Gualoupi (*Pericarpium Trichosanthis*) injection in combination with conventional therapy for the treatment of angina pectoris: a Meta-analysis

Zhu Yao, Xia Wei, Liu Weiwei, Xu Chongbai, Gu Ning

**Abstract**

**OBJECTIVE:** To use a Meta-analysis to review the efficacy and safety of Gualoupi (*Pericarpium Trichosanthis*) injection (PTI) in the treatment of angina pectoris.

**METHODS:** We searched the available literature up to January 2015 using Chinese National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), the Wanfang database, PubMed and other English language databases to identify randomized controlled trials of PTI for the treatment of angina pectoris. Two reviewers independently retrieved and extracted the information. Software Review Manager 5.3 was used for statistics analysis.

**RESULTS:** Fourteen studies involving 1621 patients were identified. Compared with conventional therapy alone or conventional therapy plus other Traditional Chinese Injections (TCMIs), PTI plus conventional therapy significantly improved clinical efficacy [odds ratio (OR) = 3.56, 95% confidence interval (CI) (2.65, 4.77)] (based on 14 studies), electrocardiograph efficacy [OR = 3.20, 95% CI (2.26, 4.51)] (based on 7 studies), and efficacy for Traditional Chinese Medicine Syndromes [OR = 3.13, 95% CI (1.43, 6.89)] (based on 3 studies). Moreover, compared with conventional therapy alone or conventional therapy plus other TCMIs, PTI plus conventional therapy significantly decreased the levels of plasma viscosity [mean difference (MD) = −0.47, 95% CI (−0.76, −0.17)] (based on 3 studies), and plasma low-density lipoprotein [MD = −0.94, 95% CI (−1.57, −0.30)] (based on 3 studies). Eleven studies reported some mild adverse reactions, and no serious adverse drug reactions were observed.

**CONCLUSION:** PTI was found to be effective and safe for the treatment of angina pectoris. This study had certain limitations; thus, more rigorously designed, multi-center, randomized controlled trials in larger populations should be performed to support this observation.

**Key words:** *Pericarpium Trichosanthis; Angina pectoris; Treatment outcome; Safety; Meta-analysis**

*INTRODUCTION*

Angina pectoris is a clinical syndrome caused by coro-
nary artery insufficiency, resulting in acute, transient myocardial ischemia and hypoxia. The main symptom of angina is paroxysmal precordial crushing pain, which is often located behind the sternum and may radiate to the left arm. Exertion, agitation, and cold air can precipitate angina pectoris, although a short period of rest or administration of nitrates can provide rapid relief. Angina pectoris can be divided into several types, usually according to the World Health Organization (WHO) classification and Braunwald classification. WHO classification divides angina pectoris into three types: angina pectoris of effort, angina pectoris at rest, and mixed type angina pectoris. According to Braunwald classification, the classifications are stable angina pectoris, unstable angina pectoris, and variant angina pectoris. In recent years, the incidence of angina pectoris has increased in China in line with improving living standards. Given that angina pectoris can lead to sudden death and myocardial infarction, it is considered a serious health threat. Currently, the main therapy for angina pectoris includes the administration of nitrates, anti-coagulants, antiplatelet agents, calcium channel blockers, β-blockers, ACEI, ARB and lipid-lowering drugs, as well as Traditional Chinese Medicine. Gualoupi (Pericarpium Trichosanthis) injection (PTI) is the extracted liquid of Gualoupi (Pericarpium Trichosanthis), a Traditional Chinese Medicine (TCM), can regulate Qi, open the airways and reduce phlegm, and dissipate blood stagnation. Recent pharmacological studies have shown that Gualoupi (Pericarpium Trichosanthis) can regulate lipid metabolism, exert antiatherosclerotic effects, and protect the vascular endothelium. It has also been reported to protect against ischemia reperfusion injury, hypoxia, and calcium antagonism. PTI has in recent years become widely used for treating angina pectoris, with several clinical trials confirming its efficacy and safety. In this study, we performed an analysis of multiple independent clinical randomized controlled trials (RCTs) to systematically review the efficacy of PTI combined with conventional therapy in the treatment of angina pectoris.

MATERIALS AND METHODS

Inclusion criteria
Type of study: RCTs, whether blinded or using allocation concealment, were included. The numbers of participants in test groups and control groups was required to be greater than 10. The publishing language was not restricted, and selected cases were without severe organic disease or complications. Objective of study: patients must have had a clinical diagnosis of angina pectoris, and clear diagnostic criteria must be referred to in the paper. There were no restrictions on patient age, sex or race. Test and control groups should be comparable. Interventions: the test group must include PTI, administered according to conventional protocols. The starting time, dosage, and treatment duration were not restricted. Control groups were permitted to use conventional treatment such as nitrates, aspirin, calcium antagonist (verapamil), β-blockers (metoprolol sustained-release tablets), angiotensin receptor blocker (ARB), angiotensin converting enzyme inhibitors (ACEI), and statins. Some other Traditional Chinese Injections (TCMIs), such as yiqi fumai injection (freeze-dried) (YFI), breviscapine injection (BI), salvia injection (freeze-dried) (SI), danhong injection (DHI), compound danshen injection (CDI), and danshen injection (DI) were also permitted to use in control groups. PTI was not permitted to use in control groups. Clinical criteria: clear clinical criteria should be referred to in the paper. Outcome measures: the outcome measures should include at least one out of clinical efficacy, electrocardiograph (ECG) efficacy, hemorheology (plasma viscosity), serum lipid [low-density lipoprotein (LDL) cholesterol], and efficacy for Traditional Chinese Medicine Syndromes (TCMS) (phlegm and static blood binding).

Exclusion criteria
Simple descriptive studies and duplicate publications were excluded from the analysis, as were studies in which not all subjects had been diagnosed with angina pectoris. Non-therapeutic clinical research, animal experiments and research on tissues and cells were also excluded, as were review articles and theoretical discussions. Studies in which patients had other serious organic diseases were not permitted.

Document retrieval
The following online databases were screened, up to January 2015: Chinese Scientific Journal Database (VIP), the China National Knowledge Infrastructure (CNKI), the Wanfang database, PubMed and other English language databases. We also performed manual screening of relevant literature. To increase the detection rate, we also reviewed the references of searched literature and included related research where applicable. Search terms included "Pericarpium trichosanthis injection", "PTI", "Gualoupi", "Gualoupi injection", "Gualoupi Zhusheyue", "angina pectoris", "coronary artery disease", "coronary heart disease", "Xinjuantong", "Guaxinbing", "randomized controlled trial", "controlled clinical trial", "randomized", "Suiji Duizhao Shiyan", "Duizhao Linchuang Shiyan", and "Suiji". The search strategy was presented as follows: Search strategies used for PubMed and other English language databases were as follows: #1: Pericarpium trichosanthis injection [MeSH Terms] OR PTI [Title/Abstract] OR Gua lou pi [Title/Abstract] OR Gua lou pi injection [Title/Abstract] #2: Angina pectoris [MeSH Terms] OR Coronary ar-
terapy disease [MeSH Terms] OR coronary heart disease [MeSH Terms]

#3: Randomized controlled trial [Title/Abstract] OR Controlled clinical trial [Title/Abstract] OR Randomized [Title/Abstract]

#4: #1 AND #2 AND #3

Search strategies used for CNKI and other Chinese language databases were as follows (search terms were used as free-text terms and translated into Chinese):

#1: Gua lou pi zhu she ye [MeSH Terms] OR Gua lou pi [Title/Abstract]

#2: Xinjiaotong [MeSH Terms] OR Guanxinxing [MeSH Terms]

#3: Suiji Duizhao Shiyan [Title/Abstract] OR Dui zhao lin chuang shi yan [Title/Abstract] OR Suiji [Title/Abstract]

#4: #1 AND #2 AND #3

Data extraction and assessment of methodological quality

Two reviewers screened for qualified literature according to the inclusion criteria, and performed data extraction on the selected material. The information extracted included general details (e.g., title, author, and year of publication), methodological quality (random sequence generation, allocation concealment, or blinding), subjects (diagnostic criteria, inclusion criteria, and baseline data comparability), intervention study (drug name, dosage, route of administration, and treatment duration), outcome indicator (e.g., clinical efficacy or ECG efficacy). A cross-check was then conducted, and any disagreement was resolved through discussion or third-party opinion.

Two reviewers independently assessed the methodological quality of the included trials according to the Cochrane risk of bias tool, which addresses random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. For each item, three levels were defined: low, unclear, and high risk of bias.

Data analysis

We used Revman 5.3 software provided by the Cochrane Collaboration for data analysis. For count data, odds ratio (OR) was used with a confidence interval (CI) of 95%. For measurement data, mean difference (MD) was used, also with a CI of 95%. We used Chi-square-based Q tests and the $I^2$ statistic to assess heterogeneity levels. A $P$ value greater than 0.10 indicated no significant heterogeneity. We defined high, moderate, and low $I^2$ levels as 75%, 50%, and 25%, respectively. We defined a two-tailed $P$-value of 0.05 as statistically significant. We used a fixed-effects model to estimate the results when there was no or low heterogeneity and a random-effects model when heterogeneity was moderate or high. Where some degree of clinical and methodological heterogeneity was observed, a subgroup analysis was first performed. However, if heterogeneity remained, random effects model analysis was used. Furthermore, funnel plots were constructed to analyze potential publication bias, the stability of the results were evaluated using sensitivity analysis.

RESULTS

Search results

We retrieved 152 articles from five databases using search terms. Using manual screening, no relevant information was identified. After excluding irrelevant or duplicate studies, we selected 16 papers for further assessment. Following review of the full texts, a further two studies that did not meet the inclusion criteria (outcome measures) were excluded. Finally, 14 RCTs involving 1621 patients were selected for analysis. The study selection process is illustrated by a flow diagram in Figure 1.

Characteristics of selected studies

Of the 1621 patients included in the 14 RCTs, 843 were in test groups while 745 were in control groups. The average age of patients ranged from 45 to 75 years. All patients were diagnosed as having angina pectoris for periods of time ranging from 2 to 15 years. The control groups had received valid conventional treatment as well as TCMIs such as danshen and dan-hong injections, while test groups had received PTI, also based on a conventional treatment schedule. PTI doses ranged from 8 to 12 mL, administered intravenously once per day over a course of 14-15 d [with the exception of Xie YX which used 7-10 d]. The characteristics and intervention details of the included studies are summarized in Tables 1 and 2.

Quality assessment

Study quality was evaluated using the Cochrane risk of bias tool. As shown in Figures 2 and 3, the methodological quality of the 14 included studies was poor. Although all included trials were RCTs, only two studies described the methods used to generate the random sequence (random digits table and lottery) and none described the allocation concealment procedure. Only one study described its blinding method (double blinding). No studies reported incomplete results, however, and two studies appeared to feature selective reporting.

Clinical efficacy

Among the 14 studies included in this analysis, 1621 patients had participated (843 in test groups and 778 in control groups). The test for heterogeneity was not significant ($P = 0.49$, $I^2 = 0%$), so the fixed mode was chosen for analysis. Results suggested that PTI combined with conventional therapy was more effective than conventional therapy alone or with other drugs. As shown in Figure 4, the difference was significant between the two groups ($OR = 3.56$, 95% CI (2.65,
Records identified through database searching (n = 152); PubMed, Cochrane library; EMBASE (n = 0); Cnki (n = 122); Wanfang (n = 13); VIP (n = 17)

Additional records identified through other sources (n = 0)

Total (n = 152)

Exclude (n = 136)

Duplicated (n = 27)

Irrelevant, animals study, reviews (n = 109)

Full-text articles assessed for eligibility (n = 16)

Exclude (n = 2)

Did not meet the inclusion criteria (Unsuitable outcome measures, n = 2)

Studies included in Meta-analysis (n = 14)

Figure 1 Flow chart of literature search
EMBASE: Excerpt Medica Database; VIP: China Science and Technology Journal Database.

Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number (T/C)</th>
<th>T/C (M vs F)</th>
<th>Age (T/C) (years)</th>
<th>Course of disease (T/C)</th>
<th>Outcome measures</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang M 20111</td>
<td>50/50</td>
<td>20/30 vs 24/26</td>
<td>56.7±8.66/58.4±10.16</td>
<td>Unclear</td>
<td>(1) (2) (3) (7)</td>
<td>None</td>
</tr>
<tr>
<td>Liu L 20144</td>
<td>59/56</td>
<td>39/20 vs 32/24</td>
<td>62.3±8.3/64.2±10.7</td>
<td>Unclear</td>
<td>(1) (2) (4) (5)</td>
<td>Yes</td>
</tr>
<tr>
<td>Sun J 20122</td>
<td>119/111</td>
<td>Unclear</td>
<td>40.7</td>
<td>Unclear</td>
<td>(1) (6)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Jiang D 20135</td>
<td>20/20</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>(1) (4) (7)</td>
<td>None</td>
</tr>
<tr>
<td>Fu Q 20111</td>
<td>48/46</td>
<td>29/26 vs 19/20</td>
<td>60.5±7.78/62.5±7.23</td>
<td>Unclear</td>
<td>(1) (8)</td>
<td>None</td>
</tr>
<tr>
<td>Song HY 20094</td>
<td>54/48</td>
<td>28/25 vs 26/23</td>
<td>60.3±4.41/59.8±9.63</td>
<td>Unclear</td>
<td>(1) (6) (9)</td>
<td>None</td>
</tr>
<tr>
<td>Mo ZM 20055</td>
<td>93/93</td>
<td>51/48 vs 42/45</td>
<td>63.4±4.27/62.1±5.2</td>
<td>11.3±3.2/8.8±2.6</td>
<td>(1) (6) (9)</td>
<td>None</td>
</tr>
<tr>
<td>Zhao RZ 20106</td>
<td>117/109</td>
<td>79/61 vs 38/48</td>
<td>60.5±6.7/61.4±5.8</td>
<td>Unclear</td>
<td>(1) (3) (5) (6)</td>
<td>Yes</td>
</tr>
<tr>
<td>Zheng WX 20087</td>
<td>73/35</td>
<td>39/22 vs 34/13</td>
<td>56.3±9.4/54.8±9.6</td>
<td>6.4±1.0/6.5±1.2</td>
<td>(1) (2)</td>
<td>Yes</td>
</tr>
<tr>
<td>Gao QZ 20058</td>
<td>60/60</td>
<td>28/25 vs 32/35</td>
<td>55.2±12.4/55.21±11.4</td>
<td>Unclear</td>
<td>(1) (2) (3) (7)</td>
<td>None</td>
</tr>
<tr>
<td>Liu Y 20139</td>
<td>30/30</td>
<td>16/18 vs 14/12</td>
<td>61.3±6.5/62.4±7.21</td>
<td>Unclear</td>
<td>(1) (2)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Xu XJ 201410</td>
<td>40/40</td>
<td>24/22 vs 16/18</td>
<td>70.5±4.2/69.5±3.25</td>
<td>5.15±2.83/5.19±2.87</td>
<td>(1) (2)</td>
<td>None</td>
</tr>
<tr>
<td>Xie YX 201411</td>
<td>30/30</td>
<td>19/20 vs 11/10</td>
<td>60.1±9.3/57.9±8.84</td>
<td>9.53±7.85/9.13±6.68</td>
<td>(1) (4)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Huang XB 201412</td>
<td>50/50</td>
<td>28/30 vs 22/20</td>
<td>56.8±55.1</td>
<td>Unclear</td>
<td>(1) (2)</td>
<td>None</td>
</tr>
</tbody>
</table>

Notes: (1) clinical efficacy; (2) ECG efficacy; (3) hemorheological indexes, plasma viscosity; (4) efficacy for TCMS, phlegm and static blood binding together; (5) nitric oxide (NO), endothelin (ET); (6) comparison of the frequency, interictal period, and duration of angina pectoris, before and after treatment; (7) serum lipid index, LDL; (8) incidence of cardiovascular events; (9) comparison of ECG within 24 h and myocardial oxygen consumption index, before and after treatment. T: test group. C: control group. M: male. F: female.

4.77)], Z = 8.43, P < 0.000 01). The publication bias of included studies was identified using funnel-shape plots (Figure 5). The results showed that the funnel-shape plot was generally symmetrical, indicating that the included studies had virtually no publication bias.
Random sequence generation (selection bias)  
Allocation concealment (selection bias)  
Blinding of participants and personnel (performance bias)  
Blinding of outcome assessment (detection bias)  
Incomplete outcome data (attrition bias)  
Selective reporting (reporting bias)  
Other bias

Table 2 Intervention details of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Dosage</th>
<th>Durance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang M 2011</td>
<td>PTI + CT</td>
<td>10 mL q.d.</td>
<td>14</td>
</tr>
<tr>
<td>Liu L et al 2014</td>
<td>PTI + CT</td>
<td>12 mL q.d.</td>
<td>14</td>
</tr>
<tr>
<td>Sun J 2012</td>
<td>PTI + CT</td>
<td>12 mL q.d.</td>
<td>14</td>
</tr>
<tr>
<td>Jiang D 2013</td>
<td>PTI + CT</td>
<td>8 mL q.d.</td>
<td>14</td>
</tr>
<tr>
<td>Fu Q 2011</td>
<td>PTI + CT</td>
<td>12 mL q.d.</td>
<td>14</td>
</tr>
<tr>
<td>Song HY et al 2009</td>
<td>PTI + CT</td>
<td>12 mL q.d.</td>
<td>14</td>
</tr>
<tr>
<td>Mo ZM et al 2005</td>
<td>PTI + CT</td>
<td>12 mL q.d.</td>
<td>14</td>
</tr>
<tr>
<td>Zhao RZ et al 2010</td>
<td>PTI + CT</td>
<td>12 mL q.d.</td>
<td>14</td>
</tr>
<tr>
<td>Zheng WX 2008</td>
<td>PTI + CT</td>
<td>12 mL q.d.</td>
<td>14</td>
</tr>
<tr>
<td>Gao ZQ et al 2005</td>
<td>PTI + IM (SA)/IM + VP (UA)</td>
<td>10 mL q.d.</td>
<td>15</td>
</tr>
<tr>
<td>Liu Y et al 2013</td>
<td>PTI + YFI + CT</td>
<td>12 mL q.d. (PTI)</td>
<td>14</td>
</tr>
<tr>
<td>Xu XJ 2014</td>
<td>PTI + CT</td>
<td>12 mL q.d.</td>
<td>14</td>
</tr>
<tr>
<td>Xie YX et al 2014</td>
<td>PTI + CT</td>
<td>8 mL q.d.</td>
<td>7-10</td>
</tr>
<tr>
<td>Huang XB 2014</td>
<td>PTI + CT</td>
<td>12 mL q.d.</td>
<td>15</td>
</tr>
</tbody>
</table>


Subgroup analysis

Subgroup analysis was performed on clinical efficacy according to the injection dosage. The selected studies were divided into three subgroups: 8 mL dosage, 10 mL dosage, and 12 mL dosage. The results presented in Figure 6 show that, compared with the drugs used by the control groups, PTI combined with conventional therapy improved clinical efficacy more significantly, except in the 8 mL dosage subgroup. [8 mL: OR = 2.20, 95% CI (0.62, 7.87), Z = 1.21, P < 0.23].

Sensitivity analysis

We selected 14 studies based on clinical efficacy to perform the sensitivity analysis. We replaced fixed effects methods with random effects methods and excluded literatures which represented the most 3 and least 7 weighted. As shown in Figure 7 (sensitivity analysis with random-effects methods), [OR = 3.40, 95% CI (2.52, 4.60)]; in Figure 8 (sensitivity analysis excluding the most weighted study), [OR = 3.94, 95% CI (2.87, 5.42)]; and in Figure 9 (sensitivity analysis excluding the least weighted study), [OR = 3.18, 95% CI (2.36, 4.29)], respectively. Compared with the previous results, OR values did not change significantly following different interventions, indicating the stability of this result.

ECG efficacy

Seven studies were included in this analysis, among which heterogeneity testing of ECG efficacy showed good homogeneity (P = 0.48, I² = 0%). Therefore, the fixed effects model was used for further analysis. The Meta-analysis showed that PTI in combination with conventional therapy was more effective than conventional therapy alone or with other drugs. The difference was significant between the two groups [OR = 3.20, 95% CI (2.26, 4.51), Z = 6.59, P < 0.000 01]. The results are shown in Figure 10.
Efficacy for TCMS (phlegm and static blood binding together)

Three studies measured the efficacy for TCMS (phlegm and static blood binding together) as an outcome measure, including 215 patients. A test of heterogeneity was not significant ($P = 1.00, I^2 = 0\%$). Therefore, the fixed effects model was taken for analysis. As shown in Figure 11, the result [OR = 3.13, 95% CI (1.43, 6.89), $Z = 2.84, P = 0.004$], which is statistically significant, showed that PTI combined with conventional therapy had a higher effective rate than that in the control group.

Serum plasma viscosity

There were three studies that mentioned plasma viscosity, and a heterogeneity test showed that the studies on plasma viscosity had a considerable degree of heterogeneity ($P < 0.0001, I^2 = 93\%$). We therefore used the random effects model for statistical analysis. As shown in Figure 12, the results were significantly different [MD = −0.47, 95% CI (−0.76, −0.17), $Z = 2.07, P = 0.002$], indicating that PTI combined with conventional therapy was more effective at reducing serum plasma viscosity than conventional therapy alone or with other drugs.

Serum LDL

In the three studies that assessed LDL, heterogeneity testing showed a considerable degree of heterogeneity ($P = 0.0001, I^2 = 89\%$), so we used the random effects model for statistical analysis. As shown in Figure 13, the results were significantly different [MD = −0.94, 95% CI (−1.57, −0.30), $Z = 2.90, P = 0.004$], indicating that PTI combined with conventional therapy was more effective at reducing serum LDL than conventional therapy alone or with other drugs.

Safety evaluation

Eleven studies reported adverse reactions, mainly local skin itching, facial flushing, and occasional dizziness, which were improved by adjusting the medication drip rate. Overall, PTI is reported to have few adverse reactions, is considered safe and reliable, and is widely used in clinical practice.
PTI is a product of TCM. Although PTI in combination with conventional therapy has been widely used to treat angina pectoris, no systematic review on its efficacy and safety in the treatment of angina pectoris has been published to date. RCTs were selected and reviewed in this work with a view to providing guidance and evidence for the clinical use of PTI.

From a TCM perspective, common causes of the angina pectoris include stress, overeating, cold, and emo-
The disease, however, can occur at rest and without any inducing factors. The main pathogenesis of angina pectoris is blockage of the heart vessels. Although it mainly affects the heart, its occurrence is
mostly related to the dysfunction of the liver, spleen and kidneys. Its root belongs to deficiency while its branch belongs to excess. The former includes Qi deficiency, Yang deficiency, and deficiency of Qi and Yin, while the latter includes Qi stagnation and the retention of cold, phlegm and blood stasis, which may combine to cause the disease.\(^2\)\(^,\)\(^9\)\(^,\)\(^20\)\(^,\)\(^21\) Gualoupi (Pericarpium Trichosanthis) is extracted from the dried pericarp of the cucurbitaceous plant Trichosanthes kirilowii and processed using modern biological techniques.\(^2\) A previous pharmacological study showed that the alkaloid of Gualoupi (Pericarpium Trichosanthis) clearly inhibited platelet aggregation induced by adenosine diphosphate and arachidonic acid in rabbits,\(^22\) and also reduced the maximum platelet aggregation rate and inhibited thrombosis in blood vessels.\(^9\) Other studies reported that Gualoupi (Pericarpium Trichosanthis) could reduce calcium influx in vascular smooth muscle cells, reduce the myocardial oxygen consumption index, improve myocardial oxygen supply, reduce hypoxia, thus relieving myocardial ischemia.\(^22\)\(^,\)\(^23\) Furthermore, Gualoupi (Pericarpium Trichosanthis) was shown to increase collateral circulation in the coronary artery and subsequently relieve myocardial ischemia.\(^24\) Meta-analysis is one of the most reliable methods for the evaluation of drug efficacy and safety, and can also provide clinicians with evidence to guide their clinical practice. In this study, we chose clinical efficacy, ECG efficacy, efficacy for TCMS, plasma viscosity, and LDL cholesterol levels as outcome measurements for analysis. The Meta-analysis showed that compared with conventional therapy alone or conventional therapy plus other TCMIs (YFI, BI, SI, DHI, DI) in control.
groups, PTI plus conventional therapy significantly improved clinical efficacy, ECG efficacy, and efficacy for TCMS as well as significantly decreased the levels of plasma viscosity, and LDL. From the subgroup analysis, the difference was statistically significant ($P < 0.05$) in the 10 and 12 mL dosage groups with sensitivity analysis confirming the findings. In terms of safety, 11 studies reported adverse reactions which were improved by adjusting medication levels, suggesting that PTI is safe to use in clinical practice.

One limitation of this analysis was the quality of the selected articles. No large-scale RCTs were identified, and only two studies described specific methods of random sequence generation. The remaining trials did not provide specific details of the randomization process, but mentioned only that patients were randomly allocated into two groups. To conform whether randomization was adequately conducted in the trials, we attempted to contact the authors by telephone or email but unfortunately received no replies. We suggested that researchers should strictly adhere to the basic principles of reporting clinical trials, such as those defined in the Consolidated Standards of Reporting Trials statement. None of the included trials described the allocation concealment procedure, and only one mentioned blinding (but without an explanation of the implementation method). This systematic review only included published studies and lacked relevant "gray literature", which might have contributed to selection bias. Two studies potentially featured selective reporting, which may have had an effect on the results of this Meta-analysis. However, as shown in Figures 14 and 15, results were shown to be robust after excluding these reports. As no English language literature was included in this review, and as all results were positive, some degree of publication bias may exist in this study. For future clinical trials of TCM therapies, we recommend that researchers conduct rigorously designed and conducted RCTs that accurately reflect the effects of drugs and correctly guide clinical medication protocols.

Overall, despite some shortcomings in this analysis, the results suggest that PTI is efficacious and safe for the treatment of angina pectoris, and thus has some reference value for clinical practitioners. More large-scale, multi-centered, rigorously designed RCTs are required to provide more accurate data to further verify the efficacy and safety of PTI.

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