Safflower yellow injection combined with conventional therapy in treating unstable angina pectoris: a meta-analysis

Dezhao Kong, Wei Xia, Zhe Zhang, Lei Xiao, Dongchao Yuan, Yue Liu, Guanlin Yang

**Abstract**

**OBJECTIVE:** To evaluate the clinical efficacy of safflower yellow injection combined with conventional therapy in treating unstable angina pectoris.

**METHODS:** We searched online databases: Chinese journal full-text database, China National Knowledge Infrastructure, Wanfang database, Chinese journal full-text database, Pubmed, ScienceDirect, Embase, and the Cochrane Library with manual-screening of relevant literature. Eligible randomized controlled trials (RCT) on angina pectoris were included. We conducted meta-analysis using the RevMan 5.1 software from The Cochrane Collaboration. We treated the relief rate of angina symptoms and electrocardiograph (ECG) as evaluation.

**RESULTS:** Seven articles, including in 1134 patients, were enrolled after the evaluation. There was no significant heterogeneity among the studies ($\chi^2=1.08, df=6, P=0.98, I^2=0\%$). The safflower yellow injection with conventional therapy has a higher effective rate than the control group in relieving the symptoms of angina pectoris [odds ratio (OR) $=2.95$, 95\% CI (1.81, 4.81)] and improving ischemic ECG [OR $=2.85$, 95\% CI (1.67, 4.86)]. The difference was statistically significant in the "80 mg dosage" and "100 mg dosage" subgroups ($P<0.05$) for improving clinical symptoms and ECG. The funnel graphic was nearly symmetrical. Sensitivity analysis suggested that the results were stable.

**CONCLUSION:** Safflower yellow injection as an adjunct therapy with conventional drugs shows advantages in easing the clinical symptoms of unstable angina and improving ECG over basic therapy alone. However, the conclusions should be interpreted with care until more high-quality RCTs are reported.

**Key words:** Safflower yellow injection; Angina, unstable; Meta-analysis

**INTRODUCTION**

Coronary artery disease is heart disease with myocardial ischemia and hypoxia caused by coronary atherosclerosis or stenosis. These symptoms coupled with coronary artery spasms and changes are collectively known as coronary heart disease. The incidence of angina pectoris has increased in recent years with improving living standards of Chinese, dietary changes, and increased stress. Angina pectoris has become the leading cause of death in China. The nomenclature and di-
agnostic standards of ischemic heart disease were published by World Health Organization in 1979. WHO divided ischemic heart disease into five types including occult coronary heart disease, angina, myocardial infarction, ischemic cardiomyopathy and sudden-death. Angina is further divided into three types: exertional angina, spontaneous angina, and mixed angina. Exertional angina includes stable exertional angina pectoris, the first episode of angina pectoris and progressive angina pectoris. Except stable exertional angina, the rest are unstable. These subcategories are included in the “unstable angina diagnosis and treatment recommendations” developed by the Chinese Medical Society of Cardiology in 2000.

In recent years, safflower yellow injection (SYI) has been widely used for treating unstable angina pectoris. There have been many clinical trials reported confirming its effectiveness and safety.13 Honghua (Flos Carthami), a traditional Chinese medicine, can activate blood and dredge the meridians, removing stasis and relieving pain.14 Ben Cao Hui Yan said, “Honghua (Flos Carthami) is a medicine breaking blood stasis, activating blood circulation, mediating blood, and adjusting blood.”15 Modern pharmacological studies have shown that its main chemical ingredients “safflower yellow pigment” have efficacy for some conditions. It can improve myocardial energy metabolism, reduce ischemic damage,16 and inhibit the activation of neutrophils.17 Some researchers report that it can soften artery atherosclerosis,18 reduce myocardial ischemia,19 and resist inflammation by inhibiting nitric oxide (NO) and prostaglandin E2 (PGE2).20 SYI was made with safflower yellow pigment as the main ingredient. The common route of administration of SYI are injection and powder. Both were used in studies analyzed in this paper. In this study, we performed an analysis of multiple independent clinical randomized controlled trials (RCTs) to estimate the odds ratio (OR) and to systematically review the efficacy of SYI combined with conventional therapy in treating unstable angina.

MATERIALS AND METHODS

Data sources
We searched the literature according to the “Cochrane Handbook for Systematic Reviews of Interventions” published by The Cochrane Collaboration. We screened the online databases: Chinese journal full-text database (1989-August 2012), China National Knowledge Infrastructure (CNKI) (1979-August 2012), Wanfang Database (1977-August 2012), Pubmed (1950-2012), ScienceDirect (1823-2012), Embase (2009-2012), and the Cochrane Library (1948-2012). We also performed some manual-screening of relevant literature. The last search was performed on 30 August 2012.

Search strategies
We used terms depending upon the working language of the databases. Terms we used were: “Carthamus tinc-

torius injection,” “Honghua (Flos Carthami),” “SYI,” and “unstable angina”. The following search strategy was used in PubMed and other English databases: (a) carthamus tinctorius injection; (b) Honghua (Flos Carthami); (c) SYI; (d) SYI; (e) SYI; (f) SYI; (g) SYI. For searching the CNKI data and other Chinese databases, the following search strategy was used: (a) SYI; (b) unstable angina; (c) SYI; (d) SYI; (e) AND 2

Exclusion criteria
We developed the inclusion and exclusion criteria according to the Cochrane Collaboration Handbook criteria. (a) Trials must be a randomized, controlled design. (b) Diagnosis of unstable angina should follow the “unstable angina diagnosis and treatment recommendations” developed by the Chinese Medical Society of Cardiology in 2000, or standards developed by the American College of Cardiology and American Heart Association. (c) Selected cases should be without severe organic diseases or complications. (d) The control group was given conventional treatment for the secondary prevention of coronary heart disease such as nitrates, aspirin, and adrenergic receptor blockers, statins, and angiotensin II receptor antagonists. However, the experimental group was given SYI based on the conventional treatment. (e) There was no use of positive drugs such as Danshen injection, safflower injection, Hongdan injection and Chuaxiong injection. (f) Powder for injection ranged from 50-150 mg, without limits on the manufacturer or dosage forms. (g) The signals should be at least one of the symptoms of angina response rate and electrocardiograph (ECG) improvement rate, and should meet the evaluation standard.

Exclusion criteria
The exclusion standards were: (a) unpublished literature; (b) no control group set in the documents; (c) quasi-experimental design; (d) no clearly identified result assessment; (e) repeated original literature; or (f) multiple contributions of one manuscript.

Symptom improvement standards
We performed the standard of symptom improvement according to the “Guidelines for clinical research of Traditional Chinese Drug treating angina pectoris.”21 After a course of treatment, the improvement of symptoms should be at least 80%, or nitroglycerin tablet consumption should decrease by 80% (i.e., significant symptomatic improvement). The improvement of symptoms should be at least 50%, or nitroglycerin tablet consumption should decrease by 50% (i.e., basic symptomatic improvement).
ECG improvement standard
We set out the ECG improvement standard according to the "Diagnosis and treatment guidelines for Chinese common cardiovascular and cerebrovascular disease." If the ST segment and T wave returned to normal then there was significant ECG improvement. If the ST segment recovered at least 0.05 mv, and the T wave inversion decreased more than 50% there was basic ECG improvement.

Data synthesis and statistical analysis
We used the Revman 5.1 software provided by "The Cochrane Collaboration" to analyze the collected data. An OR with 95% confidence intervals (CI) was chose to count data. A fixed-effect model of the Mantel-Haenszel method was used to pool these OR if there was no significant heterogeneity. Subgroup analyses were performed to explore more information. We used the Q test and I² test to analyze the heterogeneity across studies. A condition of P<0.05 was defined as a signal of heterogeneity. A condition of I²>50% suggested the data might not be probable to be combined.

In addition, we created a funnel plot to analyze potential publication bias, and tested the stability of the results by using sensitivity analysis.

Risk of bias in individual studies
According to the "Cochrane risk of bias tool" and "CONSORT 2010 checklist," two reviewers independently assessed the quality of included studies in items such as randomization, allocation concealment, and blinding.

RESULTS
Search results
The process of study selection is shown in Figure 1. Overall, we collected 92 articles in Chinese, 354 in English, and 5 through manual screening. We screened 28 papers for full text after we sieved out the obviously ineligible and repeated documents. We screened out 21 of these studies for reasons such as lack of control group, and multiple contributions of one manuscript. Finally, seven articles were included in this review.

Figure 1 Process of searching and screening study
CNKI: China National Knowledge Infrastructure; WF: Wangfang data; VIP: Chinese journal full-text database.
Characteristics of included trials
All enrolled patients were diagnosed as having unstable angina pectoris. The control group was given the basic treatment widely recognized as valid, and the experimental group was given SYI based on the same essential treatment. SYI dosage ranged from 50-150 mg once a day intravenously, with a course of 14-15 days (only "Liu JH 2009" used 10 days). The screened results by the two reviewers were the same (Table 1).

Quality assessment
We included 1134 subjects in seven papers, with average samples of 162. There were 554 total patients in the trial group and 580 in the control group. All studies showed comparability or no significant difference between the two groups (P>0.05). One study described the random methods, and another included adverse drug reactions. All studies did not drop out of the clinical trials (Table 2).

Information from the CONSORT 2010 checklist conformity is shown in Table 3. The rates (total items actually reported/total number of items in CONSORT 2010) were: 100% for title and abstract, 71.43% for introduction, 85.87% for results, 66.67% for discussion, and 29.4% for methods. The rate of abiding by overall CONSORT 2010 of all included studies was 44.02%, indicating 44.02% of all items were satisfactorily reported on average.

Table 1 Characteristics of included trials in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Included number</th>
<th>Treatment (day)</th>
<th>Dosage of SYI mL</th>
<th>Positive control</th>
<th>Concomitant medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jin C 2011</td>
<td>45-75</td>
<td>65</td>
<td>65</td>
<td>14</td>
<td>150</td>
<td>None</td>
</tr>
<tr>
<td>Wei ZF 2010</td>
<td>45-78</td>
<td>310</td>
<td>348</td>
<td>10-14</td>
<td>100</td>
<td>None</td>
</tr>
<tr>
<td>Yu XW 2011</td>
<td>60-78</td>
<td>41</td>
<td>39</td>
<td>15</td>
<td>100 (80)</td>
<td>None</td>
</tr>
<tr>
<td>Liu JH 2009</td>
<td>42-78</td>
<td>28</td>
<td>20</td>
<td>10</td>
<td>50</td>
<td>None</td>
</tr>
<tr>
<td>Zhou SJ 2011</td>
<td>45-75</td>
<td>38</td>
<td>38</td>
<td>14</td>
<td>100 (80)</td>
<td>None</td>
</tr>
<tr>
<td>Tang Q 2011</td>
<td>52-76</td>
<td>43</td>
<td>42</td>
<td>14</td>
<td>150</td>
<td>None</td>
</tr>
<tr>
<td>Xia HZ 2010</td>
<td>60±8.5</td>
<td>31</td>
<td>31</td>
<td>14</td>
<td>100</td>
<td>None</td>
</tr>
</tbody>
</table>

Notes: T: test group; C: control group; SYI: Safflower yellow injection.

Table 2 Characteristics of included trials in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Angina symptom relief</th>
<th>ECG improvement</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T</td>
<td>C</td>
<td>T</td>
</tr>
<tr>
<td>Jin C 2011</td>
<td>60</td>
<td>53</td>
<td>59</td>
</tr>
<tr>
<td>Wei ZF 2010</td>
<td>301</td>
<td>322</td>
<td>NA</td>
</tr>
<tr>
<td>Yu XW 2011</td>
<td>39</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Liu JH 2009</td>
<td>26</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>Zhou SJ 2011</td>
<td>35</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>Tang Q 2011</td>
<td>41</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>Xia HZ 2010</td>
<td>30</td>
<td>27</td>
<td>NA</td>
</tr>
</tbody>
</table>

Notes: ECG: electrocardiograph; T: test group; C: control group; NA: no data available.

Table 3 Total number of items compliant with the "CONSORT 2010 checklist"

<table>
<thead>
<tr>
<th>Author</th>
<th>Title and abstract</th>
<th>Introduction</th>
<th>Methods</th>
<th>Results</th>
<th>Discussion</th>
<th>Other information</th>
<th>Total of each study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jin C</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Wei ZF</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Yu XW</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Liu JH</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Zhou SJ</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Tang Q</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Xia HZ</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Total of each</td>
<td>14</td>
<td>10</td>
<td>35</td>
<td>41</td>
<td>14</td>
<td>0</td>
<td>114</td>
</tr>
</tbody>
</table>

Rated percentage (%) 100.00 71.43 29.41 58.57 66.67 0.00 44.02

Notes: rated percentage is total items actually reported in all studies/total number of items in CONSORT 2010 checklist.
The Cochrane risk of bias tool gave risk of bias within studies in Figure 2, 3: low bias in incomplete outcome data, unclear bias in selective outcome reporting, blinding of participants, personnel and outcome assessors, sequence generation (except for study 11), allocation concealment and other sources of bias.

Symptoms of angina

Meta-analysis of the seven studies showed no heterogeneity between studies ($\chi^2=1.08$, df=6, $P=0.98$; 0.05, $I^2=\%$). Therefore, the fixed effects model (M-H: Mantel-Haenszel formula) could be taken for analysis.

In Figure 4, the summary odds ratio (OR) of the number of angina attacks decreased by ≥50% was 2.86, 95% CI (1.78, 4.59). The diamond in the forest plot is on the right side of the middle line. The overall effect of test $Z=4.35, P=0.00001$ tells that efficacy of SYI with basic therapy on the symptoms of angina pectoris was much better than the control. Posted bias assessment of the included studies is shown in Figure 5. The funnel graphics are almost symmetrical, suggesting no publication bias.

ECG improvement

Among the five studies among 419 patients, with 215 in the test group and 204 in the control group. No obvious heterogeneity existed among the studies ($\chi^2=2.94$, df=4, $P=0.57$; 0.05, $I^2=\%$). Therefore, we used the fixed effect model analysis (MH Fixed method) to analyze. The results are shown in Figure 6. The diamond is in the right side of the middle line. The efficacy of SYI on ECG was significantly superior to that of drugs in the control group [OR=2.85, 95% CI (1.67, 4.86)] ($Z=3.84, P=0.00001$).
We made the subgroup analysis according to the dosage of injection. Studies were divided into four subgroups: 50 mg dosage, 80 mg, 100 mg, and 150 mg. The results showed that SYI with conventional therapy had a higher effective rate than routine therapy alone in the control group, except the subgroup "50 mg dosage" (Z=1.63, P=0.10). Five studies were divided into three subgroups about ECG improvement. Subgroup "80 mg dosage" had a higher effective rate than that in the control group on ECG improvement (Z=3.30, P=0.001). The difference was insignificant in subgroup "50 mg dosage" and "150 mg dosage" on ECG improvement (P>0.05) (Figure 7, 8).

### Subgroup analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SYI with conventional therapy</th>
<th>Conventional therapy</th>
<th>Total</th>
<th>Odds Ratio</th>
<th>Heterogeneity: Chi², df, P; Test for overall effect: Z, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jin C2011</td>
<td>59</td>
<td>65</td>
<td>52</td>
<td>65</td>
<td>28.6% 2.46 [0.87, 6.93] M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Liu JH2009</td>
<td>25</td>
<td>28</td>
<td>15</td>
<td>20</td>
<td>11.2% 2.78 [0.58, 13.32] M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Tang Q2011</td>
<td>36</td>
<td>41</td>
<td>25</td>
<td>39</td>
<td>11.2% 7.09 [1.85, 27.23] M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Zhou SJ2011</td>
<td>34</td>
<td>38</td>
<td>28</td>
<td>38</td>
<td>17.6% 3.04 [0.86, 10.73] M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>215</td>
<td></td>
<td>152</td>
<td>204</td>
<td>100.0% 2.85 [1.67, 4.86] M-H, Fixed, 95% CI</td>
</tr>
</tbody>
</table>

### Sensitivity analysis

To perform the sensitivity analysis, we replaced fixed

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**Figure 5** Post-test bias assessment of the included studies

**Figure 6** Meta-analysis results of electrocardiograph improvement

**Figure 7** Subgroup analyses on symptoms of angina
effects methods with random effects methods, excluded literature which had the largest number of samples, and short treatment course.

As shown in Figure 9, 10, and 11: \( OR=2.85, 95\% CI (1.77, 4.57); OR=2.97, 95\% CI (1.63, 5.39); \) and \( OR=2.83, 95\% CI (1.50, 5.33), \) respectively. \( OR \) values did not change significantly under different interventions, suggesting the stability of this result.

### Adverse reactions

Six studies described adverse reactions. Only one study had minor side-effects including rash and dizziness, which were improved by adjusting the medication drip rate.

### DISCUSSION

SYI is a product of Traditional Chinese Medicine. However, the efficacy of the combined use of SYI and basic therapy remains controversial. In China, it is common to use SYI with routine therapy to treat unstable angina. However, no systematic review has been published in English, which hinders SYI’s ability to gain worldwide recognition. We reviewed current RCTs to provide evidence for the use of SYI as an adjunctive therapy for unstable angina. Each study took broadly accepted diagnostic standards to determine treatment outcomes. In this study, we took the two signals of effects in symptoms and ECG improvement for analysis, which fully reflect the effectiveness of treating unstable angina pectoris. Meta-analysis is the best method of literature analysis in evidence-based medicine. It can save costs and time integrating the data of multiple independent studies to increase sample size and to improving test performance. Moreover, it can provide clinicians with evidence-based medical evidence to guide their clinical practice. This meta-analysis showed that the efficacy of SYI combined with conventional therapy was better than basic therapy alone in terms of relieving symptoms of angina and ECG. From subgroup analyses, the difference was statistically significant \( (P<0.05) \) in the subgroup "80 mg dosage" and "100 mg dosage." Therefore, we suggested that the dosage of SYI in treating unstable angina should be 80 or 100 mg. Sensitivity analysis suggested that the results were stable. However, further clinical trials need to be performed before any firm conclusions can be drawn. Evidence from these articles and our analysis suggest that conventional therapy combined with SYI has an advantage in treating unstable angina.

There are several limitations in this study. First, only one study reported the randomization method. A lack of descriptions of randomization methods and allocation concealment may have biased the results. Second, blinding was not clearly described in any of the trials, which may overestimate the efficacy of the treatment group. In spite of the difficulty of implementing blinding methods of TCM clinical research, it is necessary to use blinding during the measurement of outcomes. Third, there were variations in manufacturing stan-
standards and two studies\textsuperscript{10,12} had a very short treatment course. These factors may contribute to heterogeneity among the studies. Nevertheless, the results proved to be stable after excluding these reports (Figure 11).

Fourthly, the follow-up period is an important factor for the medical efficacy for patients with unstable angina pectoris. This meta-analysis included seven RCTs with short follow-up periods, which may influence the result. More studies with longer follow-up periods are needed to prove this trend. Fifthly, some studies reported the signals such as blood lipids and blood viscosity.\textsuperscript{9,12-14} However, methodological heterogeneity\textsuperscript{31} may be caused by different instruments. Therefore, these signals were not used in our analysis. Sixthly, publication bias may exist in the study. Although we thoroughly screened the English database, there were no English studies. Additionally, all the studies are positive results. Some negative results may be unreported and therefore, are not included in the review.

As most of the studies reviewed in the TCM field come from China, Chinese researchers should formally train in clinical trial design. Future trials should describe randomization methods, allocation concealment, and blinding methods during clinical research and measuring outcomes. Otherwise, it is difficult to exclude the possibility of biases in the assessment of clinical efficacy, symptom scores, and other outcome indexes. Withdrawal and follow-up data are also necessary. Publishers play an important role in this effort as well. Researchers should strictly obey “The Randomized Controlled Experiment Report Specification-Consort,”\textsuperscript{32} especially in TCM clinical trials to provide quality evidence for the second evaluation and to increase the strength of the arguments.

This meta-analysis found that SYI combined with conventional therapy for unstable angina is more effective than basic therapy alone in terms of improving the symptoms of angina and ECG. However, this conclusion should be interpreted with care because of the low quality of the included trials. More rigorous design, large samples, multicenter, and high-quality RCTs need to be performed before any firm conclusions can be drawn.

**ACKNOWLEDGEMENTS**

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REFERENCES


