following items: (a) quasi-randomized trials whose methods of allocation included date of birth, date of admission, or alternation; (b) duplicate reports, studies with the data was incorrect, inconsistency or incomplete and unavailable articles; and (c) other administration route of Chinese medicine, such as herbal injection, fumigation and so on.

Study Selection and Data Extraction

Two authors (Mei J and Ju JQ) independently screened the titles and abstracts of the achieved citations from primary searching. Full text of the articles of potential interest were download for further evaluation, those meeting inclusion criteria were included in the final review.

The following contents were extracted from the included trials independently by the authors: publication data (authors, publication year, sample size, age, gender); treatment protocol (Chinese medicine name, Western medicine name and dose);

duration of treatment; main outcomes; adverse events; duration of follow-up. Missing data were achieved through contacting with authors of the original studies by telephone, email or fax.

Quality Assessment of Trials

The methodological quality of trials was assessed independently using criteria from the Cochrane Handbook for Systematic Review of Interventions, version 5.1.0.[25] The items included random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias (defined as baseline data comparability). The risk of bias was categorized as low, unclear, or high. The discrepancies were resolved through consensus. Disagreements between the two authors were resolved by discussion and if needed, arbitrated by a third author (Xu H or Xu FQ).

Statistical Methods

Data were summarized using relative risk (RR) with 95% confidence interval (CI) for discontinuous outcomes or mean differences (MD) with 95% CI for continuous outcomes. RevMan5.3 software from the Cochrane Collaboration was used for data analyses. Data was assessed by both fixed effect model and random effect model, but only reported random effect analysis if the heterogeneity was statistically significant.[26] Statistical heterogeneity was tested by examining I^2, meaning that an I^2 larger than 50% indicated the possibility of statistical heterogeneity,[27] and the value of $P<0.05$ was regarded as statistically significant. If heterogeneity was low ($I^2<50\%$ or $P>0.05$), the fixed effects model was used. If heterogeneity was high ($I^2>50\%$ or $P<0.05$), the random effect model was used and subgroup analyses were conducted to determine the evidence for the different control if data were sufficient. Publication bias was explored by funnel plot analysis if the group included more than 10 trials.[26]

RESULTS

Study Selection

The search of 7 databases identified 1,151 citations for further evaluation. Full texts of 126 articles were read, and 17 trials[4-20] met the inclusion criteria. However, it was found that, as a baseline data of 1 trial,[20] both actual average BNP of two groups did not meet the item (LVEF ⩾50%) after reading the article. Thus, finally 16 trials were included in the review.

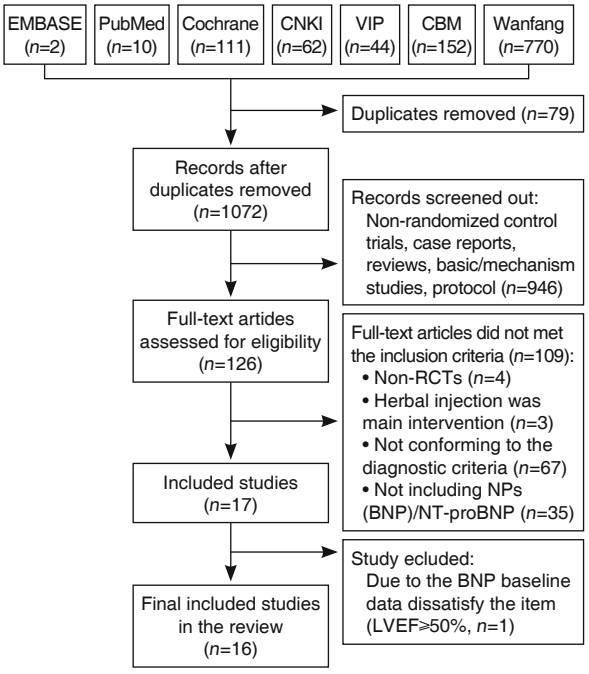

Figure 1. Study Flow Chart of Heart Failure Patients with HFpEF

Details of the study flow were shown in Figure 1.

Study Characteristics

All studies were performed in China, and the studies involved a total of 1,320 patients with HFpEF. In addition, all studies exhibited comparable baseline patient characteristics, including age and gender. And there were no significant differences among them. Characteristics of included trials were listed in Appendix 3.

Types of comparisons included herbal capsule *versus* no treatment,[18] herbal pill *versus* placebo,[12] and others were OCHM (including herbal decoction, herbal capsule and herbal powder) plus CWM *vs*. CWM. The OCHMs contained 2 Chinese patent medicine (CPMs), Qili Qiangxin Capsule (芪苈强心胶囊) and Shexiang Baoxin Pill (麝香保心丸), and some Chinese medicine decoctions (CMDs). CWM included oxygen uptake, rest-cure, and low-salt diet, with medicines including ACEIs, ARBs, beta-receptor, blockers, diuretics, aldosterone receptor blockers, digitalis preparation, drugs belonging to ester nitrate, and others recommended in Chinese guidlines for diagnosis and treatment of heart failure.

Primary evaluated outcomes of this review included BNP or NT-proBNP. The levels of BNP and NT-proBNP were reported in 9 trials[4,6,9,11,13,16-19] and

7 trials[5,7,8,10,12,14,15] respectively. ORR was reported in 12 trials.[4,6,7,9-11,14-19] Secondary outcomes included MLHFQ, 6MWT, were reported in 7 trials,[4,8,10,12,13,15,18] 5 trials,[4,12,13,15,16] respectively. Only 3 trials[7,13,14] mentioned follow-up duration, which were all 6 months.

Methodological Quality Assessment

According to the previously mentioned criteria, all included trials were assessed as having high risk of bias (Figure 2).

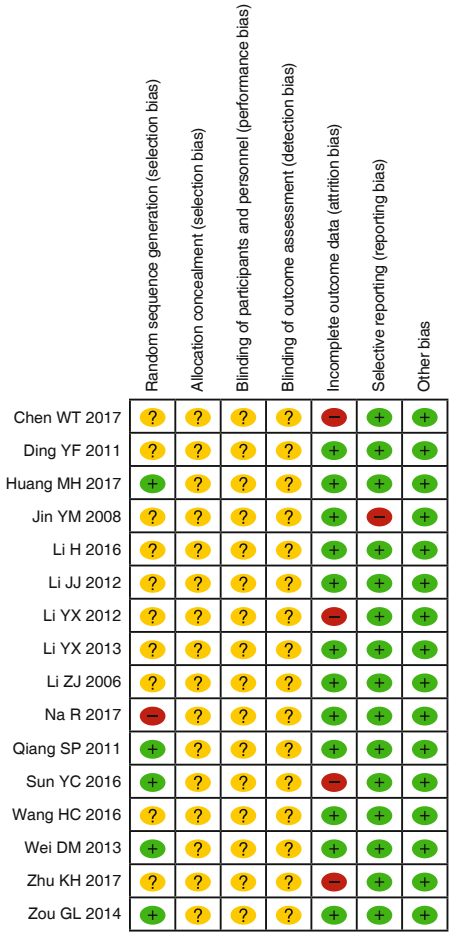

Figure 2. Summary of the Risk of Bias Assessment for Included Trials

Only 6 trials[5,7,12-14,17] reported the methods of randomization, 5 trials[5,7,12,14,17] of them used a random number table, with 1 trial[20] assessed as high risk of bias due to randomization by registration order. All trials did not mention whether or not they had adequate allocation concealment methods. Three[7,13,14] of the trials mentioned follow-up.

Fourteen trials[4-7,9-11,13-19] used OCHM as add-on treatment for CWM; 1 trial[12] used placebo as control group, and another trial[8] compared OCHM with no treatment in control group. Three trials[8,10,12] served CPMs as interventions for comparing the curative effect with CWM. Thus, all of the included trials were assessed as high risk of bias on the control factor of blinding to participants. Insufficient information was provided to judge the performance bias induced by lack of blinding to statistician and outcome assessors.

There are 4 trials[4,6,10,14] which were assessed as high risk of bias in incomplete outcome data, since they reported the numbers and reason for missing data in each group, but not used adequate statistical methods to deal with the missing data. Fifteen trials[4-10,12-19] were assessed as low risk of reporting bias, and the last one was evaluated as high risk of reporting bias due to the incomplete reporting of pre-defined outcomes. No methods of sample size calculation were apparent in all of the included trials, and it was difficult to determine whether a study was fraudulent. All of the trials were evaluated as at an unclear risk of other bias.

Outcome Measures

BNP or NT-proBNP

Figure 3 and Appendix 4 present the findings of the 16 trials included which were divided into BNP and NT-proBNP group for meta-analysis by the types of tested natriuretic peptides. For the 2 meta-analyses, OCHMs alone or in combination with CWM had abilities to decrease plasma natriuretic peptides (BNP group: MD=–37.29, 95% CI –53.08 to –21.50, 809 participants, P<0.00001; NT-proBNP group: MD=–236.04, 95% CI –356.83 to –115.25, 511 participants, P=0.0001) compared with the control group. Highly significant heterogeneity was found among the 2 meta-analyses (BNP group: I^2=59%, P<0.0001; NT-proBNP group: I^2=97%, P=0.0001).

In NT-proBNP group, the trials were divided into 2 types which were placebo/no medicine and CWM by intervention types of control groups. OCHM *vs*. placebo/no medicine group included 2 trials,[8,12] and meta-analysis showed that the experimental group and control group had no obvious difference on decreasing NT-proBNP level (MD=–168.64, 95% CI –470.90 to 133.63, 136 participants, P=0.27) with significant heterogeneity (I^2=67%, P=0.08). OCHM plus CWM *vs*. CWM group included 5 trials,[5,7,10,14,15] and meta-analysis showed that the experimental group and the control group had obvious difference on decreasing

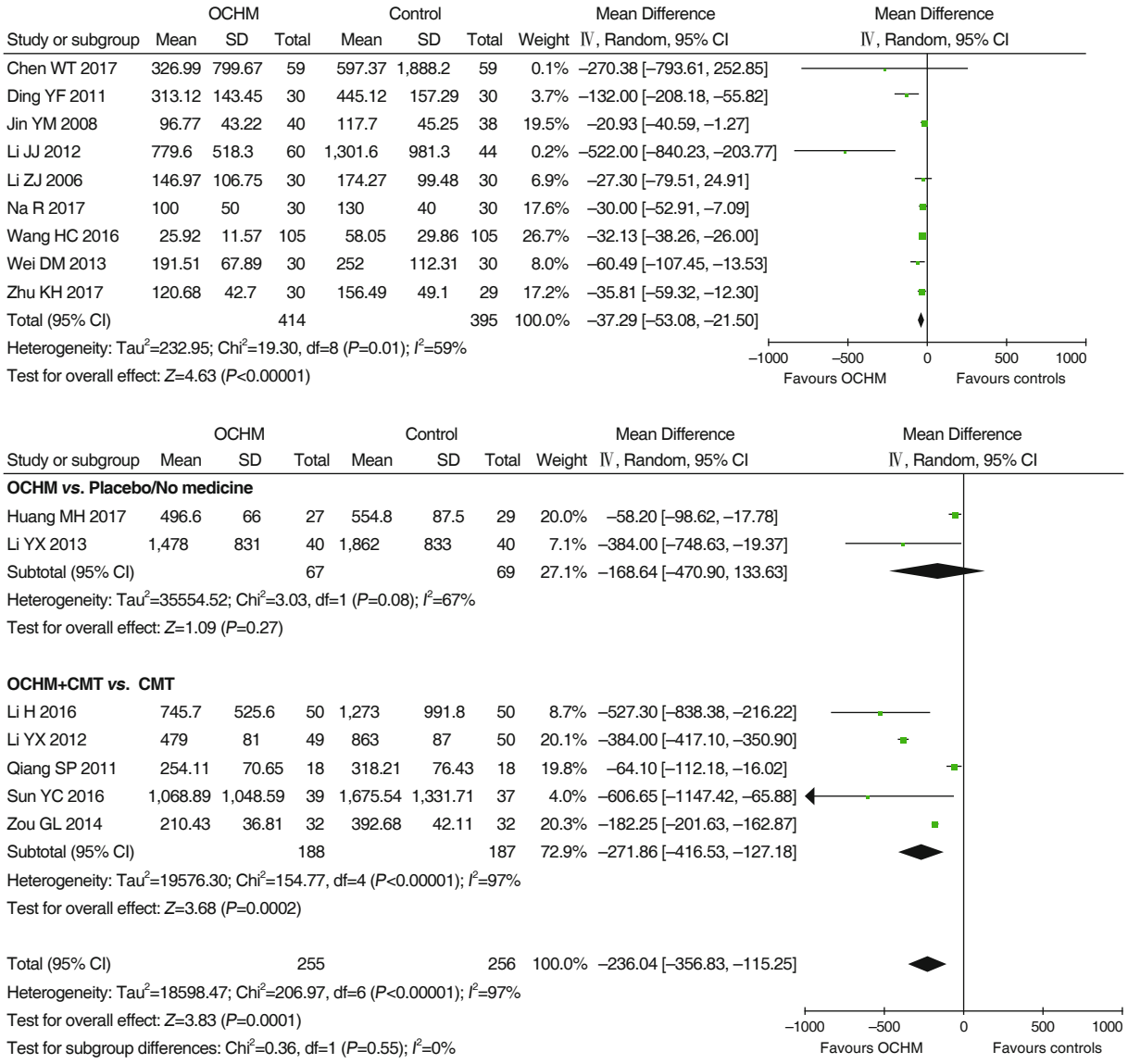

Figure 3. Forest Plot of Improvement on BNP

NT-proBNP level (MD=–271.86, 95% CI –416.53 to –127.18, 375 participants, *P*=0.0002) with significant heterogeneity (I^2=97%, *P*<0.00001). The difference between subgroups was not obvious (I^2=0%, *P*=0.55).

Appendix 5 shows two subgroup analysis of NT-proBNP group between CPM and CMD. CPM subgroup included 3 trials,[8,10,12] and meta-analysis showed that the experimental and control group had no obvious difference on decreasing NT-proBNP level (MD=–259.02, 95% CI –536.26 to 18.23, 235 participants, *P*=0.07) with significant heterogeneity (I^2=99%, *P*<0.00001). CMD subgroup included 4 trials,[5,7,14,15] and meta-analysis showed that the experimental group and control group had obvious difference on decreasing NT-proBNP level (MD=–190.06, 95% CI –308.99 to –71.12, 276 participants, *P*=0.0001) with significant heterogeneity (I^2=97%, *P*<0.00001). The difference between subgroups was not obvious (I^2=0%, *P*=0.65).

Overall Response Rate

Twelve trials[4,6,7,9-11,14-19] reported ORR and found an obvious difference (*P*<0.00001) between OCHM plus CWM and CWM alone on ORR (RR 1.17, 95% CI 1.11 to 1.24, 1,088 participants). Only 1 trial[10] served CPM as intervention, and CMDs were used in others. No heterogeneity was found among the 12 trials (I^2=0%, *P*=0.77, Appendix 6).

6MWT Assessment

Six trials[4,8,12,13,15,16] reported that 6MWT was

divided into subgroup which was OCHM plus CWM *vs*. CWM group and OCHM *vs*. placebo/No medicine group. The total meta-analysis showed that experimental groups with OCHM did not achieve more improvement (MD=44.70, 95% CI 0.77 to 88.63, 624 participants, *P*=0.05) than control groups (including CWM, placebo, no medicine). The meta-analyses of two subgroups had similar results (OCHM plus CWM *vs*. CWM: MD= 30.93, 95% CI –5.24 to 67.10, 488 participants, *P*=0.09; OCHM *vs*. placebo/no medicine: MD=79.45, 95%CI –26.27 to 185.18, 136 participants, *P*=0.14) with total analyses. Highly significant heterogeneity was found among these 6 studies (I^2=93%, *P*<0.00001). The difference between subgroups was not obvious (I^2=0%, *P*=0.39). The results of the meta-analysis are shown in Appendix 7.

MLHFQ

Seven trials[4,8,10,12,13,15,16] reported MLHFQ was divided into subgroup which was OCHM plus CWM *vs*. CWM and OCHM *vs*. placebo/no medicine. The total meta-analysis showed that experimental groups with OCHM achieved a greater improvement (MD=–9.94, 95% CI –16.77 to –3.11, 723 participants, *P*=0.004) than control groups (including CWM, placebo and no medicine), which meant that OCHM could decrease the score of MLHFQ. Highly significant heterogeneity was found among these 7 studies (I^2=94%, *P*<0.00001). The meta-analyses of OCHM plus CWM *vs*. CWM subgroup had similar result (MD=–6.87, 95% CI –12.98 to –0.76, 587 participants, *P*=0.03) with total analyses and showed significant heterogeneity (I^2=89%, *P*<0.00001) between groups. The meta-analyses of OCHM *vs*. placebo/no medicine subgroup showed that experimental groups with OCHM did not achieve more improvement (MD=–17.54, 95%CI –37.43 to 2.36, 136 participants, *P*=0.08) than control groups (including CWM, placebo, no medicine). Significant heterogeneity was found (I^2=97%, *P*<0.00001) between the experimental and the control groups. The difference of subgroups was not obvious (I^2=0.9%, *P*=0.32). The results of the meta-analysis are shown in Appendix 8.

Appendix 9 shows two subgroup analysis of MLHFQ group between CPM and CMD. CPM subgroup included 3 trials,[8,10,12] and meta-analysis showed that the experimental group and control group had obvious difference on improving MLHFQ (MD=–14.19, 95% CI –27.30 to –1.08, 235 participants, *P*=0.03) with significant heterogeneity (I^2=96%, *P*<0.00001). CMD subgroup included 4 trials,[4,13,15,16] and meta-analysis between the experimental and control group did not present obvious difference on promoting MLHFQ (MD=–6.71, 95% CI –14.81 to 1.38, 488 participants, *P*=0.10) with significant heterogeneity (I^2=92%, *P*<0.00001). The difference between subgroups was not obvious (I^2=0%, *P*=0.34).

Adverse Events

Adverse events were monitored in 12 trials.[4,6-11,14-16,18,19] Nine trials[4,6,8-11,14,15,18] demonstrated no adverse events between experimental groups with OCHM and CWM. In the remaining 3 trials, 1 trial[7] reported more defecation per day (3/32) in experimental group; the other[19] displayed cough (3/30) and hypotension (2/30) in control group; the last[16] described weakness (2/105), cardiopalmus (1/105), edema (3/105), cough (8/105) in experimental group, while weakness (3/105), cardiopalmus (4/105), edema (5/105), cough (6/105) in control group. All of the reported adverse events were not severe and well-tolerated. Meta-analysis showed that there was no difference in the frequency of adverse events between experimental and control groups (RR 0.78, 95% CI 0.13 to 4.50, *P*=0.78, Appendix 10).

Publication Bias

To detect possible publication bias, the 12 trials[4,6,7,9-11,14-19] were analyzed that compared OCHM with CWM in terms of the ORRs with a random effects model. The funnel plot of ORR was asymmetrical, indicating the presence of publication bias (Figure 4). The detection of publication bias was not available for other outcomes as the included trials were less than 10.

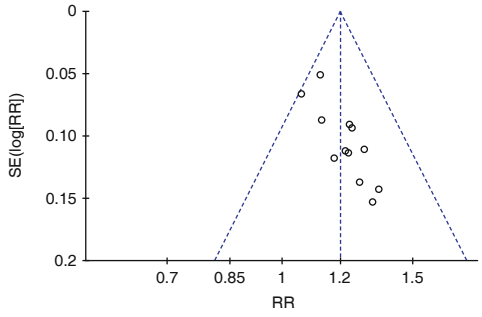

Figure 4. Forest Plot of Improvement of NT-proBNP between CPM and CMD

DISCUSSION

HFpEF is more common in the elderly, women and patients with a history of hypertension and atrial fibrillation, but there is not specific treatment to reduce hospitalization or mortality for HFpEF.[1]

Therefore, OCHM has been used to treat HFpEF-like symptoms (such as breathlessness, ankle swelling and fatigue) for centuries in China. In the recent decades, OCHM approaches have been supported by increasing clinical trials and reviews on decreasing BNP and symptom-improving effects for heart failure.[28,29] Results from previous studies showed that OCHM, as a complementary treatment, may improve ventricular function and the quality of life of HFpEF patients. However, the role of OCHM in the treatment of HFpEF is not unclear. We aimed to provide the latest systematic review and meta-analysis to summarize the existing evidence of OCHM as an effective treatment for HFpEF. Unlike previous meta-analysis,[30] whose diagnosis was inappropriate due to outdated references and the primary outcomes in the report were inconsistent, this article only focused on OCHM for patients with HFpEF, while herbal injections were excluded.

With concerns on 12 of 16 trials, this meta-analysis about the ORR showed that OCHM combined with CWM were more effective than CWM for HFpEF. Due to the poor methodological quality of the included trials and the insufficient number of trial participants, only limited evidence showed experimental group with OCHM may get better effect on BNP or NT-proBNP, MLHFQ, but the results had very significant heterogeneity. Subgroup meta-analysis between CPM and CMD showed that there were different results on NT-proBNP and MLHFQ comparing with CWM. The analysis results showed that the two CPMs may have more therapeutic effect on MLHFQ, but not on NT-proBNP, and CMD came to the opposite conclusion. The treatment duration may lead to the difference between CPM and CMD. No significant differences were found between experimental groups and control groups on 6MWT. Finally, use of OCHM seemed safe and well-tolerated for patients with HFpEF. In summary, though the strength of the evidence was low, we found potential effect of oral herbal preparations for patients with HFpEF on some key symptoms' improvement.

Low levels of evidence in this review were mainly caused by the poor quality and small sample size of original included trials. Only 5 out of 16 trials reported on how the participants are randomly assigned to the intervention groups. The other trials simply mentioned "randomization", with none of the trials indicating the use of allocation concealment and blinding. Three of the trials specified follow-ups.

This study suggests that OCHM can effectively improve the cardiac function of patients with HFpEF, but the results have very significant heterogeneity. The inconsistency of findings of herbal medicine's effect on improving main outcomes of HFpEF among these trials further reduced the internal validity of the evidence.

Although we searched both Chinese and English databases, all of the included trials were retrieved from Chinese literature, which may have introduced potential selection bias and limited the external generalization of the evidence.

Due to the insufficient quality of trials that were analyzed, it is not appropriate to authenticate the effectiveness of OCHMs in treating HFpEF at the present time. Purposefully designed trials with high methodological quality are needed to validate the effect of OCHMs for patients with HFpEF.

Conflicts of Interest

The authors declare that there is no conflict of interests.

Author Contributions

Xu FQ conceived the topic and helped to draft the manuscript. Mei J and Ju JQ collected the references and wrote the manuscript. The submission and revision of manuscript were completed by Xu FQ and Xu H.

Electronic Supplementary Material: Supplementary materials (Appendixes) are available in the online version of this article at https://doi.org/10.1007/s11655-019-2704-8.

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