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Full Length Research Paper

Compound Danshen dripping pills for stable angina: Meta-analysis of randomized controlled trials

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The aim of this study was to perform a meta-analysis of randomized controlled trials (RCTs) comparing the compound Danshen dripping pill (DSP) with isosorbide dinitrate (ID) in treatment of stable angina. A search of MEDLINE and CNKI (China national knowledge infrastructure) databases was performed to investigate studies published from 1966 to 2010. Trials comparing the use of DSP versus ID in treating stable angina were assessed. Of the 245 studies screened, 15 RCTs including 1536 patients (DSP therapy 847; ID therapy 689) were analyzed. There was evidence that DSP treatment improved symptoms more than ID treatment (93.4% vs. 73.8%, odds ratios (OR) 4.92 points, 95% confidence intervals (CI) 3.36~7.20). DSP as compared to ID treatment also resulted in superior electrocardiograms (ECG) improvements (69.7% vs. 46.3%, OR 2.75 points, 95% CI 2.14~3.55). In addition, the results showed that DSP plus routine therapy compared with ID plus routine therapy increased the improvement in symptoms (93.6% vs. 79.2%, OR 4.04 points, 95% CI 2.16~7.56) and ECG results (70.8% vs. 51.3%, OR 2.72 points, 95% CI 1.79~4.12). The study suggested that DSP is an effective therapy option with which to treat stable angina.

Key words: Danshen, meta-analysis, angina pectoris.

INTRODUCTION

The compound Danshen dripping pill (DSP, fufang Danshen diwan in Chinese) consists of active herbal ingredients extracted from *Salvia miltiorrhiza* (Danshen in Chinese), *Panax notoginseng* (Sanqi in Chinese) and *Cinnamomum camphora* (Bingpian in Chinese). DSP represents an important and widely used drug for the prevention and treatment of cardiovascular diseases in China (Gao et al., 2003).

Phytotherapy has been used widely to treat human diseases (Neelkamal, 2009). Pharmacological studies have indicated that some traditional Chinese medicines can be used to treat cardio-cerebrovascular disease (Wu et al., 2007). The traditional herbal medicine Danshen has long been regarded as highly effective in activating circulation (Cheng, 2006). As one of the most commonly used drugs in China, DSP is mainly employed for therapeutic purposes, such as angina pectoris, chest tightness and ischemic alterations in the electrocardiograms (ECGs) (Zhu et al., 2004).

DSP has also been registered as a drug in several countries, including Vietnam, Russia, Cuba, the Korean Republic, and Saudi Arabia. DSP is the first traditional Chinese medicine product approved for phase II and phase III clinical trials by the Food and drug administration (FDA) in the USA (Zhou et al., 2005). Although DSP has been used for treatment of stable angina for many years, but its effectiveness has not been

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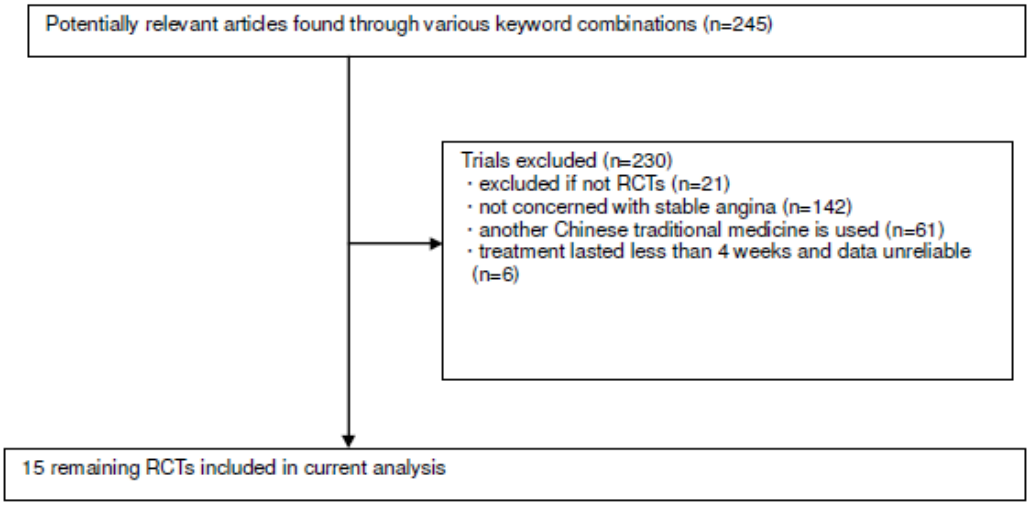

Figure 1. Analysis of the search results.

studied systematically. The current study of the meta-analysis of randomized controlled trials (RCTs) sought to determine the effects of DSP in the treatment of stable angina pectoris in comparison with isosorbide dinitrat (ID), which is the most commonly used clinical drug in mono-therapy or in combination with routine therapy.

MATERIALS AND METHODS

Search strategy

Medline (Nation Library of Medicine, USA) and CNKI (China national knowledge infrastructure, China) were searched to identify RCTs published in the area of coronary heart disease and DSP therapy from 1966 to September 16, 2010. The key words used in publication searches included Danshen, compound Danshen dripping pills, coronary heart disease, angina and treatment.

Data extraction

Data were independently extracted by two authors (Yanli Wang and Kena Wei) from inclusion trials, and any disagreement was subsequently resolved by discussion. Details extracted from the RCTs included the name of the first author, year of publication, age of participants in the DSP group and the control group, male-female ratio in each group, sample size and number of treatment responses in each group.

Inclusion criteria

The inclusion criteria applied were as follows:

(1) Patients included in the study were diagnosed with stable angina pectoris; (2) the study was conducted as an RCT; (3) DSP (mono-therapy or combination with routine therapy) was compared with ID (mono-therapy or combination with routine therapy); (4) no other traditional Chinese medicine except DSP was used; (5) treatment lasted 4 weeks or more.

Data analysis

The included trials were categorized by the type of treatment intervention, and the following comparisons were made:

(1) DSP versus ID; and (2) DSP plus routine therapy versus ID plus routine therapy. In the meta-analysis, a random effects model was used because of the indicated variability in patient populations among the 15 trials. The measure of association used in this meta-analysis was odds ratios (OR) with a 95% confidence interval (CI), as calculated by RevMan 4.2 (The Cochrane Collaboration, Oxford, UK). A statistically significant result was assumed when the 95% CI did not include one. A funnel plot was carried out to assess publication bias.

RESULTS

Literature search

Of the 245 publications identified through the electronic database search, 15 matched the selection criteria (Figure 1) (Zhang, 2009; Pan, 2008; Huang et al., 2004; Feng and Guo, 2002; Yao et al., 2002; Dong and Zhang, 2001; Zhu, 2001; Xue and Liu, 2001; Zhao, 2001; Gao and Wu, 2000; Zhu, 1999; Wang, 2008; Qiao et al., 2006; Fu, 2005; Li and Yang, 2005). There was unanimity between the two authors regarding the selection of related publications (Yanli Wang and Kena Wei,).

Clinical trial characteristics

The 15 trials included a total of 1536 patients (DSP therapy 847, ID therapy 689) were from Chinese patients. All trials showed angina symptom improvement and angina ECG improvement. The effective (including markedly and effective) and the invalid (including invalid and aggravation) were used as the criteria for efficacy judgments. The characteristics of the 15 included trials are summarized in Table 1.

Table 1. Characteristics of the trials included in the meta-analysis.

Study	Method	Participants	Intervention
Zhang, 2009.	RCT, not blinded Comparison: individuals Duration: 8 weeks	60 people (68 to 74 years) 46 male and 14 female	1 DSP (10 pills TID) 2 ID (10 mg TID)
Pan, 2008.	RCT, not blinded Comparison: individuals Duration: 6 weeks	80 people (51 to 70 years) 49 male and 31 female	1 DSP (10 pills TID) 2 ID (10 mg TID)
Huang et al., 2004.	RCT, not blinded Comparison: individuals Duration: 8 weeks	78 people (45 to 76 years) 47 male and 31 female	1 DSP (10 pills TID) 2 ID (10 mg TID)
Feng and Guo, 2002.	RCT, not blinded Comparison: individuals Duration: 8 weeks	120 people (40 to 70 years) 78 male and 42 female	1 DSP (10 pills TID) 2 ID (10 mg TID)
Yao et al., 2002.	RCT, not blinded Comparison: individuals Duration: 8 weeks	100 people (40 to 69 years) 77 male and 23 female	1 DSP (10 pills TID) 2 ID (10 mg TID)
Dong et al., 2001.	RCT, double blinded Comparison: individuals Duration: 4 weeks	60 people (40 to 72 years) 47 male and 13 female	1 DSP (10 pills TID) 2 ID (10 mg TID)
Zhu, 2001.	RCT, not blinded Comparison: individuals Duration: 8 weeks	160 people (40 to 70 years) 80 male and 80 female	1 DSP (10 pills TID) 2 ID (10 mg TID)
Xue and Liu, 2001.	RCT, not blinded Comparison: individuals Duration: 8 weeks	192 people (--) 139 male and 53 female	1 DSP (10 pills TID) 2 ID (10 mg TID)
Zhao, 2001.	RCT, not blinded Comparison: individuals Duration: 8 weeks	60 people (--) --	1 DSP (10 pills TID) 2 ID (10 mg TID)
Gao and Wu, 2000.	RCT, not blinded Comparison: individuals Duration: 8 weeks	90 people (38 to 74 years) 56 male and 34 female	1 DSP (10 pills TID) 2 ID (10 mg TID)
Zhu, 1999.	RCT, not blinded Comparison: individuals Duration: 8 weeks	90 people (50 to 82 years) 71 male and 19 female	1 DSP (10 pills TID) 2 ID (10 mg TID)
Wang, 2008.	RCT, not blinded Comparison: individuals Duration: 8 weeks	121 people (49 to 81 years) 78 male and 43 female	1 DSP (10 pills TID)* 2 ID (10 mg TID)*
Qiao et al., 2006.	RCT, not blinded Comparison: individuals Duration: 4 weeks	120 people (49 to 60 years) 90 male and 30 female	1 DSP (10 pills TID)* 2 ID (10 mg TID)*
Qiao et al., 2006.	RCT, not blinded Comparison: individuals Duration: 4 weeks	120 people (49 to 60 years) 90 male and 30 female	1 DSP (10 pills TID)* 2 ID (10 mg TID)*

Table 1. Contd.

Fu, 2005.	RCT, not blinded Comparison: individuals Duration: 4 weeks	75 people 53 male and 22 female	1 DSP (10 pills TID)* 2 ID (10 mg TID)*
Li and Yang, 2005.	RCT, not blinded Comparison: individuals Duration: 6 weeks	130 people (38 to 78 years) 78 male and 52 female	1 DSP (10 pills TID)* 2 ID (10 mg TID)*

DSP, compound Danshen dripping pill; ID, isosorbide dinitrate; BID, twice a day; QD, once a day; TID, three times a day; *, routine therapy aspirin 0.1 mg QD + lotension 5 mg QD + fluvastatin 40 mg QD + metoprolol tartrate 25mg BID (Wang, 2008); aspirin + calcium antagonist + β-receptor block agent + ACEI + Lipid-lowering drugs (Li and Yang, 2006); aspirin 75 mg QD + hydrochlorothiazide 6.25 mg QD (Fu, 2005), aspirin 75 mg QD (Fu, 2005); lipid-lowering drugs + aspirin (Li and Yang, 2005).

Meta-analysis

DSP versus ID

A total of 11 tested DSP against ID. A meta-analysis of the 11 trials (n = 1090) showed a significant increase in symptom improvement after treatment with DSP as compared with ID (93.4% vs. 73.8%, OR 4.92 points, 95% CI 3.36~7.20) (Figure 2). DSP also showed a significant increase upon ECG, as compared with ID (69.7% vs. 46.3%, OR 2.75 points, 95% CI 2.14~3.55) (Figure 3).

DSP plus routine therapy versus ID plus routine therapy

In all 4 trials, symptom improvement was greater for patients treated with DSP plus routine therapy as compared with patients treated with ID plus routine therapy (93.6% vs. 79.2%, OR 4.04 points, 95% CI 2.16~7.56) (Figure 2). The ECG improvement was also greater for patients treated with DSP plus routine therapy as compared to patients treated with ID plus routine therapy (70.8% vs. 51.3%, OR 2.72 points, 95% CI 1.79~4.12) (Figure 3).

Publication bias

Figure 4 shows a 'funnel plot' of the trials used in the meta-analysis. This is a scatter plot of the treatment effects estimated from the individual studies, which are plotted on the horizontal axis against the standard error of the estimate, which is shown on the vertical axis. Thirteen trials included in the meta-analysis lie on the 95% CI line and two lie outside the 95% CI line, implying the existence of some publications bias.

DISCUSSION

Stable angina is the most prevalent manifestation of coronary artery disease. It is a clinical syndrome that is characterized by a deep, viselike pain that is felt beneath the breastbone and over the heart and stomach, which sometimes radiates into the left shoulder and down the inner side of the left arm. Stable angina involves stenosis of the coronary artery, due to the increase in cardiac muscle burden, which results in rapid and temporary ischemia and heart muscle hypoxia (Daly et al., 2006). The mechanism of how DSP treats stable angina pectoris is not clear. Notably, Danshen (*S. miltiorrhiza*), the main component in DSP, is one of the most versatile Chinese herbal drugs and has been used for hundreds of years in the treatment of cardiovascular diseases. Currently, Danshen is widely used in several countries including the United States.

Clinical studies have shown that Danshen can improve microcirculation, induce coronary vasodilatation, suppress the formation of thromboxane, inhibit platelet adhesion and aggregation, and protect against myocardial ischemia, leading to improvement in both brachial flow-mediated dilation and carotid intima-media thickness (Zhou et al., 2005; Cheng, 2007; Wing et al., 2009). Experimental studies have also found that Danshen can inhibit oxidative modification of low-density lipoproteins and platelet aggregation via suppression of Ca^{2+} mobilization and arachidonic acid liberation. Danshen also reduce atherosclerosis through a cholesterol-lowering effect and possesses antioxidant effects that prevent endothelial damage, induces an endothelium-dependent vasodilation in coronary arterioles, protects the myocardium against hypertrophy, and relaxes rat coronary artery by inhibition of calcium channels (Wu et al., 2009; Karmin et al., 2001; Takahashi et al., 2002; Wu et al., 1998; Lam et al., 2008; Pank et al., 2008). Side effects were also reported.

Some studies showed that there was mild gastrointestinal reaction during administration of DSP; patients were willing to continue the DSP treatment after taking other gastrointestinal drugs. Furthermore, taking the pill with food limited the severity of gastrointestinal side effects (Zhang, 2009; Pan, 2008; Feng and Guo, 2002; Zhao, 2001; Gao and Wu, 2000; Zhu, 1999; Wang, 2008). However, the current data from RCTs did not allow a full analysis of drug safety due to the limited amount of data; therefore, we suggest that more trials about the side

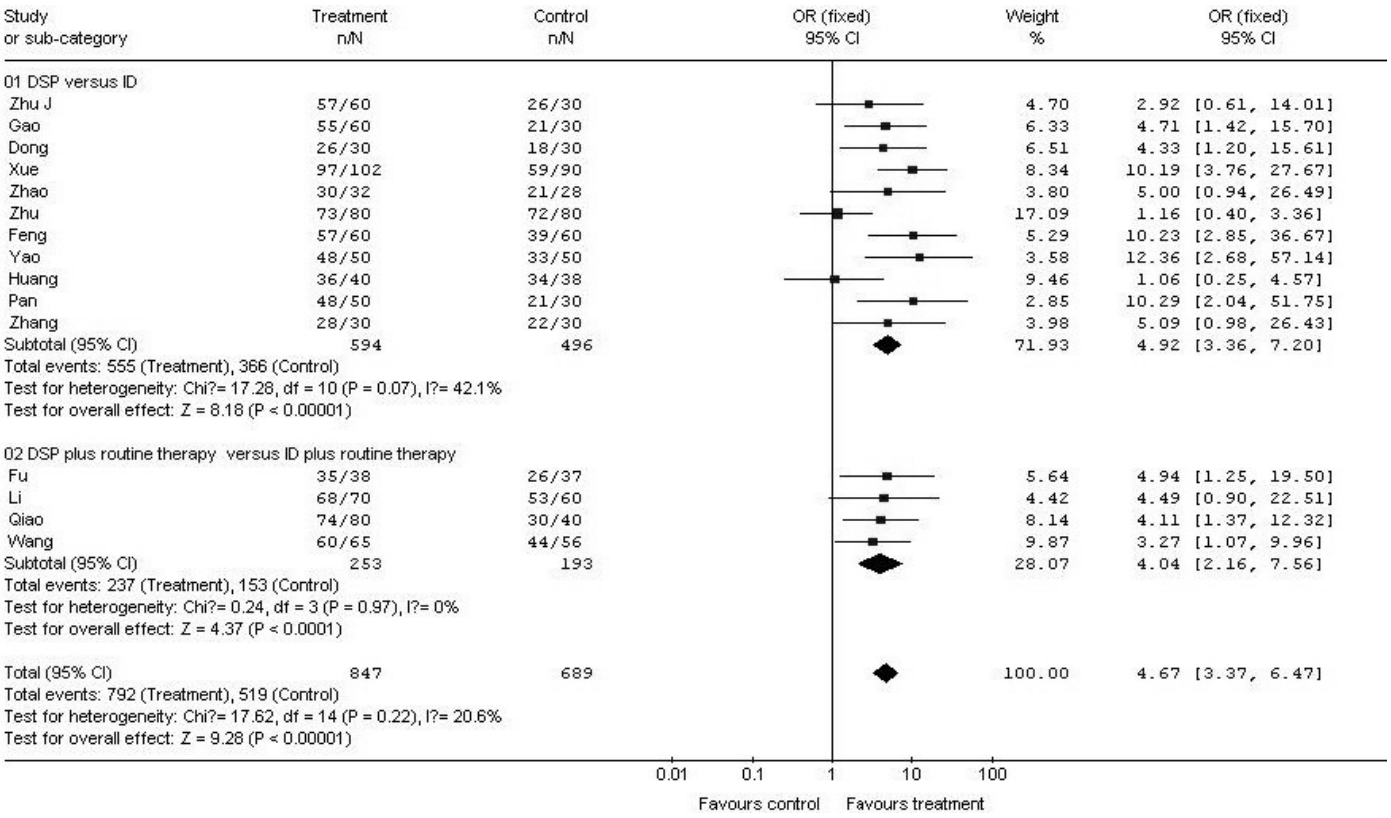

Figure 2. Symptom improvement. OR, odds ratios; CI, confidence interval; test for heterogeneity, chi-squared statistic with its degrees of freedom (d.f.) and P-value; inconsistency among results, I^2; test for overall effect; Z-statistic with P-value.

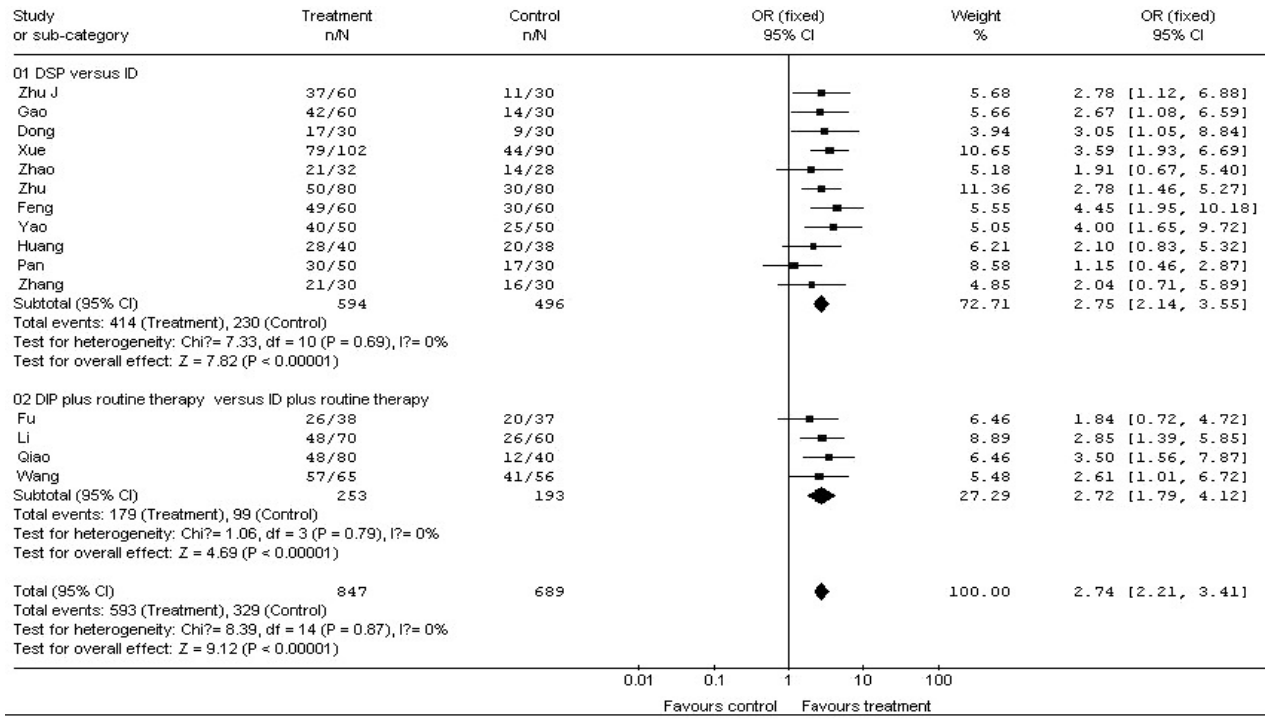

Figure 3. ECG improvement. ECG, electrocardiogram; OR, odds ratios; CI, confidence interval; test for heterogeneity, chi-squared statistic with its degrees of freedom (d.f.) and P-value; inconsistency among results, I^2; test for overall effect; Z statistic with P-value.

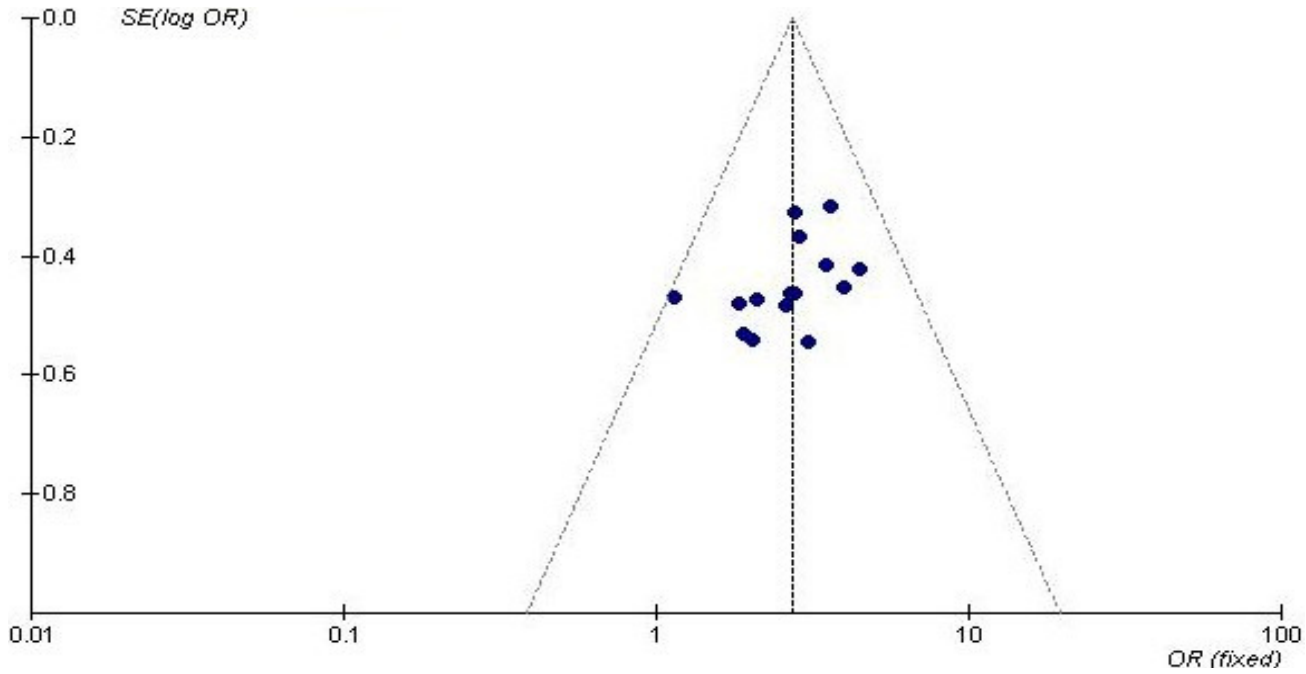

Figure 4. Funnel plot illustration. Trials are marked with dots. Dashed lines marks 95% confidence intervals.

effects of DSP are required to evaluate the safety of DSP. Based on 15 RCTs, the meta-analysis suggested that DSP is an effective therapy option to treat stable angina; the treatment results are better than those obtained with ID. However, there were limitations of the current meta-analysis. First, because DSP is a Chinese herbal medicine, all trials evaluated in this study were from patients of Chinese origin, raising an important question as to whether DSP is also effective for non-Chinese patients.

The US FDA has approved DSP's safety and effectiveness in US as shown by the US FDA's phase II clinical trials in July, 2010, and phase III investigations will be initiated soon. Therefore, it is possible that DSP will become the first traditional Chinese medicine product approved by the US FDA. Secondly, non-uniform criteria of efficacy were used to evaluate the included studies: Some used clinical observation (pain control) and others used ECG to evaluate the effects of after DSP and ID administration. One set of guidelines was derived from the Clinical assessment of coronary heart disease and ECG standards (1979), and the other was derived from the cardiovascular system guiding principles for clinical research on drugs (1993).

For most of the trials, the method of randomization was not reported clearly; only one of the studies used a double-blind design (Dong and Zhang, 2001), and described withdrawals and dropouts. Therefore, all the studies had a low Jaded scores (Jadad et al., 1996). Despite its limitations, we think that the current study offers useful information about the use of Chinese DSP for stable angina in humans.

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