Efficacy and safety of ginkgo injections in the treatment of angina pectoris caused by coronary heart disease in China: a network Meta-analysis and systematic review

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Abstract

OBJECTIVE: To assess the clinical efficacy and safety of ginkgo injections (GIs) combined with conventional treatment (CT) against angina pectoris (AP) due to coronary heart disease (CHD).

METHODS: Randomized controlled trials (RCTs) that used GIs to treat AP were searched in SinoMed, PubMed, China National Knowledge Infrastructure Database, Chinese Scientific Journals Database, Wanfang Database, Embase and Cochrane Library until March 2017. The Cochrane “risk of bias” method was used to evaluate the methodological quality of RCTs. Data were analyzed using Stata v13.1 and WinBUGS v1.4.3.

RESULTS: A total of 73 RCTs involving 7621 patients were included. A Bayesian network Meta-analysis of RCTs was undertaken, and the advantages of four types of GI-supplemented CT in AP treatment were determined.

CONCLUSION: GI-assisted CT was more effective against AP than CT alone. However, based on the limitations of the study, additional high-quality RCTs are required to confirm our findings.

Keywords: Ginkgo injections; Angina pectoris; Network Meta-analysis; Systematic review

INTRODUCTION

Coronary heart disease (CHD), also known as "ischemic heart disease", is a type of heart disease caused by atherosclerosis or vasospasm resulting from vascular stenosis (or even blockage) that leads eventually to myocardial ischemia, hypoxia or necrosis. CHD is a cardio-cerebrovascular disease that threatens human health. Angina pectoris (AP) is a clinical manifestation of CHD, and it is divided into "unstable" and "stable" forms. Typically, AP is caused by emotional stress or exertion. The typical clinical manifestations of stable AP are discomfort and symptoms of the chest precipitated by physical activity (e.g., running, walking). Moreover, unstable AP may occur unpredictably when patients are at rest.

Ginkgo biloba, commonly known as "ginkgo" and the "maidenhair tree", is the only species in the division Ginkgophyta. Studies have shown that ginkgo extract includes flavonoids, terpene lactones, organic acids and amino acids as well as other active ingredients. Ginkgo
extract has been shown to improve AP symptoms. Various preparations of ginkgo are used in the clinic: ginkgo leaf extract and dipyridamole (GD); shuxuening (SXN); extract of Ginkgo biloba leaves (EGB); ginkgolide (GK); folium ginkgo extract and tertram ethyppyazine sodium chloride (FT).

No study has compared the efficacy, safety, advantages and disadvantages of the five types of ginkgo injection treatment (GIT) mentioned above for AP. However, several randomized controlled trials (RCTs) have been conducted to compare two types of GIT.

METHODS

Search strategy

Two authors (DT and YYC) searched the following databases from inception until March 2017: Embase, PubMed, Cochrane Library, SinoMed, China National Knowledge Infrastructure Database (CNKI), Chinese Scientific Journals Database (VIP) and Wanfang Database. Detailed search strategies are illustrated in Supplementary Figure 1. "Gray literature" or ongoing studies were not retrieved from OpenGrey and Science.gov databases. Using PubMed as an example, the search strategies are as follows.

#1 "angina pectoris [Mesh]"
#2 "angina pectoris [Abstract/Title]" OR "stable angina pectoris [Abstract/Title]" OR "unstable angina [Abstract/Title]"
#3 #1 OR #2
#4 "Ginkgo Leaf Extract and Dipyridamole Injection [Abstract/Title]" OR " Extract of Ginkgo Biloba Leaves Injection [Abstract/Title]" OR " Shuxuening Injection [Abstract/Title]" OR " Ginkgolide injection [Abstract/Title]" OR " Floium Ginkgo Extract and Tertram Ethyppyazine Sodium Chloride Injection [Abstract/Title]"
#5 #3 AND #4

Inclusion criteria

Included studies had to meet specific conditions. Studies had to be RCTs with or without blinding. Patients were diagnosed with AP without limitations on age, sex, race or disease severity. AP criteria were based on World Health Organization diagnostic criteria, the Nomenclature and Diagnostic Criteria for Ischemic Heart Disease in 1981, Chinese Branch of Cardiovascular Disease in 2000 or the American College of Cardiology and American Heart Association diagnostic criteria in 2000. The experimental group was treated with GIs plus CT, including nitrate preparations, β-blockers or calcium antagonists and low-molecular-weight heparin calcium. The control group was treated solely with CT or with the same regimen as the experimental group. Primary outcomes of the studies were total efficacy against AP and effect upon electrocardiography (ECG). Secondary outcomes were whole-blood viscosity, plasma viscosity, fibrinogen level, high-sensitivity C-reactive protein (hs-CRP) level, low-density lipoprotein (LDL) level, and prevalence of adverse drug reactions/adverse drug events (ADRs/ADEs).

The standard of clinical curative effect was based on the guiding principles of the Chinese Branch of Cardiovascular Disease in 2000. The standard of AP was graded into three levels: "significant curative effect" meant that AP frequency after treatment was reduced by > 80%; "curative effect" meant that AP frequency after treatment was reduced by > 50% but not > 80%; "no curative effect" meant that AP frequency after treatment was reduced by < 50% or there was no reduction. The standard of ECG was set as three levels: a "normal" or "almost normal" electrocardiogram indicated a significant curative effect; The ST segment depression increased more than 0.05 mV, but didn’t return to normal, the main lead negative T waves were shallowed over 50% or The T wave shifted from flat to vertical; "unchanged" or "worsened" symptoms indicated invalid treatment.

Exclusion criteria

RCTs were excluded if: (a) interventions involved acupuncture or other methods of treatment using Traditional Chinese Medicine; (b) the diagnostic criteria or criteria for efficacy evaluation of the study were not clear; (c) the study was repetitive or the full text was unavailable; (d) data were incorrect, incomplete, repetitive or not available.

Data extraction and quality assessment

Two researchers (Tan D and Liu S) conducted (independently) the article search, data extraction, quality assessment and RCT selection to ascertain if the studies met the inclusion criteria. A third investigator (Wu JR) was recruited to settle disagreements. Extracted information comprised the names of the authors, year of publication, course of treatment, participants’ age and sex, outcomes, intervention, and information about ADRs/ADEs.

The Cochrane Collaboration’s tool was used by two investigators (Tan D and Liu S) to evaluate biases in the included RCTs: random sequence generation; blinded outcome assessment; blinded of participants and personnel; allocation concealment; selective reporting; incomplete outcome data and other biases. Each study was rated as "high", "unclear" or "low" bias. A high bias indicated an incorrect randomization method, no allocation concealment or no blinding. An unclear bias indicated that the results were not described in the study. A low bias indicated correct ran-
domination methods, appropriate blinding without violation during implementation and a detailed description of study methods. All disagreements were resolved by a third researcher (Wu JR).

**Statistical analyses**

Bayesian NMA was carried out using WinBUGS 1.4.3 (Medical Research Council Bio-statistics Unit, Cambridge, UK) and STATA v13.1 (Stata, College Station, TX, USA). Results are reported as the standard mean difference or odds ratios with 95% confidence intervals (CI) for all comparisons of interventions. The Markov chain parameter was set to 70,000. The annealing algorithm was applied to the first 10,000, and the latter 60,000 were used for sampling. When there was a closed loop, the consistency of the direct comparison was verified with the indirect comparison. Simultaneously, ranking of the interventions was done by Surface Under the Cumulative Ranking (SUCRA). Finally, a funnel map was used to detect potential publication biases.

**RESULTS**

**Literature search**

A total of 2917 relevant RCTs were obtained. After several rounds of screening, 73 \(^{15-85}\) were included in the study (Figure 1). In total, 7621 patients in 73 studies were involved: 3932 cases in the experimental group and 3689 cases in the control group. Patients were diagnosed with AP from CHD and met the diagnostic criteria. All experimental-group interventions were intravenous infusions of ginkgo, and the dose was 10 to 40 mL/d. Control-group interventions were CT with or without EGb. Treatments received by all patients within 28 d were recorded, and most of the treatments lasted 14 d (46/73) (Table 1). The network diagram of Gls and CT (conventional treatment) are shown in Figure 2.

**Quality assessment**

The quality of all included RCTs was evaluated using the Cochrane Collaboration’s tool. Randomization was mentioned in all RCTs, but only six RCTs \(^{15,19,24,65,69}\) described the method of randomization, which involved a random number table; one RCT \(^{17}\) was a double-blinded study, and two RCTs \(^{70,71}\) were single-blinded studies. All included RCTs had complete outcome data. The included RCTs did not provide information about other biases (Figure 3).

**Efficacy of GIT against AP**

Sixty-five RCTs \(^{13-26,29,30,32,33,41-43,44-66,70-72,73,75-81,83-85}\) reported the total efficacy of five types of interventions (XN, EGb, GD, FT and CT) against AP (Figure 2). Meta-analysis showed that compared with CT alone, the four types of GIT combined with CT exhibited significantly improved total efficacy against AP; and there were significant between-group differences. There were no significant differences among the four GI-supplemented interventions (Figure 4).

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**Figure 1 Research selection flow chart**

Records identified through database searching \((n = 1291)\)

Additional records identified through other sources \((n = 0)\)

Records after duplicates removed \((n = 1291)\)

Records screened \((n = 1291)\)

Full-text articles assessed for eligibility \((n = 613)\)

Studies included in qualitative synthesis \((n = 73)\)

Studies included in quantitative synthesis (Meta-analysis) \((n = 73)\)

Records excluded \((n = 678)\):
- not relevant \((n = 259)\);
- interventions do not match \((n = 296)\);
- review \((n = 52)\);
- not RCT \((n = 33)\);
- unreasonable grouping \((n = 38)\)

Full-text articles excluded, with reasons \((n = 540)\):
- basic information is not complete \((n = 16)\);
- interventions do not match \((n = 221)\);
- efficacy evaluation/diagnostic criteria do not match \((n = 79)\);
- random method error \((n = 22)\);
- irrelevant \((n = 171)\);
- other reasons \((n = 31)\)

Records excluded \((n = 1291)\):
- not relevant \((n = 259)\);
- interventions do not match \((n = 296)\);
- review \((n = 52)\);
- not RCT \((n = 33)\);
- unreasonable grouping \((n = 38)\)
Table 1 Basic information of the included studies

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<th>Age (years)</th>
<th>Case number (E/C)</th>
<th>Experimental group intervention</th>
<th>Control group intervention</th>
<th>Course of treatment (days)</th>
<th>Result outcome</th>
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<td>FT (250 mL)+CT</td>
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<td>60/60</td>
<td>SXN (20 mL)+CT</td>
<td>EGb (20 mL)+CT</td>
<td>14</td>
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Notes: M: male; F: female; E: experimental group; C: control group; d: days; CT: conventional treatment, including nitrate preparations, β-blockers or calcium antagonists and low-molecular-weight heparin calcium; GD: ginkgo leaf extract and dipryridamole; SXN: shuaxuen; EGb: extract of Ginkgo biloba leaves; FT: folium ginkgo extract and tetramethylpyrazine sodium chloride. Outcomes: 1 total efficacy against AP, and effects upon 2 electrocardiography, 3 fibrinogen level, 4 plasma viscosity, 5 whole-blood viscosity, 6 level of low-density lipoprotein, 7 hs-CRP level and 8 prevalence of adverse drug reactions/adverse drug events.
Probability sorting analyses showed that GD + CT (SUCRA = 72.03%) was the best treatment method, exhibiting improved total efficacy against AP, and was followed by FT + CT (68.7%), SXN + CT (59.4%) and EGb + CT (49.6%) (Figure 5).

Effect of GIT upon ECG
Forty-one RCTs reported the total effect of five types of interventions (SXN, EGb, GD, FT and CT) upon ECG (Figure 6). Compared with CT alone, the four types of GIT and combination therapy with CT exhibited significantly improved total effect upon ECG, and there were significant between-group differences. There were no significant differences among the four GI-supplemented interventions (Figure 4).

Inconsistency test
There was one triangular loop present in the two outcomes of the Bayesian NMA. The consistency test showed that there were no significant inconsistencies in the study [ratios of odds ratios (ROR) for AP = 1.069, 95% CI (1.00, 1.23); ROR for ECG = 1.056, 95% CI (1.00, 1.28)] (Figures 8 and 9).

Publication bias
Two funnel plots of the total efficacy against AP and effect upon ECG were not symmetrical, which may indicate a publication bias (Figures 10 and 11).

Hemorheological indices
Fibrinogen (g/L): fourteen RCTs reported the effects of five types of intervention (SXN, EGb, GD, FT and CT) upon fibrinogen levels. The following treatment comparisons were significant: EGb + CT versus CT; GD + CT versus CT; SXN + CT versus CT; SXN + CT versus GD + CT; SXN + CT versus EGb + CT; SXN + CT versus FT + CT. Other in-

Figure 3 Risk of bias summary

Figure 4 Results of network Meta-analysis of total effectiveness

Results are represented by the OR and 95% CI for efficacy against AP (lower-left quadrant) and efficacy upon electrocardiogram (upper-right quadrant). CT: conventional treatment; AP: angina pectoris; GD: ginkgo leaf extract and dipyridamole; SXN: shuxuening; EGb: extract of Ginkgo biloba leaves; FT: folium ginkgo extract and tertram ethypyrine sodium chloride.
The following treatment comparisons were significant: EGb + CT versus CT; SXN + CT versus CT. Other intervention comparisons were not significantly different (Table 2).

Probability sorting analyses showed that GD + CT (SUCRA = 91.6%) was the best treatment method based on the improvement of plasma viscosity, followed by SXN + CT (58.1%) and EGb + CT (33.6%). Whole-blood viscosity (mPa·s): eight RCTs reported the effects of four types of intervention (SXN, EGb, GD and CT) on whole-blood viscosity. The following treatment comparisons were significant: GD + CT versus CT; EGb + CT versus CT; SXN + CT versus CT. Other interventions comparisons were not significantly different (Table 2).

Probability sorting analyses showed that GD + CT (SUCRA = 95.0%) was the best treatment method based on the improvement of whole-blood viscosity, followed by EGb + CT (60.8%) and SXN + CT (43.8%).

**hs-CRP (mg/L)**

Eight RCTs reported the effects of four types of intervention (SXN, EGb, GD and CT) on hs-CRP levels. The following treatment comparisons were significant: EGb + CT versus CT; SXN + CT versus CT. Other intervention comparisons were not significantly different (Figure 12).

Probability sorting analyses showed that SXN + CT (SUCRA = 83.5%) was the best treatment based on the improvement of hs-CRP levels, followed by EGb + CT (53.4%) and GD + CT (50.2%).

**LDL (mmol/L)**

Five RCTs reported the effects of four types of intervention (SXN, FT, GD and CT) on LDL levels. Compared with CT alone, only SXN + CT improved LDL levels significantly; significant between-group differences were not significantly different (Table 2).
ferences were observed. There were no significant differences among the other intervention comparisons (Figure 12).

Probability sorting analyses showed that SXN + CT (SUCRA = 94.3%) was the best treatment method based on the improvement of LDL levels, followed by FT + CT (46.3%) and GD + CT (29.9%).
GD + CT exhibited the best therapeutic effect on plas-
terventions, SXN + CT, GD + CT and EGb + CT, im-
showed significant improvements on plasma viscosity. Three
interventions, SXN + CT, GD + CT and EGb + CT, im-
through Bayesian NMA of RCTs, the
sults were published in Chinese. Second, literature
tnsual analyses showed that the prevalence
of ADRs/ADEs from GI-supplemented CT was
litative analyses showed that the prevalence
of ADRs/ADEs from GI-supplemented CT was
up strategy, with regard to the total efficacy of GIT against AP
ed in only Chinese and English databases may

testinal discomfort, bradycardia, flushing, and low
blood pressure.

**DISCUSSION**

We combined indirect and direct evidence with Bayes-
ian NMA to rank the efficacy of each intervention
mpared with CT alone, SXN + CT was better than
other intervention based on its effect on LDL lev-
less. Finally, qualitative analyses showed that the preva-
ence of ADRs/ADEs from GI-supplemented CT was
ow our study had three main limitations. First, the includ-
ed RCTs were published in Chinese. Second, literature
retrieval in only Chinese and English databases may
lead to overlooking studies in other languages. Third,
methods used to generate the allocation sequence and
methods for allocation concealment were not
clear in most articles and could have led to biases
lection, performance and measurement), which might
have resulted in exaggeration of the clinical curative
effect.

In conclusion, through Bayesian NMA of RCTs, the
advantages of four types of GI-assisted CT for AP treat-
ment were determined. However, based on the limita-
tions of these RCTs, additional research should be con-
ducted to confirm the findings in our study.

<table>
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<th>Interventions (E/C)</th>
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<th>Whole blood viscosity</th>
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<td>SXN + CT vs CT</td>
<td>-9.44 (-10.35, 8.54)</td>
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<td>EGb + CT vs CT</td>
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<td>-0.002 (-1.86, 0.84)</td>
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<td>GD + CT vs CT</td>
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<td>FT + CT vs CT</td>
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<td>-</td>
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<td>EGb + CT vs GD + CT</td>
<td>-0.78 (-2.41, 0.84)</td>
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<td>GD + CT vs FT + CT</td>
<td>-1.24 (-3.40, 0.90)</td>
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Notes: SMD: standardized mean difference; CI: confidence interval; E: experimental group; C: control group; CT: conventional treatment, including nitrate preparations, β-blockers or calcium antagonists and low-molecular-weight heparin calcium; GD: ginkgo leaf extract and dipyridamole; SXN: shuxuening; EGb: extract of Ginkgo biloba leaves; FT: folium ginkgo extract and tertram ethyprazine sodium chloride.

**Table 2 Results of the Network Meta-analysis of the hemorheological index (SMD (95% CI))**

**Figure 12 Results of the network Meta-analysis of hs-CRP and low-density lipoprotein levels**

Results are the SMD and 95%CI for hs-CRP (lower-left quadrant) and low-density lipoprotein (upper-right quadrant). SMD: standardized mean difference; CI: confidence interval; hs-CRP: high-sensitivity C-reactive protein; GI: ginkgo leaf extract and dipyridamole; SXN: shuxuening; EGb: extract of Ginkgo biloba leaves; FT: folium ginkgo extract and tertram ethyprazine sodium chloride; CT: conventional treatment.
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