Chinese patent medicine Xuefu Zhuyu capsule for the treatment of unstable angina pectoris: A systematic review of randomized controlled trials

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Summary

Background: Xuefu Zhuyu Capsule (XFZY) has been commonly used for relieving chest pain in patients with coronary heart disease (CHD). Randomized controlled trials (RCTs) on XFZY in treating unstable angina (UA) have not been systematically reviewed. Objective: This study aims to provide a PRISMA-compliant systematic review to evaluate the efficacy of XFZY in treating UA. Methods: An extensive search of 7 medical databases was performed up to June 2013. RCTs involving XFZY or combined with conventional drugs versus conventional drugs were identified. Meta-analysis was performed to evaluate the cardiovascular effects of XFZY. Rev Man 5.0 was used for data analysis.

KEYWORDS
Xuefu Zhuyu; Guan xin bing (coronary heart disease); Bu Wen Ding Xin jiao tong (unstable angina pectoris)
Results: 8 RCTs were included in this review. Statistical analysis of the results showed that XFZY combined with conventional drugs had significant effect on relieving angina symptoms (RR: 1.26 [1.16, 1.38]; P < 0.00001) and improving ECG (RR: 1.20 [1.04, 1.38]; P = 0.01) compared with conventional drugs alone. No severe adverse events were reported.

Conclusions: XFZY combined with conventional drugs appears to have potential cardiovascular effects in treatment of UA with few adverse events. However, further rigorous designed trials are still needed.

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Introduction

Angina pectoris, a symptom of coronary heart disease (CHD), manifests as stress-induced ischemic episodes resulting in severe chest pain. 1 When the same symptoms occur at rest or become severe, unstable angina (UA) is the diagnosis. 2 UA is an acute coronary syndrome and should be treated as an emergency. It can increase risk of acute myocardial infarction (heart attack) and severe cardiac arrhythmias which leading to sudden death. 3 Therefore, treatment should begin as soon as possible after onset of unstable angina. The ACC/AHA guidelines support anti-ischemia therapy, antiplatelet therapy and antithrombotic therapy. Anti-ischemia therapies include nitroglycerin, beta blocker, and oxygen as required. Antiplatelet therapies include aspirin, clopidogrel, and platelet glycoprotein IIb/IIIa inhibitor. Antithrombotic therapies include heparin and low-molecular-weight heparin. 4,5 Therapeutic aims are to improve quality of life by decreasing anginal attacks and to prevent myocardial infarction and death. But not all of these drugs are useful in every form of UA, and treatment is symptomatic rather than curative. 6 The other drawbacks of current anginal medications are adverse effects and drug resistance. 7 Treatment of UA with good prognosis remains a challenging clinical issue.

Chinese herbal medicine (CHM) has a 3000-year-old history with unique theories for concepts of etiology and systems of diagnosis and treatment. 8 Recently, there is a growing and sustained interest in the benefits of CHM and potential drug interactions with western medications, especially for patients with UA. 9,10 CHM has been used for activating the blood and resolving stasis in clinical practice for the treatment of UA in China. Xuefu Zhuyu Tang, a famous formula for treating Xueyu (blood
stagnation), consists of rehmannia root (shengdi), peach seed (taoren), Safflower (honghua), Chinese angelica (danggu), red peony root (chishao), platycodon root (jiegeng), orange fruit (zhiqiao), hare’s ear root (chaihu), Sichuan lovage root (chuanxiong), two-toothed achyranthes root (niuxi), and prepared liquorice root (gancao). Xuefu Zhuyu Tang has been made into various high standard pharmaceutical preparations such as capsule, pill, tablet, granule and oral liquid. For instance, Xuefu Zhuyu Capsule (Hong Ren Tang Pharmaceutical Co., Ltd., Tianjin, China) consists of rehmannia root (shengdi) 43.24 mg, peach seed (taoren) 43.24 mg, Safflower (honghua) 43.24 mg, Chinese angelica (danggu) 43.24 mg, red peony root (chishao) 43.24 mg, platycodon root (jiegeng) 32.44 mg, orange fruit (zhiqiao) 32.44 mg, hare’s ear root (chaihu) 32.44 mg, Sichuan lovage root (chuanxiong) 43.24 mg, two-toothed achyranthes root (niuxi) 21.62 mg, prepared liquorice root (gancao) 21.62 mg. The total dose is 2.4 g for one day. Experimental studies have shown that XFZY can increase coronary blood flow, improve the cardiac microcirculation, prevent platelet aggregation, and accommodate blood lipids.\textsuperscript{11,12}

Several studies published in China have reported that XFZY can enhance the effect of relieving of angina symptoms, decreasing the dosage of nitroglycerin and lessening side effects for patients with UA.\textsuperscript{13–16} Liu et al.\textsuperscript{16} had undertaken meta-analysis of Chinese patent medicine Xuefu Zhuyu capsule for the treatment of angina pectoris, which include stable and unstable angina pectoris trials together. However, the evidence supporting or disproving its cardiovascular effects is not robust. Our review presents a more vigorous attempt to examine the efficacy and safety of XFZY for patients with UA.

**Methods**

**Search strategy**


**Types of studies**

Randomized controlled trials that evaluate the cardiovascular effects of XFZY for UA were included. Quasi-RCTs were not considered.

**Types of participants**

The participants who suffering from and being treated for angina pectoris were included, regardless of the disease and severity. Diagnosis of UA was according to "the 2002 ACCF/AHA Guideline for the Diagnosis and Management of Patients with Unstable Ischemic Heart Disease (2002 ACCF/AHA)"\textsuperscript{17} or "the International Society and Federation of Cardiology/World Health Organization (ISFC/WHO)."\textsuperscript{18}

We did not intend to make any restrictions on age, gender, and race.

**Types of interventions**

The medicine of treatment group was XFZY combined with conventional drugs for patients with UA regardless of manufactures, preparation form, dose and duration. The study was designed to compare the effectiveness and safety of XFZY used only or in combination with conventional drugs versus conventional drugs alone or plus placebo.

**Types of outcome measures**

The primary outcome measures were mortality due to ischemic heart disease and the incidence of a heart event (e.g. AMI, severity arrhythmia, heart failure, revascularization). The secondary outcome measures were: (1) reduction of angina symptoms (e.g. Effective symptomatic improvements should achieve at least 50% or 80% reduction in frequency of feeling angina chest pain),\textsuperscript{18} (2) ECG improvement (e.g. Effective ECG improvements should achieve at least 0.05 mV lowering at ST segment in ECG or nearly normal ECG during an exercise test),\textsuperscript{18} and (3) quality of life.\textsuperscript{18} The adverse events were also measured.

**Study selection**

The titles and abstracts of potentially relevant references were identified through the literature search and reviewed independently by 2 reviewers (X. Yang, and X. Xiong) according to predefined criteria. Discrepancies regarding whether to include or exclude a study were resolved by consensus with other investigator (J. Wang).

**Data extraction**

The following data were extracted: (1) citations (authors of study, year of publication), (2) methodological information, (3) participants (sample size, age), (4) detailed information of interventions and controls, (5) outcome measures, and (6) adverse events. Two reviewers (X. Xiong, X. Yang) checked the disagreement of data extraction. Differences in data extraction were resolved by discussion.

**Trial quality assessment**

Two authors (Y. Zhang, G. Yang) independently assessed the methodological quality of included RCTs using Cochrane risk of bias tool. The qualities of included RCTs were assessed according to seven specific domains: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome data (attrition bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other
bias. When completing each of the seven domains for a study, information was provided according to RevMan 5.0: (1) a description of included study; and (2) their judgment on the risk of bias as a consequence of this. This judgment is categorized by using one of the three answers: 'high risk', 'unclear risk' and 'low risk'.

### Statistical analysis

Meta-analysis was performed if the intervention, control, and outcome were the same or similar. According to RevMan 5.0 provided by Cochrane Collaboration, dichotomous data were expressed as risk ratio (RR) and continuous outcomes as weighted mean difference (WMD), with their 95% confidence intervals (CI) respectively. The statistical heterogeneity was examined with the I²-test, where I² values of 50% or more were considered to be indicators of a substantial level of heterogeneity. In the absence of significant heterogeneity (I² < 50%), we pooled data using a fixed-effect model, otherwise we using random effects model (I² > 50%).

### Result

#### Literature search and study selection

Our initial searches finally identified 610 articles according to the search strategy, among which 252 studies were excluded because of duplicated publication. After checking the abstracts, 405 articles were excluded because of non-clinical studies, with obvious error, or with study objectives different from the aim of this review, etc (Fig. 1). Full texts of 53 articles were retrieved for further identification, and finally 8 RCTs were included according to the inclusion criteria. The included RCTs were all conducted in China and published in Chinese.

### Characteristics of the trials included

The characteristics of included RCTs were summarized in Table 1. The number of participants ranged from 28 to 50, with a total of 534 patients (265 patients in treatment groups) in the 8 studies. The age of the participants ranged from 35 years to 82 years. The studies included only interventions with XFZY plus conventional drugs versus conventional drugs alone or plus placebo. Because no RCTs of XFZY versus conventional drugs alone or plus placebo was founded. Conventional drugs referred to treatment according to the guidelines for UA, including platelet aggregation inhibitor (aspirin), nitrates, beta-blockers, calcium channel blockers, and ACE inhibitors. The total treatment duration ranged from 1 weeks to 8 weeks. Reductions in angina symptoms and improvement in ECG were the most commonly measured outcomes in the included studies. None trial adopted mortality as primary outcome. 1 trial reported the quality of life of UA patients.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Sample (T/C)</th>
<th>Diagnosis standard</th>
<th>Age</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Course (week)</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 Qiu and Yang 2012 [21]</td>
<td>30/30</td>
<td>1979</td>
<td>40–78</td>
<td>XFZY + conventional drugs</td>
<td>Conventional drugs</td>
<td>2</td>
<td>RAS</td>
</tr>
<tr>
<td>22 Zhang and Song 2006 [22]</td>
<td>50/50</td>
<td>ISFC/WHO 2002 ACCF/AHA</td>
<td>35–79</td>
<td>XFZY + Conventional drugs</td>
<td>Conventional drugs</td>
<td>3</td>
<td>RAS, ECG</td>
</tr>
<tr>
<td>23 Wang 2011 [23]</td>
<td>40/40</td>
<td>2002 ACCF/AHA</td>
<td>60.3 ± 8.3</td>
<td>XFZY + Conventional drugs</td>
<td>Conventional drugs</td>
<td>4</td>
<td>RAS, adverse event</td>
</tr>
<tr>
<td>24 Zhao et al. [24]</td>
<td>30/31</td>
<td>1979 ISFC/WHO</td>
<td>46–65</td>
<td>XFZY + Conventional drugs</td>
<td>Conventional drugs</td>
<td>1</td>
<td>RAS</td>
</tr>
<tr>
<td>25 Li et al., 2008 [25]</td>
<td>30/30</td>
<td>2002 ACCF/AHA</td>
<td>50–70</td>
<td>XFZY + isosorbide</td>
<td>Isosorbide dinitrate, aspirin</td>
<td>4</td>
<td>RAS, ECG</td>
</tr>
<tr>
<td>27 Wang and Lou 2009 [27]</td>
<td>28/28</td>
<td>1979 ISFC/WHO</td>
<td>Not clear</td>
<td>XFZY + Conventional drugs</td>
<td>conventional drugs</td>
<td>2</td>
<td>RAS, ECG,</td>
</tr>
</tbody>
</table>

Notes: XFZY: Xuefu Zhuyu Capsule; RAS: reduction of angina symptoms.
Methodological quality of included trials

All of these studies indicated randomization with a single-center, parallel-design, but most of them did not describe it clearly. 2 trials\(^{26,28}\) reported that the random sequence was generated by a random digits table. None of trials describe allocation concealment and methods of assessing compliance. 1 trial\(^{26}\) mentioned that they were single blind of subjects, but included no descriptions of the procedures. 1 trial\(^{26}\) reported drop-out or withdraw, but none of trials had a pre-trial estimation of sample size, which indicated the lack of statistical power to ensure appropriate estimation of the therapeutic effect.

Primary outcomes

None trial adopted mortality as primary outcome. There was no report of ischemic heart disease and the incidence of a heart event (e.g. AMI, severity arrhythmia, heart failure, revascularization).

Reduction of angina symptoms (RAS)

A total of 7 trials\(^{21–25,27,28}\) with 477 patients used reduction of angina symptoms (RAS) to measure the outcome. It is showed homogeneity in the results (\(P=0.74, I^2=0\)). Thus, we did a quantitative data synthesis (meta-analysis) by fixed-effects model. The outcome shows a statistically significant difference in favor of the combination group of XFZY and conventional drugs (RR: 1.26 [1.16, 1.38]; \(P<0.00001\)). It is suggested that XFZY plus conventional drugs had a better effect on relieving symptoms of angina (Table 2).

<table>
<thead>
<tr>
<th>Trials</th>
<th>Intervention (n/N)</th>
<th>Control (n/N)</th>
<th>RR [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>XFZY plus conventional drugs versus conventional drugs</td>
<td>1</td>
<td>26/30</td>
<td>19/30</td>
<td>1.37 [1.01, 1.86]</td>
</tr>
<tr>
<td>XFZY plus conventional drugs versus conventional drugs</td>
<td>1</td>
<td>47/50</td>
<td>41/50</td>
<td>1.15 [0.99, 1.33]</td>
</tr>
<tr>
<td>XFZY plus conventional drugs versus conventional drugs</td>
<td>1</td>
<td>37/40</td>
<td>30/40</td>
<td>1.23 [1.01, 1.51]</td>
</tr>
<tr>
<td>XFZY plus conventional drugs versus conventional drugs</td>
<td>1</td>
<td>28/30</td>
<td>21/31</td>
<td>1.38 [1.06, 1.79]</td>
</tr>
<tr>
<td>XFZY plus isosorbide dinitrate and aspirin versus isosorbide dinitrate and aspirin</td>
<td>1</td>
<td>28/30</td>
<td>24/30</td>
<td>1.17 [0.95, 1.43]</td>
</tr>
<tr>
<td>XFZY plus conventional drugs versus conventional drugs</td>
<td>1</td>
<td>25/28</td>
<td>18/28</td>
<td>1.39 [1.02, 1.88]</td>
</tr>
<tr>
<td>XFZY plus conventional drugs versus conventional drugs</td>
<td>1</td>
<td>28/30</td>
<td>21/30</td>
<td>1.33 [1.04, 1.72]</td>
</tr>
</tbody>
</table>

ECG improvement

A total of 4 trials\(^{22,25,27,28}\) with 276 patients used ECG to measure the outcome. It is showed homogeneity in the results (\(P=1.2400, I^2=0\)). Thus, we did a quantitative data synthesis (meta-analysis) by fixed-effects model. The outcome shows a statistically significant difference in favor of the combination group of XFZY and conventional drugs (RR: 1.20 [1.04, 1.38]; \(P=0.01\)). It is suggested that XFZY plus conventional drugs had a better effect on improving ECG (Table 3).

<table>
<thead>
<tr>
<th>Trials</th>
<th>Intervention (n/N)</th>
<th>Control (n/N)</th>
<th>RR [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>XFZY plus conventional drugs versus conventional drugs</td>
<td>1</td>
<td>36/50</td>
<td>30/50</td>
<td>1.20 [0.90, 1.60]</td>
</tr>
<tr>
<td>XFZY plus isosorbide dinitrate and aspirin versus isosorbide dinitrate and aspirin</td>
<td>1</td>
<td>27/30</td>
<td>23/30</td>
<td>1.17 [0.93, 1.48]</td>
</tr>
<tr>
<td>XFZY plus conventional drugs versus conventional drugs</td>
<td>1</td>
<td>24/28</td>
<td>20/28</td>
<td>1.20 [0.91, 1.59]</td>
</tr>
<tr>
<td>XFZY plus conventional drugs versus conventional drugs</td>
<td>1</td>
<td>23/30</td>
<td>19/30</td>
<td>1.21 [0.86, 1.69]</td>
</tr>
</tbody>
</table>

Improvement of life quality

Two trials\(^{26,28}\) reported the improvement of life quality of patients after 4–8 weeks of treatment with XFZY combined with conventional drugs. The statistical data show that XFZY plus conventional drugs was better than conventional drugs alone with regard to relieving body symptoms (MD: 8.03 [1.12, 14.96]) and promoting anginal stability (MD: 12.13 [4.61, 19.65]).

Publication bias

Due to no sufficient number of trials, we failed to perform funnel plot to detect publication bias.

Adverse effect

Five trials\(^{23,28}\) reported adverse effects relating to the treatment by XFZY combined with conventional drugs. The adverse effects included headache and nausea. The approximate rates of these adverse effects were 2% (6/265) and
1.5% (4/265) respectively. No severe adverse events were reported.

Discussion

This systematic review included 8 randomized trials and a total of 534 participants. The main findings of this systematic review were that XFZY combined with conventional drugs demonstrated potential effect on relieving symptoms of angina (RR: 1.26 [1.16, 1.38]; P < 0.00001) and improving ECG (RR: 1.20 [1.04, 1.38]; P = 0.01) compared to conventional drugs alone. XFZY as an adjunctive treatment to conventional drugs has good effects on treating patients with UA. However, the evidence remains weak due to the low-quality of the trials. Thus, available data are not adequate to draw a definite conclusion of combination therapy for UA. And the positive findings should be interpreted conservatively due to the following facts.

Firstly, the quality of the included RCTs was generally low. (1) Randomization: all the included trials claimed randomization; however, 2 trials provided sufficient information on randomization.20,28 The other trials mentioned randomization but without further details, which did not allow a proper judgment of the conduct of the trials. It could lead to selection bias. (2) Blinding: only 1 trial26 mentioned that they were single blind of subjects, but included no descriptions of the procedures. The rest studies were lack of any blinding method, either blinding of participants and personnel or blinding of outcome assessment. It could directly lead to performance bias due to patients and researchers being aware of the therapeutic interventions for the subjective outcome measures. (3) Sample size: none of trials had a pre trial estimation of sample size, which indicated the lack of statistical power to ensure appropriate estimation of the therapeutic effect. And all of the included trials were of single center. Sample size calculation should be conducted before enrollment. (4) Placebo controlled: 1 trial26 had placebo control, which use “A+B versus B+placebo of A”; however, the rest included trials used “A+B versus B” design which patients were randomized to receive XFZY plus conventional drugs treatment versus conventional drugs control treatment without a rigorous control for placebo effect. Consequently, positive conclusions would be draw due to nonspecific placebo effects. (5) Analysis of data: only 1 trial26 had reported the dropouts, but without the intention-to-treat analysis. Therefore, the positive findings should be interpreted conservatively. It could lead to attrition bias. Nevertheless, there were 2 trials25,26 conducted by 3–7 authors. The rest 6 trials were only conducted by one or two authors. It is difficult to accomplish an RCT which including randomization, allocation concealment, blinding and analysis by less than 3 doctors. It could also lead to performance bias.20–22

Secondly, all the included trials used reduction of angina symptoms or ECG test as the main outcomes. There were only a few trials report the original data about the frequency and duration of chest pain or reduction of nitroglycerin dose, however it was indicated a substantial level of heterogeneity of these data, and meta-analysis did not be adopt. All the RCTs claimed that the positive effect of XFZY combined with conventional drugs is better than conventional drugs alone. Negative findings almost have not been reported. We tried to conduct extensive searches for unpublished material, but no unpublished “negative” studies were found, which could lead to publication bias.

Thirdly, patients in UA should be treated carefully because the risk of acute MI and severe cardiac arrhythmias may increase and lead to sudden death. Indeed, none of the included trials reported the mortality rate or the incidence of complications. It is likely to require longer periods of treatment due to the duration of included trials only ranged from 1 to 8 weeks. Moreover, the severity of angina symptoms may exacerbate without reasonable treatment, thus a longer follow-up period with serial measurements of outcomes is suggested to determine the long-term efficacy of Chinese patent medicine.23–25

Fourthly, the safety problem of integrative medicine therapy with both conventional western medicine and tradition medicine is generally concerned.26,27 Herb-drug interaction is an important focus of this systematic review. There were 2 trials reported the adverse effect of XFZY in combination with conventional drugs. The main adverse effects included headache (6/265) and nausea (4/265). Considering that limited report of adverse events, conclusions on the safety of XFZY could not be drawn.

Generally, as the quality of 8 trials reviewed and included in meta-analysis were generally weak, further high quality trials are needed to assess the effectiveness of XFZY combined with conventional drugs in treating UA. To improve the trial design quality, future researchers should follow the basic guidelines for reporting clinical trials such as the CONSORT statement, and treatment process should be monitored rigorously and reported appropriately in the future clinical trials.38–42

Conclusion

Our systematic review suggest that XFZY in combination with conventional drugs may have good effect on reducing angina symptoms and improving ECG with few side effects for patients with UA. However, the definite conclusion cannot be drawn due to the low quality of included trials. More rigorously designed, large-sample, randomize controlled trials should be performed in the future.

Conflicts of interests

All authors declare that they have no conflicts of interests.

Acknowledgments

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