Sini decoction as an adjuvant therapy for angina pectoris: a systematic review of randomized controlled trials

Wu Jin, Yuan Dongchao, Yang Mingqian, Xia Wei, Zhang Zhe, Zhang Huiyong, Fei Yutong, Yang Guanlin

Abstract

OBJECTIVE: To systematically assess the effects and safety of Sini decoction as an adjuvant therapy for patients with angina pectoris.

METHODS: We searched PubMed, Excerpt Medica Database, the Cochrane library, Wanfang Database, China National Knowledge Infrastructure Database, China Science and Technology Journal Database from the date of its inception until August 1, in 2014. Available literatures were selected according to the inclusion criteria. Two reviewers finished data extraction, checked the data and assessed the methodological quality of studies, independently. The Review Manage Software 5.1.0 was used for data analysis.

RESULTS: Six trials involving 453 participants were eligible. None of the trials reported the mortality due to angina pectoris. The secondary outcomes showed that Sini decoction, together with nitroglycerin when necessary, may have some effects on reducing the number of angina attacks and the amount of nitroglycerin. But in terms of reducing the duration of angina and improvement of electrocardiogram, there were no statistical differences between Sini decoction group and isosorbide dinitrate group. Only one reported that no adverse events were found.

CONCLUSION: Based on this systematic review, Sini decoction can reduce the dosage of nitroglycerin, when compared with isosorbide dinitrate group. And there were no enough evidence in the papers to draw any conclusions for the safety of Sini decoction.

INTRODUCTION

Cardiovascular disease (CVD) and other noninfectious
chronic disease (NCD) has become one of the global concerns, especially in developing countries.\(^1\) CVD is the primary cause of death worldwide. It is estimated that, up to 2030, there will be 23.3 million people dead due to CVD.\(^2\) According to World Health Organization, about 4.23 million people died of Coronary Artery Heart Disease (CHD) every year.\(^3\) The American Heart Association (AHA) study found that the heart attack caused by angina accounted for 18% and it also cost a lot.\(^4\)

Angina pectoris (AP) with the symptoms of intense tightness or heavy pressure in the chest, radiating to the neck, jaw, shoulder, back, arm, and epigastric region can be caused by myocardial ischemia.\(^5\) Nowadays, we usually treated the AP by drugs, intervention therapy and so on. The 2011 updated guidelines of the AHA recommended the following drugs for the secondary prevention in patients with coronary atherosclerosis, which were antiplatelet drugs, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blocker (ARB), aldosterone antagonists and B-Blocker. In addition, risk factors should also be controlled positively such as blood pressure, blood lipids, blood glucose and body weight, as well as combining with cardiac rehabilitation therapy.\(^6\) The Sini decoction is a recipe documented in the On Harm Caused by Cold a medical textbook in Traditional Chinese Medicine (TCM). It was originally used to treat shaoyin diseases in terms of TCM theory. In the 1960s, there were already some literature reporting the treatment of cold limbs with Sini decoction. But most of them were case reports mainly discussing their personal pplication and understanding of Pathogeneity, about 4\(^2\) million people died of Coronary Vascular Disease (CVD) in 2013 and the number of deaths due to CVD will increase to 23\(^2\) million people dead by 2030, there will be 23.3 million people dead due to CVD.\(^2\)

Additionally, citations of relevant systematic reviews were also searched for any potential studies that were missed in the electronic database.\(^7\) A sample retrieval strategy for Pubmed was:

- 1 Search “Sini tang” [Supplementary Concept] (27)
- 3 Search #1 AND #2 (2)
- 4 Search “randomized controlled trial” [Publication Type ] (387312)
- 5 Search “controlled clinical trial” [Publication Type ] (88811)
- 6 Search “randomized controlled trials” [Mesh] (97040)
- 7 Search “random allocation” [Mesh](7)
- 8 Search “double blind method” [Mesh] (16)
- 9 Search “single-blind method” [Mesh] (20112)
- 10 Search #4 OR #5 OR #6 OR #7 OR #8 OR #9
- 11 Search “animals” [Mesh] (1778183)
- 12 Search #10 NOT #1 (2081)
- 13 Search “clinical trial” [Publication Type ] (796197)
- 14 Search “exp clinical trials” (no results)
- 15 Search “clin$ adj25 trial$”. (no results)
- 16 Search ((singl$ OR doubl$ OR trebl$ OR tripl$) adj25 (blind$ OR mask$)) (no results)
- 17 Search “Random allocation” [Mesh] (82467)
- 18 Search “research design” [Mesh] (343867)
- 19 Search #13 OR #14 OR #15 OR #16 OR #17 OR #18 (1027986)
- 20 Search #19 NOT #11 (18833)
- 21 Search #20 NOT #11 (18833)
- 22 Search “comparative study” [Publication Type ] (1691637)
- 23 Search “exp evaluation studies” (no results)
- 24 Search “follow up studies” [Mesh] (16)
- 25 Search “prospective studies” [Mesh] (15)
- 26 Search “control croups” or “volunteers” [Mesh] (12630)
- 27 Search #22 OR #23 OR #24 OR #25 OR #26 (1711379)

**METHODS**

This systematic review had already been registered on PROSPERO (http://www.crd.york.ac.uk/prospero/). And the registration number is: CRD42014015036.

**Search strategy**


The search terms included Fuzi (Radix Aconiti Lateralis Preparata), Ganjiang (Rhizoma Zingiberis), stir-frying with liquid adjuvant Gancao (Radix Glycyrrhizae), Sini, CHD and angina. In the Chinese database, all the terms were used as the key words ("prepared common monkshood daughter root or dried ginger or glycyrrhiza or Sini decoction" and "CHD or angina"). In the English database, the search terms included "Sini decoction or Sini tang" as a MeSH term, and then "CHD or angina or AP" for a second retrieval. Studies published in both English and Chinese were retrieved. Additionally, citations of relevant systematic reviews were also searched for any potential studies that were missed in the electronic database.\(^8\) Sample retrieval strategy for Pubmed was:

- #1 Search "Sini tang" [Supplementary Concept] (27)
- #2 Search “angina pectoris” [Mesh] or “angina stable” [Mesh] or “angina unstable” [Mesh] (47554)
- #3 Search #1 AND #2 (2)
- #4 Search “randomized controlled trial” [Publication Type ] (387312)
- #5 Search “controlled clinical trial” [Publication Type ] (88811)
- #6 Search “randomized controlled trials” [Mesh] (97040)
- #7 Search “random allocation” [Mesh](7)
- #8 Search “double blind method” [Mesh] (16)
- #9 Search “single-blind method” [Mesh] (20112)
- #10 Search #4 OR #5 OR #6 OR #7 OR #8 OR #9
- #11 Search “animals” [Mesh] (1778183)
- #12 Search #10 NOT #1 (2081)
- #13 Search “clinical trial” [Publication Type ] (796197)
- #14 Search “exp clinical trials” (no results)
- #15 Search “clin$ adj25 trial$”. (no results)
- #16 Search ((singl$ OR doubl$ OR trebl$ OR tripl$) adj25 (blind$ OR mask$)) (no results)
- #17 Search “Random allocation” [Mesh] (82467)
- #18 Search “research design” [Mesh] (343867)
- #19 Search #13 OR #14 OR #15 OR #16 OR #17 OR #18 (1027986)
- #20 Search #19 NOT #11 (18833)
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- #22 Search “comparative study” [Publication Type ] (1691637)
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- #24 Search “follow up studies” [Mesh] (16)
- #25 Search “prospective studies” [Mesh] (15)
- #26 Search “control croups” or “volunteers” [Mesh] (12630)
- #27 Search #22 OR #23 OR #24 OR #25 OR #26 (1711379)
Eligibility criteria
Types of studies: two reviewers independently selected available randomized controlled trials (RCTs), regardless of blinding methods, types of publication and languages.

Types of participants
AP with the symptoms of intense tightness or heavy pressure in the chest, radiating to the neck, jaw, shoulder, back, arm and epigastric region can be caused by myocardial ischemia. Those participants were already diagnosed as AP, according to the nationally or internationally recognized diagnostic criteria. If traditional Chinese syndromes were diagnosed, they also should have the nationally established diagnostic criteria.

Types of interventions
The interventions of test group included Sini decoction only or Sini decoction together with basic western medicine treatment. The preparation form of Sini decoction had no limitation, such as decoction, capsules and so on. Moreover, the control group could choose western medicine treatment, including basic therapy, positive drug and placebo. The duration of the treatment should be more than 2 weeks.

Types of comparisons
The comparisons test group included Sini decoction only or Sini decoction together with basic western medicine treatment. Moreover, the control group could choose western medicine treatment, including basic therapy, positive drug and placebo.

Types of outcomes
The outcomes were as follows: (a) The primary outcome was fatality. (b) The secondary outcomes contained number of angina attacks, duration of angina attacks, dosage of nitroglycerin, angina symptoms changes, improvements of ECG and adverse events. However, the following studies would be excluded. (a) Those were repeated literatures. (b) Those had incomplete data, when we couldn’t contact the authors or still couldn’t gain the data information even after contacting the authors. (c) TCM preparations were used to control group.

Study selection
Two reviewers independently screened the titles and abstracts of each searched article for potentially eligible studies. And then the full texts were screened for the second time. Disagreement was solved by discussion or the third person.

Data collection and extraction
RCTs evaluating the effects and safety of Sini decoction as an adjuvant therapy for patients with AP were included. Titles and abstracts of searched studies were firstly screened. Then, those possibly eligible were determined eligible by reviewing full text. The inclusion criteria were applied by two authors independently. Any disagreements were resolved by referring to the original article and by discussion.

Data were collected independently by two authors in a data extraction form, using Microsoft excel 2003. The following characteristics of the trials were recorded on the extraction form: study (author, year), sample size, gender, age, characteristics of participants, intervention of control group and treat group, duration, baseline, outcome measure, completion rates and indicators of acceptability to users. Disagreements were resolved by reviewing the original paper and by consultation. If there were any important missing data, the authors would be contacted by email or phone whenever possible. The articles which finally still had missing data should be excluded.

Three reviewers independently extracted the data from eligible studies, using Microsoft excel 2003 to conduct extraction forms. Reviewers extracted the following data: study (author, year), sample size, gender, age, characteristics of participants, intervention of control group and treat group, duration, baseline, outcome measure, completion rates and indicators of acceptability to users. If there were any important missing data, the authors would be contacted by email or phone whenever possible. The articles which finally still had missing data should be excluded.

Risk of bias
Two reviewers independently assessed the risk of bias for each article, according to the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0. The items included the random sequence generation, allocation concealment, blinding of participants and personnel, the blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias (selection bias, non-responder bias, information bias, language bias and multiple publication bias). In this study, language bias and multiple publication bias may exist. Disagreements were resolved by discussion and adjudicated by a third reviewer when necessary.

Data analysis
Data were analyzed with the RevMan software (version 5.1.0, RevMan software, London, England) from The Cochrane Collaboration. Dichotomous data were presented as risk difference (RD), such as improvements of ECG. While continuous data were presented as mean difference (MD), such as the number of angina attacks, duration of angina attacks, dosage of nitroglycerin. Both dichotomous data and continuous data used 95% confidence intervals (CI). And I-squared square measures the heterogeneity. When $I^2 \leq 30\%$, the heteroge-
neity might not be important. When $30\% < I^2 < 60\%$, the heterogeneity might be moderate. When $75\% < I^2 < 100\%$, the heterogeneity might be considerable.\textsuperscript{20} If $I^2 \leq 30\%$, we assessed the data by fixed effect analysis. On the other side, if $30\% < I^2 < 75\%$, we chose the random effect analysis. Besides, publication bias was assessed by the funnel plot, if there were sufficient studies ($n > 10$).\textsuperscript{41} If $P < 0.05$, the differences of the efficacy between interventions were considered statistically significant. The forest plots present the results of hypothesis testing.

**RESULTS**

**Search flow**

According to our initial search, 708 citations were identified in the five databases, in which 223 from the Wanfang Database, 242 from VIP, 139 from CNKI, 0 from PubMed, 0 from the Cochrane library, and 89 were searched from EMBase. Totally 340 citations were primarily selected after excluded the 368 repeated ones. Additionally, 7 relevant systematic reviews totally included 132 RCTs, in which 10 RCTs were related to Sini decoction and 122 RCTs were related to AP. By reading titles and abstracts, we excluded 413 articles due to animal experiments, not Sini decoction and not AP. A total of 37 articles went to the next round of assessment. 5 studies with abstracts were excluded, when there was no response after contacting the authors or still couldn’t gain the data information even after contacting the authors. As for the full text screening, 31 articles were excluded because of not meeting the inclusion criteria. In total, 6 randomized clinical trials were eligible and were conducted the Meta-analysis (Figure 1).\textsuperscript{35-40}

**Characteristics of the trials included**

The main data of 6 trials were summarized in Table 1. The age of 453 participants ranged from 44 to 81 years.

![Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of literature retrieval and selection](https://example.com/figure1)

Electronic databases:
- CNKI ($n = 139$)
- Wanfang ($n = 223$)
- VIP ($n = 242$)
- Cochrane Library ($n = 0$)
- PubMed ($n = 0$)
- EMBASE ($n = 89$)

Supplementary search:
- Related to sini decoction ($n = 10$)
- Related to angina ($n = 122$)

Total ($n = 825$)

375 of records after duplicates removed

450 of records screened

37 of full-text articles assessed for eligibility

6 of studies included in qualitative synthesis

6 of studies included in quantitative synthesis (Meta-analysis)

413 of records excluded:
- Animal experiments ($n = 100$)
- Unrelated to sini decoction ($n = 145$)
- Unrelated to angina pectoris ($n = 168$)

31 of full-text articles excluded, with reasons:
- Non-RCT ($n = 14$)
- Not full text ($n = 5$)
- Not meet the inclusion criteria ($n = 7$)
- Poorly design ($n = 5$)
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (TG/CG)</th>
<th>Gender (M/F)</th>
<th>Age (years)</th>
<th>Characteristics of participants</th>
<th>Intervention</th>
<th>Duration (days)</th>
<th>Baseline</th>
<th>Outcome measure</th>
<th>Adverse events</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qin J et al 2001</td>
<td>22/23</td>
<td>27/41</td>
<td>45-72</td>
<td>AP, TCMS: blood stasis-S, Qi stagnation-S, cold coagulation-S, phlegm-S, Qi deficiency-S, Yan deficiency-S</td>
<td>WMG ① ID 10 mg (3 times/d), Nitroglyceride when necessary</td>
<td>14</td>
<td>NC</td>
<td>Number of angina attacks, duration of pain, dosage of nitroglycerin, CO, IVET, PEP/LVET, changes of ATP enzyme on erythrocyte membrane, improvement of ECG</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Hu R et al 2004</td>
<td>51/51</td>
<td>44/58</td>
<td>48-79</td>
<td>CHD, TCMS: NM, Criteria: DC is M (recommendation used by the first session of National Medical Council in 1980, whose standards made by the World Health Organization in 1979), CSD is NM</td>
<td>WMG ① ID 10 mg (3 times/d), Nifedipine 10 mg (twice/d), Enteric-coated aspirin tablets 25 mg (once/d) ② Nitroglycerine when necessary</td>
<td>14</td>
<td>C</td>
<td>SV, CO, CI, EF, TC, TG, HDLC, LDLC, improvement of ECG</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Study</td>
<td>Sample size (TG/CG)</td>
<td>Gender (M/F)</td>
<td>Age (years)</td>
<td>Characteristics of participants</td>
<td>Intervention</td>
<td>Duration (days)</td>
<td>Baseline</td>
<td>Outcome measure</td>
<td>Adverse events</td>
<td>Follow-up</td>
</tr>
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<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
</tbody>
</table>
| Jin MH et al 2004 | 117/35             | 103/81       | 46-70       | - Stable AP  
- TCMS: Yang deficiency syndrome or Cold coagulation Syndrome  
- Criteria: DC is M (DC is developed by the World Health Organization), CSD is M (Heart Disease Diagnostic Criteria about TCM) | -WMG  
① ID 10 mg (3 times/d)  
② Nitroglyceride when necessary | 14   | NC       | Number of angina attacks, duration of pain, dosage of nitroglycerin; heart rate, blood pressure, oxygen consumption of myocardial, CO, LVEE, PE/LVET | During treatment, no liver and kidney damage and other adverse reactions. | NM         |
| Wang JF et al 1997 | 15/15              | 17/13        | 44-65       | - CHD  
- TCMS: NM  
- Criteria: DC is M (recommendation used by the first session of National Medical Council in 1980), CSD is NM | -WMG  
① ID 10 mg (3 times/d)  
② Nitroglyceride when necessary | 14   | NC       | Number of angina attacks, duration of pain, ST segment changes of ECG, MDA, SOD, CO, LVEDW, LVEF | NM               | NM        |
| Qin J et al 2004 | 29/30              | 51/37        | 43-81       | - Stable AP  
- TCMS: Yang-deficiency syndrome or Cold coagulation Syndrome  
- Criteria: DC is M (DC is developed by the World Health Organization), CSD is M (Heart Disease Diagnostic Criteria about TCM) | -WMG  
① ID 10 mg (3 times/d)  
② Nitroglyceride when necessary | 14   | NC       | Improvement of ECG, quality of life (somatic symptoms, healthy pleasure, level of depression) | NM               | NM        |
### Table 1: Summary of eligible RCTs of sini decoction for angina pectoris (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (TG/CG)</th>
<th>Gender (M/F)</th>
<th>Age (years)</th>
<th>Characteristics of participants</th>
<th>Intervention</th>
<th>Duration (d)</th>
<th>Baseline</th>
<th>Outcome measure</th>
<th>Adverse events</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liang et al. 2005</td>
<td>35/30</td>
<td>38/27</td>
<td>45-70</td>
<td></td>
<td>-AP -TCM: Yang deficiency syndrome or Cold coagulation Syndrome</td>
<td>-WMG</td>
<td>14</td>
<td>NC</td>
<td>Number of angina attacks</td>
<td>NM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-CMG ① ID 10 mg (3 times/d) ② Nitroglyceride when necessary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: RCT: randomized controlled trials; AP: angina pectoris; TG: treat group; CG: control group; M: male; F: female; DC: diagnostic criteria; CHD: coronary artery disease; SD: syndrome differentiation; CSD: the principle of Syndrome Differentiation; TCMS: Traditional Chinese Medicine syndrome; ID: isosorbide dinitrate; NC: not comparable; C: comparable; NM: not mentioned; M: mentioned; CMG: Chinese medicine group; WMG: Western Medicine group; ICWMG: integrated Chinese and Western Medicine group; CO: cardiac output; LVEF: the left ventricular ejection fraction; PEP/LVET: ratio of pre-ejection period to left ventricular ejection time; ATP: adenosine triphosphate; ECG: electrocardiograph; SV: stroke volume; CI: confidence interval; EF: Ejection fraction; TC: total cholesterol; TG: triglyceride; HDLC: high density lipoprotein; LDLLC: low density lipoprotein cholesterol; MDA: malondialdehyde; SOD: determination of serum superoxide dismutase; LVEDV: left ventricular end diastolic volume. Syndrome differentiation: if there is blood stasis, plus Danggui (Radix Angelicae Sinensis), Chaihu (Asari Radix et Rhizoma), Xixin (Radix bupleuri), Xiangfu (Ramulus Cinnamomi), etc. If there is Qi deficiency, plus Dangshen (Radix Codonopitri), Huangqi (Radix Astragalii Mongolic), etc. If there is phlegm, plus Gualou (Fructus et Semen Trichosanthis Kirilowii), yinyanghuo (Gelatinum Cornu Cervi), etc. If there is heat, plus Banxia (Fructus et Semen Lani), Luzao (Fructus et Semem Rehmannia), etc. If there is coagulated cold syndrome. All the included trials was evaluated by the Cochrane's method. All trials had established criteria. The completion rates of all trials are 100%. As to the indication of acceptability to users, not a trial mentioned. The sample size ranged from 40 to 152 and eligible RCTs. The mean age was all 14 days and the follow-up period were all 4 months. The other RCT compared addition of Sini decoction and isosorbide dinitrate in addition. Differences in RCTs had been diagnosed either Yang deficiency or congestive cold syndrome or in which 57% were female and 43% male.
Table 2 Assessment of risk of bias in eligible trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding participants</th>
<th>Blinding outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qin J et al 2001</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Hu R et al 2004</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Jin MH et al 2004</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Wang YM et al 1997</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Lang YM et al 2005</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Qin J et al 2004</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Figure 2 Risk of bias graph
As for random sequence generation, 1 in 6 trials was at low risk of bias. None reported allocation concealment, blinding outcome assessment, incomplete outcome data and other bias. As for selective reporting, 1 in 6 trials was at high risk of bias. As for selective reporting, all the trials were at high risk of bias.

Duration of angina attacks
Duration of angina attacks was reported in 4 trials. The 4 trials have similar interventions, thus they have clinical homogeneity. Due to the moderate statistical heterogeneity, and the data were analyzed by the fixed effect \( (\chi^2 = 3.38, \text{df} = 3, P = 0.34, I^2 = 11\%) \). In Comparison with isosorbide dinitrate, the meta-analysis showed no significance of angina attacks’ duration in Sini decoction \( [P = 0.36, MD = 0.15, 95\% CI ( - 0.17, 0.48)] \) (Figure 5).

Dosage of nitroglycerin
Dosage of nitroglycerin was reported in 3 trials. The 3 trials have similar interventions, thus they have clinical homogeneity. Due to the moderate statistical heterogeneity, and the data were analyzed by the fixed effect \( (\chi^2 = 1.04, \text{df} = 2, P = 0.59, I^2 = 0\%) \). According to the meta-analysis, the dosage of nitroglycerin in Sini decoction group was less than isosorbide dinitrate group, and there were significant difference between them \([P = 0.0008, MD = -0.54, 95\% CI (-0.85, 0.22)]\) (Figure 6).

Improvements of ECG
Improvements of ECG was reported in 6 trials. Different from other interventions, 1 trial compared Sini decoction together with Western Medicine with Western Medicine, whose effective ratio were 60.78% and 58.82%. However, there were no statistical difference between the two groups \((P > 0.05)\). 1 trial used ischemic ST-segment changes to evaluate the ECG improvement, which indicated both Sini decoction and isosorbide dinitrate, both together with nitroglycerin, could restore ischemic ST-segment \((P < 0.01)\). And the difference between two groups was not statistically significant.
The 4 trials have similar interventions, thus they have clinical homogeneity. Due to the moderate statistical heterogeneity, and the data were analyzed by the fixed effect by using the number of effective cases ($\chi^2 = 0.05, df = 3, P = 1.00, I^2 = 0\%$). According to the meta-analysis, there was no significant difference between Sini decoction and isosorbide dinitrate on improving the ECG [$P = 0.88, RD = -0.01, 95\% CI (-0.12, 0.10)] (Figure 7).

**Adverse events**

Only 1 trial mentioned there were no adverse events like liver or kidney damage, whereas the other 5 trials were lack of description of adverse events.

**DISCUSSION**

The results of this study suggest that Sini decoction may have some effects on reducing the dosage of nitroglycerin. However, there was no statistical difference between the Sini decoction group and isosorbide dinitrate group on reducing the number of angina attack, duration and ECG improvement. In addition, none of the six included literatures reported mortality, only one of them reported no adverse events, and the remaining five did not report adverse events.
Based on this systematic review, Sini decoction can reduce the dosage of nitroglycerin, when compared with isosorbide dinitrate group. There were no enough evidence to make conclusion for its safety. Thus, further rigorous and well-reported RCTs which can reflect the only effects of Sini decoction are still warranted. The main limitations are:

- Search flow: the search strategy of this study is not complete enough. The electronic databases did not include English databases and other language database and gray literature (such as meetings, seminars, etc.). Therefore, such kinds of data missing may lead to publication bias.
- The methodological quality: quality of literature retrieved was generally low in this study. Most studies only mentioned "randomization", one of the studies mentioned the random list; none mentioned the concealment of the allocation; none mentioned blinding; none reported withdraws or lost to follow-up, and there is selective reporting. In addition, only one study mentioned the baseline comparable.

Selection of subjects: four studies selected internationally recognized World Health Organization diagnostic criteria for AP; two other studies used the diagnostic criteria in the 1980 National Medical Conference "recommendation on CHD naming and diagnostic criteria" and "clinical research guidelines about medicine in cardiovascular system, from cardiovascular system of the Ministry of Health of Pharmacy and Pharmacology Base". No one explicated the types of AP. The three studies indicated the TCM syndrome differentiation, all related to the domestic standard which were diagnosed Yang deficiency or cold coagulation syndromes. They may affect the results of this study.

(c) Sample size: sample size of included studies is generally small, ranging from 30 to 152 cases. And only 453 participants were included in this study. The small sample size may impact the results of the meta-analysis.

(d) Heterogeneity: statistical heterogeneity can be found on such outcomes as number of angina attacks. The possible reasons are as follows: although all the trials have the inclusion criteria for AP, but those inclusion criteria are different; the component of Sini decoction in test groups are not totally the same. According to different syndromes, the dosage or type of several Traditional Chinese Medicine may be changed a bit, which may increase the statistical heterogeneity; the differences in manufacturer factory or quality standard of isosorbide dinitrate may also lead to heterogeneity.

Currently, we still lack rigorous multi-center, randomized controlled trials of TCM. And most literatures about TCM were of low quality. The report should imitate the international standard CONSORT format. In addition, TCM mostly met the problem about identification symptom patterns in terms of TCM theory. It is necessary to establish a unified specifications and standard for TCM symptom patterns to facilitate further trials to evaluate effects of TCM treatments based on symptom patterns.

In conclusion, according to this systematic review, Sini decoction can reduce the dosage of nitroglycerin, when compared with isosorbide dinitrate group. Moreover, Sini decoction wasn’t better than isosorbide dinitrate on reducing the number of angina attack, duration and ECG improvements. There were no enough evidence to make conclusion for the safety of Sini decoction due to the low methodological quality of the trials collected and lack of the important outcome indicators and adverse events documented.

Although the limited evidence indicated that Sini decoction together with nitroglycerin could reduce the dosage of nitroglycerin, it didn’t prove only Sini decoction was more effective than isosorbide dinitrate on the treatment of AP. According to Meta-analysis, Sini decoction wasn’t better than isosorbide dinitrate in terms of the number of angina attack, duration and ECG improvements.

ACKNOWLEDGEMENTS

Thanks every teacher to the staff in Beijing evidence-based center in University of TCM, including teacher Liu JP, teacher Cao HJ, teacher Xing JM, for he help and suggestions during the whole process. Thanks Tianshi Wu, Na Zhao and Yixin Ma for revising this manuscript. We also thank Grace Deborah kimuli for improving the beauty of the language.

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