Abstract

OBJECTIVE: To evaluate systematically the efficacy and safety of Danshenchuanxiongqin Injection (DCI) in the treatment of unstable angina pectoris (UAP).

METHODS: Randomized controlled trials (RCTs) regarding DCI used for treating UAP were searched in English and Chinese electronic databases from inception to January 2014. Two reviewers independently retrieved RCTs and extracted relevant information. The Cochrane risk of bias method was used to assess the quality of included studies, and a Meta-analysis was conducted with Review Manager 5.2 software.

RESULTS: Eleven RCTs involving 1034 participants were included. The methodological quality was relatively passable. The Meta-analysis indicated that the combined use of DCI and conventional treatment with Western Medicine (WM) was more efficacious in the outcomes of total effective rate [Relative Risk (RR) = 1.27, 95% CI (confidence interval; 1.18, 1.35), \( P < 0.00001 \)], the total effective rate of ECG [RR = 1.40, 95% CI (1.18, 1.66), \( P < 0.00001 \)], total cholesterol [Mean difference (MD) = −0.58, 95% CI (−0.83, −0.33), \( P < 0.00001 \)], total triglycerides [MD = −0.36, 95% CI (−0.54, −0.17), \( P = 0.0001 \)], and the number of ST-segment depression [MD = −0.36, 95% CI (−0.54, −0.17), \( P = 0.0001 \)]. There were two adverse drug reactions reported in one study.

CONCLUSION: Based on the systematic review, DCI combined with WM appeared to be efficacious in the treatment UAP. However, the evidence of DCI for treating UAP requires large-scale and double-blind RCTs to substantiate these findings.

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Key words: Danshenchuanxiongqin injection; Angina, unstable; Review; Meta-analysis

INTRODUCTION

Unstable angina pectoris (UAP) is a series of clinical syndromes, which belongs to ischemic cardiovascular and cerebrovascular diseases. It has the characteristics with severe chest pain, long duration, poor efficacy of nitrates, and easily deteriorating into AMI or sudden death. Therefore, UAP has been one of research hot-spots in recent years.
Modern medical research has shown that the pathological basis of UAP is local coronary artery with ischemic lesion, which is mainly related to vascular endothelial injury, platelet activation barriers, inflammation response, vasospasm, thrombosis formation and other relevant factors. Currently, the conventional therapy with Western Medicine (WM) includes anti-ischemia, anti-thrombosis, thrombolysis and lipid-lowering, however, the treated patients may have headaches, heart palpitations, or other side effects that caused by the overdosage. In view of this, to explore an efficacious, safe, convenient and economical treatment measure is very important.

In Traditional Chinese Medicine, UAP can be treated by invoking Qi and promoting blood circulation. Danshenchuanxiangqin injection (DCI) is a phytochemical drug that synthesized by Ligustrazine Hydrochloride (chemical name: 2,3,5,6-tetramethyl pyrazine hydrochloride), which is extracted from Chuanxiong (Rheumoff Chuanxiong), and tanshinol (chemical name: β-(3, 4-dihydroxyphenyl) lactic acid), which is extracted Danshen (Radix Salviae Miltiorrhiae). Modern research has shown that tanshinol can increase coronary blood flow, improve microcirculation, promote open collateral circulation, reduce extent of myocardial ischemia, and protect the ischemic myocardium. At the same time, it can improve blood rheology index, increase the hypoxia tolerance, anti-oxidation of lipid, reduce free radicals, and so on. Ligustrazine is a new calcium antagonist, which can inhibit the production of free radical, improve the activity of endogenous superoxide dismutase, inhibit platelet aggregation and fibrinosis, and regulate the lipid Metabolism. The two active ingredients are combined to have strong efficacy on dilating coronary arteries, reducing blood viscosity, improving hemodynamics and microcirculation, regulating the platelet function and anticoagulation.

There was one systematic review regarding DCI in the treatment of angina pectoris, but it may lack some preciseness that drugs used in control groups had big difference. Therefore, it is necessary to assess the current trials to systematically review the potential effect and safety for the use of DCI in the treatment of UAP.

MATERIALS AND METHODS

This study was conducted according to the Cochrane practice, including pre-specified objectives, search strategy, inclusion and exclusion criteria, quality assessment, data collection and Meta-analysis.

Study search

Randomized controlled trials (RCTs) were respectively retrieved by searching the following databases from January 1979 to January 2014: China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), Chinese Biomedical Literature Database (CBM), PubMed, and Cochrane Library. No limit placed on published language.

Different search strategies were combined as follows: for English databases, such as PubMed, the search terms included (“Danshenchuanxiangqin” [Full text] OR "danshen chuanxiongzine" [Full text] OR "danshencxuanxiangqin” [Full text] OR "danshencxuanxiangqin” [Full text] OR "danshencxuanxiangqin” [Full text] OR "danshencxuanxiangqin” [Full text]) AND (“Unstable angina pectoris” [MeSH terms] OR "angina” [MeSH terms] OR "pectoris” [MeSH terms] OR "preinfarction angina” [MeSH terms] OR "preinfarction anginas’); for Chinese databases, such as CNKI, the search terms included (“Danshencxuanxiangqin” [MeSH terms]) AND “Bu Wen Ding Xin Jiao Tong” [MeSH terms] OR “Bu Wen Ding Xing Xin Jiao Tong” [MeSH terms]).

Inclusion criteria

Studies met the following criteria were included. RCTs regarding DCI in the treatment of UAP were included, regardless of blinding. The diagnostic criterion of UAP was determined by Branch of Chinese Medical Society of Cardiology in 2000, which including the frequency of chest pain paroxysm, the duration, the activity thresholds induced angina, and the abnormal ST-segment of ECG. No limit was placed on patients’ age, gender, and races. The experiment group and control group were both given the WM therapy, such as anti-ischemia, anti-thrombosis, thrombolysis and lipid-lowering. Based on the treatment that used in the control group, DCI was given to the experiment group. The efficacy criterion was "clinical guidelines for cardiovascular system drugs", which was determined by Ministry of Health Pharmaceutical Council in 1993. The primary outcomes were the total clinical effective rate and the total effective rate of electrocardiogram (ECG). The total effective rate = (number of patients of significantly effective + number of patients of effective) / total number × 100 %. Significantly effective was determined when the same degree of exercise did not cause UAP, at least reduce over 80%, or the improvement of angina degree is over grade II. Effective was determined by the number of angina episode decreased by 50%-80%, or the improvement of angina degree in grade I - II. Invalid was determined that the number of angina episode decreased within 50% , or the improvement of angina degree within grade I , even no improvement. The total effective rate of ECG = (number of patients of significantly effective + number of patients of effective) / total number × 100 %. Significantly effective was determined when ECG moves down, and the recovery of ST-segment is over 0.1mV or return to normal at resting. Effective was determined when the recovery of ST-segment is in 0.05-0.1 mV or the inverted T-wave is lighter than 50%. Invalid was determined when ECG is the same as that before treatment at resting. Secondary outcomes were hemorheology indicators, such as total cho...
olesterol, total triglyceride; the number of ST-segment depression, and the number of adverse drug reactions (ADRs) / adverse drug events (ADEs).

**Exclusion criteria**
We excluded the studies with the patients of active bleeding or internal bleeding history, acute myocardial infarction, severe hypertension, severe liver and kidney dysfunction, and any Chinese herbal medicine was combined use in both groups.

**Date extraction and quality assessment**
For the included studies, two reviewers extracted the data, and screened them according to the inclusion criteria. Any disagreements on data extraction and study evaluation were resolved through discussion. We strictly assessed the risk of bias of the included trials according to the Cochrane risk of bias tool. This assessed random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. For each item, there were three alternative grades of risk: low risk of bias, unclear, and high risk of bias. When inadequate information was presented in the article or we were unable to explicitly judge "high" or "low", the item was judged as "unclear". Two researchers independently completed and mutually checked the allocated grades. Any dispute solved through discussion or with the assistance of a third researcher.

**Statistical analysis**
Revman 5.2 software package that produced and updated by the Nordic Cochrane Centre was used to analyze the collected data. Relative risk (RR) was used for dichotomous data, and mean difference (MD) was used for continuous variables, both with 95% confidence interval (95% CI); \( P < 0.05 \) was considered statistically significant between experimental and control group. The Chi-square test was used for checking the heterogeneity between studies, and \( I^2 \) was used to show the size of heterogeneity. If \( P > 0.1 \) and \( I^2 < 50\% \), there was determined to be little heterogeneity between studies, then we used a fixed effect model, otherwise we should use a random effect model. If the number of included trials was sufficient, a funnel plot would be carried out to assess publication bias. Sensitivity analysis was performed on to inspect the stability of the result.

**RESULTS**

**Search result**
In this review, 67 articles were retrieved from the databases listed above. After excluding duplications, reviews and obviously irrelevant studies by reading the titles and abstracts, 37 papers were downloaded for further assessment. After reading full texts, studies that did not meet the inclusion criteria, non-RCTs, or individual clinical cases were excluded. A total of 11 studies were included,\(^{1,16,19-27}\) as shown in Figure 1.

![Figure 1 Flow chart of literature search](image-url)

- Studies that retrieved through databases (\( n = 67 \)): CNKI (\( n = 31 \)), Wan fang (\( n = 4 \)), VIP (\( n = 4 \)), CBM (\( n = 26 \)), PubMed (\( n = 0 \)), Cochrane Library (\( n = 1 \))
- Studies obtained through other resources (\( n = 0 \))
- Total (\( n = 67 \))
  - Excluding duplication (\( n = 30 \))
  - Full text (\( n = 37 \))
    - Excluding cases (\( n = 1 \)), and studies not meeting the inclusion criteria (\( n = 25 \))
    - RCTs meeting inclusion criteria (\( n = 11 \))
    - RCTs included in the Meta-analysis (\( n = 11 \))

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CNKI: China National Knowledge Infrastructure Database; CBM: Chinese Biomedical Literature Database; VIP: China Science and Technology Journal Database; RCTs: randomized controlled trials.
Studies description
Eleven included studies, which involved in 1034 participants, were all published in Chinese journal literature databases from 2008 to 2013. There were 544 participants in experiment group, while 490 in control group. The average age of the patients was approximately 62.2, and all trials included more males (64.0%) than females. All the interventions in experiment groups were DCI combined with WM that the same as control group, which were primarily nitrate, aspirin, statins, low molecular weight heparin, β-blockers, and so on. DCI was from Beit Pharmaceuticals Ltd. in Guizhou, and its dosage was almost 10 mL every day. The duration of both experimental and control group was about 2 weeks. More details regarding the individual trials were presented in Table 1.

Quality of the included studies
The included studies quality was evaluated by Cochrane risk of bias tool. There were 3 studies[16,20,25] described the method that used to generate the allocation sequence, one of which was based on the order of admission, and the other two were based on the random digit table, while others only mentioned "random". And all the studies did not refer blinding. Therefore, the quality of the included studies was relatively passable, and more details of the trials were presented in Figure 2.

Total clinical effective rate
There were 9 studies[11,16,19,23,26] compared the total clinical effective rate. After the test for heterogeneity ($P = 0.50 > 0.1$, $I^2 = 0 < 50\%$), we can use a fixed-effects model. The Meta-analysis showed that the clinical efficacy of DCI combined with WM was better than control group, the statistical difference between the two groups was significant [RR = 1.27, 95% CI (1.18, 1.35), $P < 0.0001$] (Figure 3).

Sensitivity analysis
To confirm the stability of the result of the total clinical effective rate, we respectively removed the most and the least weighted, and changed from fixed mode to random mode. After removing the most weighted (Lang et al[23]) was RR = 1.29 (95% CI (1.19, 1.40)). The result of removing the least (Zhao et al[22]) was RR = 1.27 (95% CI (1.18, 1.36)). The result of changing the mode was RR = 1.22 (95% CI (1.15, 1.30)). Comparing with the previous results, only the result of changing analysis mode appeared slight differences, the other two were no obviously diversity, and there was not any outlier, so the degree of the sensitivity of the study was not high.

Publication bias
We assessed publication bias of the total effective rate with the funnel plot. The result of the figure showed that there was publication bias in the analysis (Figure 4).

Total effective rate of ECG
There were 4 studies[20,23,26] compared the total effective rate of ECG. After the test for heterogeneity ($P = 0.74 > 0.1$, $I^2 = 0 < 50\%$), we used a fixed-effects model. The Meta-analysis showed that the therapy of DCI combined WM was more effective, the statistical difference between the two groups was significant [RR = 1.40, 95% CI (1.18, 1.66), $P < 0.0001$] (Figure 5).

Total cholesterol (TC)
There were 4 studies[22-25] mentioned TC. After the test for heterogeneity ($P < 0.0001$ 0.1, $I^2 = 89% > 25\%$), we should use a random model. The result showed that the effect of experiment group was better than the control group in decreasing TC. The statistical difference between the two groups was significant [MD = $-0.58$, 95% CI ($-0.83$, $-0.33$), $P < 0.0001$].

Total triglyceride (TG)
There were 4 studies[22,24] mentioned TG. After the test for heterogeneity ($P < 0.0001$, $I^2 = 86% > 50\%$), we should use a random model. The result showed that the therapy of DCI combined WM was more effective in decreasing TG. The statistical difference between the two groups was significant [MD = $-0.36$, 95% CI ($-0.54$, $-0.17$), $P = 0.0001$].

Number of ST-segment depression
There were 3 studies[11,22,23] mentioned the number of ST-segment abnormality that appears. After the test for heterogeneity ($P = 0.15$, $P = 46\% < 50\%$), we may use a fixed model. The result showed that the effect of experiment group was better than the control group in decreasing the number of ST-segment abnormality that appears. The statistical difference between the two groups was significant [MD = $-1.12$, 95% CI ($-1.45$, $-0.80$), $P < 0.0001$].

Safety
Only 1 study[10] reported 2 ADRs in the experiment group, which presented mild rash, and disappeared by slowing down the speed of infusion and using anti-allergic drugs. There were 6 studies[11,22,23,24,26] put forward clearly no ADR in their studies, and the other 4 studies[19,22,23,27] did not pay attention to that. Accordingly, we could not conclude that DCI was absolutely safe.

DISCUSSION
Following the literature analysis, we concluded that based on WM, DCI can significantly improve the treatment effect of UAP, which represented in increasing the total clinical effective rate and the total effective rate of ECG, improving the blood flow rheology index, especially reflected in the total cholesterol and total triglyceride, and reducing the number of ST-segment depression.

In the Meta-analysis, we discussed the outcomes including the total clinical effective rate, the total effective rate of ECG, total cholesterol, total triglyceride, and the number of ST-segment depression. The total
The total clinical effective rate, the total effective rate of ECG, ST-segment depression, angina pectoris, total triglyceride should be associated with lipid level. Total cholesterol and triglycerides can well represent the changes in lipid level, therefore, total cholesterol and total triglyceride should be important indicators for evaluating the efficacy of DCI in the treatment of UAP. In addition, blood rheology level and inflammation response are also important factors to cause the instability of plaque. However, few of the included studies compared the blood viscosity coefficient, sCD40L, CRP and other inflammatory factors.

From the results of the Meta-analysis and the statistics in clinical, we could find ADRs of DCI mainly occasionally presented rash. However, because Chinese herbal injections have the characters of multi-component and multi-target, widely different among patients, and many other influence factors, we should not ignore other ADRs that may be seen in clinical. For example, Song et al reported 1 case that DCI led to shock and low blood sugar, which may be related to Danshen (Radix Salviae Miltiorrhiza) that it can decrease the blood sugar and catecholamines (CA). CA can promote the glycogen gluconeogenesis by elevating the level of cAMP, which can cause a moderating effect on glucose metabolism in the end. Therefore, the medical staffs should observe the changes of patient’s condition when applied DCI. Another ex-
ample is Feng et al. reported 18 patients presented chills, fever, headache, accompanied by shortness of breath, cyanosis, blood pressure and other symptoms when injected DCI. And they found that the severity of symptoms of ADRs and age was positively correlated. Accordingly, special attention should be given to the elderly patients in clinical. In addition, DCI was not suitable to coexist with furosemide, there were varying degrees of turbidity when they two mixed, regardless the drug concentration, which should pay more attention in clinical.

In the systematic review, there were some limitations, which mainly included the following aspects. (a) The quality of the included RCTs was just passable, and lack large-scale RCTs. 8 of 11 studies marked "random" only, but did not describe specific random alloca-
tion method, and none of the articles mentioned blinding. (b) All trials were published in Chinese, but lack of RCTs in other languages, which may be related to DCI only to be used in China, so we could not exclude potential publication bias. Therefore, more studies with rigorously designed RCTs are needed to further improvement.

In conclusion, combined with all discussed above, the results of the Meta-analysis illustrated that the combined use of DCI and WM was more efficacious in the outcomes of the total clinical effective rate, the total effective rate of ECG, total cholesterol, total triglycerides, and the number of ST-segment depression. In summary, DCI in the treatment of UAP has many significant advantages, stability efficacy, but the safety of DCI that we could not have a clear conclusion on, which need medical staffs pay more attention when used.

REFERENCES