Effectiveness of Chinese herbal medicine for primary Raynaud's phenomenon: a systematic review and Meta-analysis of randomized controlled trials

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Accepted: October 21, 2019

Abstract

OBJECTIVE: To evaluate the effectiveness of Chinese herbal medicine for primary Raynaud's phenomenon (PRP).

METHODS: The Cochrane Central Register of Controlled Trials, PubMed, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Wanfang Database were searched up to February 13, 2018. Randomized controlled trials (RCTs) on treatment of PRP with Chinese herbal medicine compared with placebo, blank control, lifestyle changes, or calcium antagonists were identified and reviewed. The quality of included trials was assessed using a risk of bias tool.

RESULTS: Eight RCTs involving 674 participants were included. The methodological quality of the included trials was generally poor. Meta-analysis of two trials showed that Buyang Huanwu Tang plus Danggui Sini Tang produced greater improvement in global symptoms than nifedipine. One trial showed that Danggui Sini Tang and a self-composed Chinese herbal medicine decoction, respectively, produced greater improvement in global symptoms than nifedipine alone. In one trial, modified Danggui Sini Tang showed greater improvement in global symptoms and arterial peak systolic velocity compared with nifedipine. One trial showed that Jiejing Tongmi Tang produced greater improvement in global symptoms, plasma endothelin, and plasma nitric oxide than cinepazide maleate injection. However, Jiejing Tongmi Tang did not produce a significant difference in skin temperature and peripheral artery blood stream drawing after cold pressor testing compared with cinepazide maleate injection. None of the trials reported frequency of attacks, duration of attacks, participant preference scores, or adverse events.

CONCLUSION: Chinese herbal medicine may have a positive effective on PRP. However, owing to weak methodology, the benefits of Chinese herbal medicine for PRP are inconclusive. More rigorously designed studies are needed to confirm these findings.

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Keywords: Chinese herbal medicine; Primary Raynaud’s phenomenon; Systematic review; Meta-analysis; Randomized controlled trials

INTRODUCTION

Primary Raynaud’s phenomenon (PRP) classically presents as symmetrical vasospasm, usually affecting both hands, brought on by a number of stimulus factors, including coldness, emotional changes, and carrying objects. The prevalence of Raynaud’s phenomenon (RP) ranges from 3% to 5%, of which the proportion of PRP is as high as 80% to 90%. PRP is very common among women and its prevalence is 9 times higher in women than in men. Although PRP is considered benign, its impact on quality of life is as serious as that of secondary RP. Currently, calcium channel blockers (CCB) are the recommended first-line drug treatment for PRP, if lifestyle modification alone has failed. However, CCB produce side effects such as headache and palpitaitons.

In Traditional Chinese Medicine (TCM) theory, PRP corresponds to several symptom patterns, including “Xuebi,” “Hanbi,” “Maibi,” and “Juezheng.” As early as 2600 BC, there is a record of PRP in Huang Di Nei Jing. Another ancient text, the Treatise on Cold Damage, first proposed the use of Danggui Sini Tang to treat PRP. In recent years, a growing number of clinical controlled trials have investigated the efficacy of Chinese herbal medicine (CHM) for PRP. Although these indicate some benefit of CHM therapy for PRP, the evidence remains inconclusive.

This systematic review aimed to evaluate the benefits and harms of CHM for people with PRP. The results of this review may provide information about improving efficacy and reducing adverse reactions in the treatment of PRP.

MATERIALS AND METHODS

This review was conducted following PRISMA checklist guidelines.

Protocol

The protocol for this review was registered at PROSPERO international register of systematic reviews (registration number CRD42018090459).

Inclusion and exclusion criteria

Types of studies: we included randomized controlled trials (RCTs). Quasi-randomized trials were excluded.

Types of participants: male or female participants, of any age or ethnic origin, who had clinical features of PRP. In the absence of an accepted definition of RP, all participants reported as having RP were included.

Types of interventions: CHM was compared with placebo, no treatment, or CCB. Trials comparing CHM plus CCB versus CCB alone were also included. CHM refers to drugs used according to TCM theory. CHM includes single herbs, such as extracts from a single herb, traditional Chinese patent medicines, and self-composed Chinese herbal compound prescriptions. No limitations were applied regarding drug preparation (i.e., decoction, oral liquid, tablet, capsule, pill, powder, or injection), mode of delivery (i.e., oral, intramuscular, or intravenous), dosage, or regimen. The types of outcome measures assessed were as follows. The primary outcomes were frequency of attacks (average attacks/week), duration of attacks (average duration per attack in minutes), severity scores, clinical global symptom scores (i.e., visual analogue scale, numerical rating scale, participant preference scores), and serious adverse events (defined as life-threatening, fatal, or requiring hospitalization or prolonged hospitalization). If the clinical global symptom score was not available, the primary outcome was global symptom improvement by whatever criteria the trial authors used. Physiological measurements (comprising digital temperature, blood flow response to hand cooling, and changes in plasma endothelin-1 (ET-1)) and non-serious adverse events (e.g., headache, tachycardia, and ankle swelling) were assessed as secondary outcomes.

Search strategy

We searched six Chinese and English electronic databases: Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Wanfang Data, PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL) from their inception date to February 13, 2018, and irrespective of language or publication status. Reference lists of all relevant trials were also hand-searched for potentially relevant trials. The detailed search strategy for PubMed is shown as bellow.

PubMed search strategy

#1 (Raynaud Disease [mh]) OR (Cold Fingers, Hereditary) OR (Raynaud’s Disease) OR (Raynauds Disease) OR (Raynaud Phenomenon) OR (Rynud) OR (Raynaud) OR (Catahrhs)

#2 (Medicine, Chinese Traditional [mh]) OR (Traditional Chinese Medicine) OR (Chinese Medicine, Traditional) OR (Zhong Yi Xue) OR (Chinese Traditional Medicine) OR (Traditional Medicine, Chinese)

#3 randomized controlled trial [pt]

#4 controlled clinical trial [pt]

#5 randomized [tiab]

#6 placebo [tiab]

#7 drug therapy [sh]

#8 randomly [tiab]

#9 trial [tiab]

#10 groups [tiab]

#11 animals [mh] NOT humans [mh]

#12 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
Study selection and Data extraction

Two authors (Zhang Jinchao and Hu Jing) independently conducted the study selection and data extraction. Disagreement was resolved by discussion, and consensus was reached through discussion with a third party (Li Ping).

The extracted data comprised the basic information about the source (e.g., author, year of publication, type of trial, and sample size), basic information about the subjects (e.g., age, gender, disease diagnosis, and TCM symptom pattern identification), trial and control interventions (e.g., drug name, different methods of application, dosage, and duration of medication), outcome information, and methodology information.

Methodological quality assessment

Two reviewers (Zhang Jinchao and Chen Zhaoxia) used the Cochrane Collaboration’s risk of bias tool to independently assess the methodological quality of the included trials. Trials were assessed according to seven quality aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias, and were classed as “low risk,” “high risk,” or “unclear risk” (indicating unclear or unknown risk of bias). Disagreements were resolved by discussion with He Xiujuan.

Data synthesis and analysis

Revman 5.3 software (Nordic Cochrane Centre, Copenhagen, Denmark) was used for data analysis. Mean differences (MD) or standardized MDs (SMD) with 95% confidence intervals (CI) were used for continuous data, and relative risk (RR) with 95% CI for dichotomous outcomes. Data not suitable for pooling analysis were synthesized qualitatively. We performed Meta-analysis for trials if there were no significant differences in study design, participants, interventions, control, and outcome measures. We tested heterogeneity using the $I^2$ statistic with significance set at 50%, and the $\chi^2$ statistic with significance set at $P < 0.10$. We used a random-effects model for pooling data with significant heterogeneity; otherwise, a fixed-effects model was used. If data were available, subgroup analysis was conducted according to drug delivery mode (oral or external use). A funnel plot was generated to explore publication bias if more than 10 trials were included.

RESULTS

Literature search results and study selection

Primary retrieval identified 242 publications. We excluded 58 duplicates and 145 obviously irrelevant publications after screening titles and abstracts. Full text papers of 39 trials were retrieved. Eight trials that fulfilled the inclusion criteria were included. The flow chart of the selection process is shown in Figure 1.

Characteristics of studies included

Eight RCTs involving 674 participants were included. A summary of the characteristics of included RCTs is shown in Table 1.

The average sample size was 86 (40-128 cases). The number of male and female participants was 100 and 614, respectively, but one trial (60 cases) did not report...
### Table 1 Characteristics of included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample (M/F)</th>
<th>Total sample</th>
<th>Age (years)</th>
<th>Course of the PRP</th>
<th>Diagnostic criteria</th>
<th>TCM syndrome</th>
<th>Intervention</th>
<th>Observation time (weeks)</th>
<th>Criteria for outcome</th>
<th>Adverse reaction</th>
<th>Follow-up period (Month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo et al 2013</td>
<td>5/35</td>
<td>40</td>
<td>18-45</td>
<td>1-22 months</td>
<td>Y</td>
<td>N</td>
<td>Self-composed CHM Decoction + Nifedipine Sustained-release Tablets Oral 2 times/d and fumigation infected part</td>
<td>4</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Liu LF et al 2016</td>
<td>N</td>
<td>60</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Danggu Sini Tang Oral 3 times/d</td>
<td>4</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Ma HY et al 2017</td>
<td>8/57/62/59</td>
<td>128</td>
<td>33.3±3.6</td>
<td>1-3 years</td>
<td>N</td>
<td>N</td>
<td>Modified Danggu Sini Tang + Nifedipine Tablets N Buyang Huanwu Tang + Danggu Sini Tang Oral 3 times/d Buyang Huanwu Tang + Danggu Sini Tang one dose daily</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>6</td>
</tr>
<tr>
<td>Qu H et al 2015</td>
<td>13/32/17</td>
<td>90</td>
<td>21-65</td>
<td>0.5-11 years</td>
<td>N</td>
<td>N</td>
<td>Nifedipine Tablets 20 mg/d, oral</td>
<td>4</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Sun GX et al 2010</td>
<td>5/26</td>
<td>62</td>
<td>21-70</td>
<td>0.5-11 years</td>
<td>N</td>
<td>N</td>
<td>Modified Danggu Sini Tang one dose daily</td>
<td>4</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Wang WD et al 2017</td>
<td>8/40/74/11</td>
<td>96</td>
<td>30.5±8.4</td>
<td>2.8±1.3 years</td>
<td>Y</td>
<td>N</td>
<td>Modified Danggu Sini Tang one dose daily</td>
<td>4</td>
<td>Y</td>
<td>N</td>
<td>6</td>
</tr>
<tr>
<td>Ye HD et al 2015</td>
<td>4/36/3/35</td>
<td>78</td>
<td>34.1±13.1</td>
<td>3.1±1.2 years</td>
<td>Y</td>
<td>N</td>
<td>Danggu Sini Tang-Nifedipine Sustained-release Tablets one dose daily</td>
<td>4</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Zhang HQ et al 2013</td>
<td>8/52/10/50</td>
<td>120</td>
<td>19-42</td>
<td>2-22 months</td>
<td>Y</td>
<td>N</td>
<td>Jiejing Tongmi Tang + Cinepazide Maleate injection one dose daily</td>
<td>4</td>
<td>Y</td>
<td>N</td>
<td>N</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>17-43</td>
<td>4-20 months</td>
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</table>

Notes: Y: reported; N: not reported; T: trial group; C: control group; M: male; F: female; PRP: primary Raynaud’s phenomenon; TCM: Traditional Chinese Medicine.
the male to female ratio. None of the eight RCTs reported the calculation method for sample size. Participant age ranged from 13 to 70 years. The duration of PRP ranged from 2 months to 13 years. Four trials reported diagnostic criteria. Three trials only mentioned that participants fit the diagnostic criteria, but specific diagnostic criteria or references were not reported. One trial did not report diagnostic criteria. No trial reported TCM symptom pattern identification. The trial interventions of six trials were CHM alone; the other two trials used CHM in combination with Western medicine. The composition and dosing frequency of modified Danggui Sini Tang in two trials were different. One trial used CHM for oral administration and external use, and the other trials used oral administration with a dosing frequency ranging from one to three times daily. The treatments lasted for 4 weeks in all included trials. The compositions and dosages of CHM formulations are shown in Table 2. The control measures included in this review were nifedipine tablet, nifedipine sustained-released tablet, and cinepazide maleate injection.

The outcomes reported comprised global symptom improvement (eight trials), changes in arterial peak systolic velocity before and after treatment (one trial), index changes in ET-1 (one trial), plasma nitric oxide (one trial), and skin temperature and peripheral artery blood stream drawing before and after cold pressor testing (one trial). For the global symptom improvement outcome, a three (markedly effective, effective, ineffective) or four (recovery, markedly effective, effective, ineffective) category measurement with different standards according to the degree of overall symptom improvement was used to evaluate treatment effects. None of the trials mentioned whether adverse reactions were monitored. All the reported outcomes

Table 2 Compositions and dosages of Chinese medicinal formulations

<table>
<thead>
<tr>
<th>Study</th>
<th>Name of Chinese medicinal formulations</th>
<th>Compositions and dosages</th>
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</thead>
<tbody>
<tr>
<td>Guo WG et al 2013</td>
<td>Danggui (Radix Angelicae Sinensis) 15 g, Guizhi (Ramulus Cinnamomni) 15 g, Baishao (Radix Paeoniae Alba) 25 g, Tongcao (Medulla Tetrapteracis) 10 g, Huangqi (Radix Astragali Mongolici) 30 g, Xixin (Pheretima Aspergillum) 5 g, Guizhi (Radix Cinnamomi) 15 g, Baizhu (Radix Achyranthis Bidentatae) 15 g, Jixiang (Poria) 10 g, Dangshen (Radix Codonopsis Lateralis) 15 g, Dazao (Fructus Jujubae) 5 g, and Gancao (Radix Glycyrrhizae) 15 g.</td>
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<tr>
<td>Liu LF et al 2016</td>
<td>Danggui Sini Tang</td>
<td>Danggui (Radix Angelicae Sinensis) 15 g, Guizhi (Ramulus Cinnamomni) 15 g, Baishao (Radix Paeoniae Alba) 9 g, Dazao (Fructus Jujubae) 9 g, Xixin (Pheretima Aspergillum) 6 g, and stir-frying with liquid adjuvant Gancao (Radix Glycyrrhizae) 6 g.</td>
</tr>
<tr>
<td>Ma HY et al 2017</td>
<td>Modified Danggui Sini Tang</td>
<td>Huangqi (Radix Angelicae Sinensis) 15 g, Baishao (Radix Paeoniae Alba) 10 g, Xixin (Pheretima Aspergillum) 5 g, and Gancao (Radix Glycyrrhizae) 15 g.</td>
</tr>
<tr>
<td>Qu H et al 2015</td>
<td>Buyang Huanwu Tang plus Danggui Sini Tang</td>
<td>Buyang Huanwu (Radix Angelicae Sinensis) 10 g, Huangqi (Ramulus Cinnamomni) 10 g, Dazao (Fructus Jujubae) 5 g, and Gancao (Radix Glycyrrhizae) 15 g.</td>
</tr>
<tr>
<td>Sun GX et al 2010</td>
<td>Buyang Huanwu Tang plus Danggui Sini Tang</td>
<td>Buyang Huanwu (Radix Angelicae Sinensis) 10 g, Yellow (Rhus verniciflua) 9 g, Dazao (Fructus Jujubae) 9 g, and Gancao (Radix Glycyrrhizae) 9 g.</td>
</tr>
<tr>
<td>Wang WD et al 2017</td>
<td>Modified Danggui Sini Tang</td>
<td>Modified Danggui Sini Tang (markedly effective, effective, ineffective) or four (recovery, markedly effective, effective, ineffective) category measurement with different standards according to the degree of overall symptom improvement was used to evaluate treatment effects. None of the trials mentioned whether adverse reactions were monitored. All the reported outcomes</td>
</tr>
<tr>
<td>Ye HD et al 2015</td>
<td>Danggui Sini Tang</td>
<td>Danggui (Radix Angelicae Sinensis) 15 g, Baishao (Radix Paeoniae Alba) 15 g, Xixin (Pheretima Aspergillum) 5 g, Guizhi (Ramulus Cinnamomni) 10 g, Baizhu (Radix Achyranthis Bidentatae) 15 g, Dazao (Fructus Jujubae) 10 g, and Gancao (Radix Glycyrrhizae) 5 g.</td>
</tr>
<tr>
<td>Zhang HQ et al 2013</td>
<td>Jieqiong Tongni Tang</td>
<td>Chaihu (Radix Bupleuri Chinenici) 10 g, Baishao (Radix Paeoniae Alba) 15 g, Zhihi (Fructus Aurantii Immaturi) 10 g, Fuji (Radix Aconiti Lateralis Praeparata) 10 g, and Ganjiang (Rhizoma Zingiberis) 10 g.</td>
</tr>
</tbody>
</table>
were measured at the end of treatment. Only one trial reported follow-up for 6 months after the end of the intervention period. However, there were no reports of whether there was any loss of follow-up and whether intention-to-treat (ITT) analysis was conducted.

**Quality assessment**
The methodological quality of eight RCTs was generally low. One trial used a random number table for randomization; the other seven trials mentioned the use of random methods for grouping but did not report how random sequences were generated. Allocation concealment was not described in any of the trials. None of the trials used blinding of participants and personnel and none reported the method of blinding outcome assessors. None of the trials reported whether there were withdrawals or dropouts, or whether ITT analysis was conducted. None of the eight RCTs had registered protocols, so we could not identify whether there was selective outcome reporting. Using the evaluation method recommended by the Cochrane Collaboration, all trials were classed as showing a high risk of bias (Figure 2).

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<tbody>
<tr>
<td><img src="image-url" alt="Risk of bias graph" /></td>
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</tbody>
</table>

**Frequency of attacks**
No trials reported these.

**Duration of attacks**
No trials reported these.

**Severity scores**
No trials reported these.

**Global symptom improvement**
Danggui Sini Tang: two trials tested the effect of Danggui Sini Tang on global symptom improvement in 138 participants with PRP. Danggui Sini Tang produced greater improvement in global symptoms than nifedipine sustained-release tablets \([RR 1.65, 95\% CI (1.19 to 2.28)]\) in one trial. The combination of Danggui Sini Tang with nifedipine sustained-release tablets also had a favorable effect on global symptoms compared with nifedipine sustained-release tablets alone \([RR 1.57, 95\% CI (1.20 to 2.25)]\) in another trial.

Modified Danggui Sini Tang: two trials tested the effect of modified Danggui Sini Tang on global symptom improvement in 226 participants with PRP. However, the specific compositions of the herbal formulae differed slightly between these two trials. One trial found that modified Danggui Sini Tang produced greater improvement in global symptoms than nifedipine sustained-release tablets \([RR 1.58, 95\% CI (1.19 to 2.10)]\). The other trial showed that a combination of modified Danggui Sini Tang and nifedipine sustained-release tablets also produced greater improvement in global symptoms compared with nifedipine sustained-release tablets alone \([RR 1.18, 95\% CI (1.01 to 1.39)]\).

Buyang Huanwu Tang plus Danggui Sini Tang: two trials tested Buyang Huanwu Tang plus Danggui Sini Tang in 152 participants with PRP. Meta-analysis of these two trials \([RR 1.19, 95\% CI (1.00 to 1.44)]\) showed that Buyang Huanwu Tang plus Danggui Sini Tang produced greater improvement in global symptoms than nifedipine tablets [overall effect \(RR 1.60, 95\% CI (1.29 to 1.99)]\].

Self-composed CHM decoction: one trial tested self-composed CHM decoction in 40 participants with PRP. A combination of self-composed CHM decoction and nifedipine sustained-release tablets produced greater improvement in global symptoms than nifedipine sustained-release tablets alone \([RR 1.64, 95\% CI (1.07 to 2.50)]\).

Jiejing Tongmi Tang: one trial tested Jiejing Tongmi Tang in 120 participants with PRP. A combination of Jiejing Tongmi Tang and cinepazide maleate injection produced greater improvement in global symptoms than cinepazide maleate injection alone [overall effect \(RR 1.60, 95\% CI (1.29 to 1.99)]\) (Figures 3, 4). See for details of global symptom improvement.

**Participant preference scores**
No trials reported these.

**Serious adverse events**
No trials reported these.

**Physiological measurements**
Modified Danggui Sini Tang produced a significantly greater improvement in arterial peak systolic velocity compared with nifedipine sustained-release tablets \([RR
A combination of Jiejing Tongmi Tang and cinepazide maleate injection had a better effect on plasma nitric oxide than cinepazide maleate injection alone \([MD 9.6 \mu mol/L, 95\% CI (4.25 to 14.95)]\) in one trial\(^a\) (120 participants).

There was no significant difference between a combination of Jiejing Tongmi Tang with cinepazide maleate in-
location concealment. Proper randomization is the best method of randomization was conducted properly. Six of the included trials provided insufficient information to estimate whether randomization (using a random number table), but the information provided was insubstantial. Only one trial reported randomization as showing a high risk of bias according to the Cochrane standard. In this review, all the included RCTs were evaluated for the authenticity of the research results. The poor methodology of the included trials had a substantial impact on the validity of the results.

Non-serious adverse events
No trials reported these.

Subgroup analysis
As only one trial reported external use of CHM, and externally applied CHM was combined with oral drugs to treat PRP, it was not possible to conduct subgroup analysis of drug delivery mode.

DISCUSSION
These findings suggest that CHM may have a positive effect on global symptoms, arterial peak systolic velocity, ET-1, and plasma nitric oxide levels in PRP patients. However, owing to the poor methodological quality of the included RCTs, it is not possible to draw a firm conclusion. There is no strong evidence to recommend the use of any CHM for PRP. The poor methodology of the included trials had a substantial impact on the authenticity of the research results. In this review, all the included RCTs were evaluated as showing a high risk of bias according to the Cochrane standard. Only one trial reported randomization (using a random number table), but the information provided was insufficient to estimate whether randomization was conducted properly. Six of the included RCTs did not report a correct method of generating a randomization sequence, and no trials mentioned allocation concealment. Proper randomization is the best way to reduce selection bias. Research indicates that more than 90% of RCT randomization methods are incorrect, and even some efficacy studies use incorrect randomization. Allocation concealment was not mentioned in any of the included trials. Generally, the results of clinical trials that are not adequately randomized or have not identified randomized concealment schemes tend to overstate the effect estimate by 37%, compared with complete randomized clinical trials. None of the included trials performed blinding. Owing to the complex composition and unique smell of CHM, the use of placebo CHM is particularly complicated and makes it difficult to implement blinding in clinical research on TCM. However, the blinding of statisticians and outcome evaluators to trial grouping and interventions can to some extent prevent subjective factors from influencing research results. No trials reported information about withdrawal or loss to follow-up. Withdrawal or loss to follow-up after random grouping can undermine the balance of baselines between two groups. ITT analysis can maximize randomized information. It is not possible to determine the presence of selective reporting of outcomes without prior registration of a trial protocol. The RCT control intervention should be affirmatively valid (positive controls) or definitely invalid (placebo or no treatment). However, our review excluded many trials because of inappropriate comparisons. Lifestyle modification is an effective current measure for improving PRP symptoms and involves changes such as keeping warm, smoking cessation, and education. However, there are no trials examining lifestyle changes as basic treatment or control measures. CCB is the recommended first-line drug treatment for PRP, if lifestyle modification alone has failed. However, this review indicated that in many trials, the efficacy of controlled drugs such as oral prostaglandins is controversial. Prostaglandins have shown some benefits; however, intravenous administration is a drawback. Oral prostaglandins are ineffective in their current form. Therefore, we excluded those studies that were inappropriate comparisons. This meant that only a small number of RCTs were included in the review, which affects the validity of the results.

Table 3 Physiological measurements of effectiveness

<table>
<thead>
<tr>
<th>Item</th>
<th>Study</th>
<th>Control intervention</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial peak-systolic velocity</td>
<td>Wang WD et al 2017</td>
<td>Modified Danshui Sini Tang</td>
<td>Nifedipine Sustained-release tablets</td>
<td>6.18 (3.08, 9.28)</td>
</tr>
<tr>
<td>ET-1</td>
<td>Zhang HQ et al 2013</td>
<td>Jiejing Tongmi Tang + Cinepazide Maleate injection</td>
<td>Cinepazide Maleate injection</td>
<td>-27.40 (−30.79,  −24.01)</td>
</tr>
<tr>
<td>NO</td>
<td>Zhang HQ et al 2013</td>
<td>Jiejing Tongmi Tang + Cinepazide Maleate injection</td>
<td>Cinepazide Maleate injection</td>
<td>9.60 (4.25, 14.95)</td>
</tr>
<tr>
<td>Skin temperature</td>
<td>Zhang HQ et al 2013</td>
<td>Jiejing Tongmi Tang + Cinepazide Maleate injection</td>
<td>Cinepazide Maleate injection</td>
<td>4.40 (−0.06, 8.86)</td>
</tr>
<tr>
<td>Peripheral artery blood stream drawing</td>
<td>Zhang HQ et al 2013</td>
<td>Jiejing Tongmi Tang + Cinepazide Maleate injection</td>
<td>Cinepazide Maleate injection</td>
<td>0.20 (−4.17, 4.57)</td>
</tr>
</tbody>
</table>

Notes: ET-1: endothelin-1; NO: nitric oxide; RR: relative risk; CI: confidence intervals.

jection and cinepazide maleate injection alone \([MD 4.40 \text{ mm}, 95\% CI (−0.06 \text{ to } 8.86)]\) in the effect on skin temperature after cold pressor testing in one trial\(^{14}\) (120 participants).

There was no significant difference between a combination of Jiejing Tongmi Tang with cinepazide maleate injection and cinepazide maleate injection alone \([MD 0.20 \text{ mm}, 95\% CI (−4.17 \text{ to } 4.57)]\) in the effect on peripheral artery blood stream drawing after cold pressor testing in one trial\(^{14}\) (120 participants).

The effects of physiological measurements are shown in Table 3.

Non-serious adverse events
No trials reported these.

Subgroup analysis
As only one trial reported external use of CHM, and externally applied CHM was combined with oral drugs to treat PRP, it was not possible to conduct subgroup analysis of drug delivery mode.

DISCUSSION
These findings suggest that CHM may have a positive effect on global symptoms, arterial peak systolic velocity, ET-1, and plasma nitric oxide levels in PRP patients. However, owing to the poor methodological quality of the included RCTs, it is not possible to draw a firm conclusion. There is no strong evidence to recommend the use of any CHM for PRP. The poor methodology of the included trials had a substantial impact on the authenticity of the research results. In this review, all the included RCTs were evaluated as showing a high risk of bias according to the Cochrane standard. Only one trial reported randomization (using a random number table), but the information provided was insufficient to estimate whether randomization was conducted properly. Six of the included RCTs did not report a correct method of generating a randomization sequence, and no trials mentioned allocation concealment. Proper randomization is the best way to reduce selection bias. Research indicates that more than 90% of RCT randomization methods are incorrect, and even some efficacy studies use incorrect randomization. Allocation concealment was not mentioned in any of the included trials. Generally, the results of clinical trials that are not adequately randomized or have not identified randomized concealment schemes tend to overstate the effect estimate by 37%, compared with complete randomized clinical trials. None of the included trials performed blinding. Owing to the complex composition and unique smell of CHM, the use of placebo CHM is particularly complicated and makes it difficult to implement blinding in clinical research on TCM. However, the blinding of statisticians and outcome evaluators to trial grouping and interventions can to some extent prevent subjective factors from influencing research results. No trials reported information about withdrawal or loss to follow-up. Withdrawal or loss to follow-up after random grouping can undermine the balance of baselines between two groups. ITT analysis can maximize randomized information. It is not possible to determine the presence of selective reporting of outcomes without prior registration of a trial protocol. The RCT control intervention should be affirmatively valid (positive controls) or definitely invalid (placebo or no treatment). However, our review excluded many trials because of inappropriate comparisons. Lifestyle modification is an effective current measure for improving PRP symptoms and involves changes such as keeping warm, smoking cessation, and education. However, there are no trials examining lifestyle changes as basic treatment or control measures. CCB is the recommended first-line drug treatment for PRP, if lifestyle modification alone has failed. However, this review indicated that in many trials, the efficacy of controlled drugs such as oral prostaglandins is controversial. Prostaglandins have shown some benefits; however, intravenous administration is a drawback. Oral prostaglandins are ineffective in their current form. Therefore, we excluded those studies that were inappropriate comparisons. This meant that only a small number of RCTs were included in the review, which affects the validity of the results.
The eight RCTs included all assessed composite outcome indicators of global symptom improvement. We assumed that frequency of attacks, duration of attacks, and participant preference scores are important efficacy indicators, but no trials reported these. The most common drawback of using composite outcome indicators is that it impairs statistical power, which leads to misleading interpretations of the results. This is because the effect of the intervention on each endpoint may be inconsistent; that is, there is a large difference in the incidence of each index or the degree of RR reduction. In addition, no trials reported safety outcomes. Therefore, we cannot definitely conclude that the CHM used here was safe.

In conclusion, owing to weak evidence, we cannot confirm that CHM is effective in treating PRP. Therefore, we cannot provide strong recommendations for the use of CHM in clinical practice. More well-designed studies are required to confirm the potential effectiveness of CHM for treating PRP.

REFERENCES