Original Paper

Clinical Therapeutic Effects of Aspirin in Combination with Fufang Danshen Diwan, a Traditional Chinese Medicine Formula, on Coronary Heart Disease: A Systematic Review and Meta-Analysis

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Key Words

Fufang-Danshen-Diwan • Coronary heart diseases • Meta-analysis • Clinical effectiveness

Abstract

Background/Aims: Coronary heart disease is characterized by vascular stenosis or occlusion resulting in myocardial ischemia, hypoxia and necrosis. In China, the combination of aspirin and Fufang Danshen Diwan (FDD), a traditional Chinese medicine formula, has been suggested in the treatment of coronary heart disease. There have been several studies comparing the effectiveness of aspirin alone and in combination with FDD to treat coronary artery disease; however, it remains unclear whether combined aspirin therapy is superior. This study was thus designed to clarify this issue through a systematic review and meta-analysis.

Methods: Databases including PubMed, EMBASE, China National Knowledge Infrastructure (CNKI) database, Wanfang Data and VIP Information were searched. Papers were reviewed systematically by two researchers and analyzed using Cochrane software Revman 5.1.

Results: Fourteen randomized controlled trials enrolling 1367 subjects were included. Meta-analyses revealed that aspirin in combination with FDD was significantly more effective at alleviating angina pectoris and improving electrocardiogram (ECG) results relative to aspirin therapy alone, reflected by the summary effects for the clinical markedly effective (OR = 2.45; 95% CI 1.95–3.08) and the total effective (OR = 3.92; 95% CI 2.87–5.36) rates. In addition, combined aspirin and FDD was significantly more efficacious than aspirin monotherapy at improving blood lipid levels, as indicated by the following outcomes: 1) reduction of TC level (SMD –1.12; 95% CI –1.49 to –0.76); 2) reduction of TG level (SMD –0.94; 95% CI –1.15 to –0.74); 3) reduction of LDL level (SMD –0.68; 95% CI –0.88 to –0.48); and 4) improvement of HDL level (SMD 0.52; 95% CI 0.04 to 0.99). No serious adverse events were reported in any of the included trials. **Conclusion:** The present meta-analysis demonstrated that aspirin in combination with FDD was more effective than aspirin alone for treating coronary heart

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disease. More full-scale randomized clinical trials with reliable designs are recommended to further evaluate the clinical benefits and long-term effectiveness of FDD for the treatment of coronary heart disease.

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Introduction

In China, Fufang Danshen Diwan (FDD), an ancient traditional Chinese medicine (TCM) formula recorded in Chinese Pharmacopoeia (2015), has been found to be effective in treating coronary heart disease without side effects [1-3]. FDD has been used for relieving symptoms caused by chest congestion, which, according to TCM theory, results from qi stagnation and blood stasis. FDD consists of following three Chinese herbs: *Salvia miltiorrhiza* Bge (Dan-Shen); *Panax notoginseng* (Burk.) F. H. Chen (San-Qi); and *Borneolum* (Bing-Pian), with Danshensu [4], protocatechuic aldehyde [4] and salvianolic acid B [4] as the major active compounds of the formula. Many clinical trials have reported beneficial effects of aspirin in combination with FDD in the treatment of coronary heart disease in China. However, it is uncertain whether there is robust evidence of clinical effectiveness and safety for aspirin in combination with FDD due to the absence of a good quality systematic assessment. There were no studies published in English assessing the effectiveness and safety of aspirin in combination with FDD for the treatment of coronary heart disease.

In the present meta-analysis of randomized controlled trials (RCTs), we sought to determine the efficacy and acceptability of aspirin in combination with FDD in patients with coronary heart disease.

Materials and Methods

Search strategy

All prospective randomized controlled trials of aspirin in combination with FDD therapy in patients with coronary heart disease were searched. Relevant studies were identified in five electronic databases: PubMed (1949 to May 2016), Embase (1966 to December 2015), CNKI database (1915 to May 2016), Wanfang Data (1990 to May 2016) and VIP Information (1989 to May 2016) using the following terms: "coronary heart diseases", "aspirin", "Fufang Danshen Diwan", "Fu Fang Dan Shen Di Wan" and "compound danshen dripping pills". The search was not restricted by language of publication.

Inclusion criteria

To be included, trials were required to meet the following criteria: (1) patients were included in the studies according to diagnostic criteria of coronary heart disease established by the WHO, International Society of Cardiology and Association (ISCA), Internal Medicine, 7th edition (IM-7th), Practice of Internal Medicine, 14th edition (PIM-14th), Guidelines for the Diagnosis of Cardiovascular Diseases in Internal Medicine, 3rd edition (GIM-3rd) or conventional diagnostic criteria (CDC) including assessment of angina pectoris and electrocardiogram (ECG) results; (2) the study was conducted as a randomized controlled trial; (3) aspirin in combination with FDD was compared with aspirin monotherapy; (4) treatment lasted 4 weeks or more; and (5) more than 60 participants were included.

Quality assessment

Methodological quality of the included studies was scored using a modified Jadad scale with added allocation concealment [5, 6]. The Jadad scale criteria are described in Table 1. Trials scoring 1–3 points were considered low-quality, while trials scoring 4–7 points were defined as high-quality.

Each trial was reviewed by three reviewers (Jianchun Huang, Xiaojun Tang and Fangxing Ye), and differences were resolved by consensus or referral to two reviewers (Junhui He and Xiaolong Kong).

Data extraction

Protocol and treatment outcome data were extracted from the trials selected for meta-analysis. Information extracted included diagnostic instruments, efficacy measures, treatment regimen (combination treatment), control condition (monotherapy), duration of treatment and sample size.

Table 1. Modified Jadad score criteria

Sequence generation (points)	Allocation concealment (points)	Blinding method (points)	Withdrawal and exit (points)
2: Appropriate	2: Appropriate	2: Appropriate	1: Described
1: Unclear	1: Unclear	1: Unclear	0: Not described
0: Inappropriate	0: Inappropriate	0: Inappropriate	

Efficacy of the randomized controlled trials (RCTs) for coronary heart disease was determined on the basis of angina pectoris and ECG results. Treatment outcomes included dichotomous and continuous data. Dichotomous data were markedly effective rate and the total effective rate, generally defined as: 1) markedly effective: symptoms of coronary heart disease significantly alleviated, significant reduction in the number of angina pectoris attacks, and ECG recovery to normal levels; 2) effective: symptoms of coronary heart disease alleviated by more than 50%, reduced pain, ST segment of ECG depression of less than 0.05 mV or initial depression of ST segment elevated by more than 0.05 mV; 3) ineffective: angina symptoms not improved but aggravated, initial depression ST segment of ECG elevated by less than 0.05 mV or (and) T wave without change; and 4) total effective: markedly effective plus effective. Continuous data were means of baseline-to-endpoint changes in blood lipid levels including TC, TG, LDL and HDL levels, and pooled standard deviations were calculated for each arm accordingly.

Data analysis

The results were reported as odds ratios (OR) with 95% confidence intervals (95% CI) for dichotomous outcomes and standardized mean differences (SMD) with 95% CI for continuous outcomes. Heterogeneity between results of trials was tested using a standard χ^2 test. The fixed-effects model was used to combine dichotomous data if homogeneity was found. Alternatively, if heterogeneity was found, the random-effects model was used. Publication bias was examined using the funnel plot method. All meta-analyses were performed using Revman 5.1, provided by the Cochrane Collaboration.

We determined treatment effects on two dichotomous outcomes, the markedly effective rate and the total effective rate, and blood lipid levels, presented as the means and standard deviations (continuous data).

Results

Included studies and characteristics

Electronic searches identified 221 citations but 192 were excluded because neither titles nor abstracts indicated that patients with coronary heart diseases were included. The remaining 29 studies were retrieved, and we excluded 15 trials for the following reasons (Fig. 1): seven studies did not meet the diagnostic or efficacy measures criteria; three studies had data that could not be abstracted; two reports included results from a small sample of participants (less than 60); one study investigated multiple medication therapies; one trial was a duplicate publication; and one trial included only elderly participants. After exclusion, a total of fourteen reports were found to be eligible [7-20]. The descriptive information for each of these ten trials is shown in Table 2.

The included trials enrolled 1367 patients with coronary heart disease, of whom 703 received aspirin and FDD combination treatment and 664 received aspirin monotherapy.

Fig. 1. Flowchart of trial selection process.

Table 2. Characteristics of 14 RCTs of aspirin in combination with FDD treatment on coronary heart disease patients for meta-analysis. T, treatment group; C, control group; TID, three times a day; QD, once a day; NR, not reported; SB, single blind. WHO, diagnostic criteria of coronary heart disease established by WHO; ISCA, International Society of Cardiology and Association; IM-7th, Internal Medicine, 7th edition; PIM-14th, Practice of Internal Medicine, 14th edition; GIM-3rd, Guidelines for the diagnosis of cardiovascular diseases in Internal Medicine, 3rd edition; CDC, conventional diagnostic criteria

Author	n		Diagnostic criteria	Intervention		Treatment duration	Randomization detail	Blindness	Jadad score
	T	C		T	C				
Fu 2014 [7]	50	50	CDC	FDD (270 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	8 weeks	Simple randomization	SB	2
Hong 2015 [8]	64	64	WHO	FDD (270 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	8 weeks	Random number table method	SB	3
Jiang 2014 [9]	33	32	CDC	FDD (270 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	8 weeks	Simple randomization	SB	2
Li 2012 [10]	34	27	WHO	FDD (240 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	8 weeks	NR	SB	1
Li 2013 [11]	40	40	IM-7 th	FDD (250 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	8 weeks	Simple randomization	SB	2
Liang et al. 2012 [12]	59	30	WHO	FDD (270 mg, TID), aspirin (25-50 mg, QD)	aspirin (25-50 mg, QD)	2 years	Simple randomization	SB	2
Sun et al. 2014 [13]	108	108	ISCA	FDD (270 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	8 weeks	Simple randomization	SB	2
Wang 2011 [14]	38	38	WHO	FDD (270 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	8 weeks	Simple randomization	SB	2
Wang 2012 [15]	40	38	WHO	FDD (270 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	12 weeks	NR	SB	1
Wang 2013 [16]	31	31	CDC	FDD (270 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	8 weeks	Simple randomization	SB	2
Wang 2015 [17]	30	30	WHO	FDD (240 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	8 weeks	Simple randomization	SB	2
Xu 2013 [18]	30	30	PIM-14 th	FDD (270 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	4 weeks	Simple randomization	SB	2
Xu 2015 [19]	94	94	ISCA	FDD (270 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	8 weeks	Simple randomization	SB	2
Yu 2015 [20]	52	52	GIM-3 rd	FDD (270 mg, TID), aspirin (100 mg, QD)	aspirin (100 mg, QD)	8 weeks	Simple randomization	SB	2

All papers were published in Chinese and identified through electronic data search. The diagnosis of coronary heart disease was confirmed with diagnostic criteria established by the WHO in six studies [8, 10, 12, 14, 15, 17], ISCA in two studies [13, 19], IM-7th, PIM-14th or GIM-3rd in three studies [11, 18, 20]; and conventional diagnostic criteria in three studies [7, 9, 16]. In all studies, participant characteristics were similar at baseline between the different treatment groups. Ages of study participants ranged from 35 to 86 years. Of the participants, 559 were women.

Trial duration ranged from 4 weeks to 2 years: eleven studies lasted 8 weeks, and the other three studies lasted 4 weeks, 12 weeks and 2 years. All interventions were administered orally.

Methodological quality

All studies were of poor methodological quality (Jadad score ≤ 3) and at high risk of bias. Descriptions of the studies were poorly reported. All trials were of a parallel design, single-center and had a positive control group. Each study's methods contained words such as "randomly divided into two groups", but only one reported the use of a random number table method [8]. For most of the trials, the age, presence of comorbidity, and other relevant clinical features of coronary artery disease were not clearly reported. However, all study's results contained words such as "the sex, age, presence of comorbidity, and other relevant clinical features of CHD were not significant differences in the two groups before the treatment". No study mentioned blinding of participants or outcome assessors. Only three of the included trials described the follow-up process clearly and none of the included trials stated whether they analyzed the data based on the ITT principle. Information on dropout rates was not provided.

Quantitative analysis

Outcome 1: markedly effective rate. Fourteen studies contributed to this analysis, providing an overall sample of 1367 patients (703 in the treatment group and 664 in the

Fig. 2. Fixed effects meta-analysis of the effect of FDD plus aspirin versus aspirin alone on the markedly effective rate.

Fig. 3. Fixed effects meta-analysis of the effect of FDD plus aspirin versus aspirin alone on the total effective rate.

control group) [7-20]. The data were analyzed using a fixed-effects model according to the test of heterogeneity ($p = 0.43$; $I^2 = 2\%$). Three studies were reported as demonstrating significant or trend significant effects on coronary heart disease [7, 13, 19], and the other eleven studies were negative [8-12, 14-18, 20]. For the principal outcome, over the treatment period, there was higher markedly effective rate in the studies of patients with aspirin and FDD combination than in studies of patients with aspirin monotherapy treatment with an odds ratio of 2.45 (95% CI 1.95–3.08; $p < 0.00001$) (Fig. 2).

Outcome 2: total effective rate. Fourteen studies contributed to this analysis, providing an overall sample of 1367 patients (703 in the treatment group and 664 in the control group) [7-20]. The data were analyzed using a fixed-effects model according to the test of heterogeneity ($p = 0.65$; $I^2 = 0\%$). Ten studies were reported as demonstrating significant or trend significant effects on coronary heart disease [7, 10-16, 19, 20], and the other four studies were negative [8, 9, 17, 18]. For the principal outcome, over the treatment period, there was higher total effective rate in the studies of patients with aspirin and FDD combination than in studies of patients with aspirin monotherapy treatment with an odds ratio of 3.92 (95% CI 2.87–5.36; $p < 0.00001$) (Fig. 3).

Outcome 3: TC level. Four studies contributed to this analysis [12, 14, 16, 19], providing an overall sample of 415 patients (222 in the treatment group and 193 in the control group). The data were analyzed using a random-effects model according to the test of heterogeneity ($p < 0.00001$; $I^2 = 64\%$). All of the studies were reported as demonstrating significant reduction of TC level effects. For the principal outcome, after the post-treatment period, SMD

Fig. 4. Random effects meta-analysis of the effect of FDD plus aspirin versus aspirin alone on the TC level. **Fig. 5.** Fixed effects meta-analysis of the effect of FDD plus aspirin versus aspirin alone on the TG level. **Fig. 6.** Fixed effects meta-analysis of the effect of FDD plus aspirin versus aspirin alone on the LDL level. **Fig. 7.** Random effects meta-analysis of the effect of FDD plus aspirin versus aspirin alone on the HDL level.

for FDD plus aspirin versus aspirin alone was -1.12 (95% CI -1.49 to -0.76 ; $p < 0.00001$); these data showed a significant difference in TC levels between the two treatment groups (Fig. 4).

Outcome 4: TG level. Four studies contributed to this analysis [12, 14, 16, 19], providing an overall sample of 415 patients (222 in the treatment group and 193 in the control group). The data were analyzed using a fixed-effects model according to the test of heterogeneity ($p = 0.87$; $I^2 = 0\%$). All of the studies were reported as demonstrating significant reduction of TG level effects. For the principal outcome, after the post-treatment period, SMD for FDD plus aspirin versus aspirin alone was -0.94 (95% CI -1.15 to -0.74 ; $p < 0.00001$); these data showed a significant difference in TG levels between the two treatment groups (Fig. 5).

Outcome 5: LDL level. Four studies contributed to this analysis [12, 14, 16, 19], providing an overall sample of 415 patients (222 in the treatment group and 193 in the control group). The data were analyzed using a fixed-effects model according to the test of heterogeneity ($p = 0.47$; $I^2 = 0\%$). All of the studies were reported as demonstrating significant reduction of LDL level effects. For the principal outcome, after the post-treatment period, SMD for FDD plus aspirin versus aspirin alone was -0.68 (95% CI -0.88 to -0.48 ; $p < 0.00001$); these data showed a significant difference in LDL levels between the two treatment groups (Fig. 6).

Outcome 6: HDL level. Four studies contributed to this analysis [12, 14, 16, 19], providing an overall sample of 415 patients (222 in the treatment group and 193 in the control group). The data were analyzed using a random-effects model according to the test of heterogeneity ($p = 0.002$; $I^2 = 80\%$). One of the studies was reported as demonstrating significant increase of HDL level effects [16], and three studies were negative [12, 14, 19]. For the principal outcome, after the post-treatment period, SMD for FDD plus aspirin versus aspirin alone was 0.52 (95% CI 0.04 to 0.99 ; $p = 0.03$); these data showed a significant difference in HDL levels between the two treatment groups (Fig. 7).

Adverse events

Adverse effects of aspirin in combination with FDD for the treatment of coronary heart diseases were not mentioned in 5 studies. There were no noteworthy adverse events in 5 studies. The remaining 4 studies reported adverse events, mostly gastrointestinal upset, including nausea, sour regurgitation, and heartburn. However, there were no statistically significant differences between the aspirin monotherapy group and FDD plus aspirin group in terms of adverse events [18]. No serious adverse events were reported in any of the included trials. The patients' routine blood, urine, stool, blood sugar, blood fat, and renal and liver function tests were not affected [10, 17].

Follow-up period

Only three of the included trials clearly described the follow-up process. No patients were lost to follow-up. The results indicated that FDD plus aspirin resulted in an improvement in quality of life indices (including physiological function, physiological role, and emotional role scores) in CHD patients after one-year follow-up [8]. In the remaining 2 trials, rates of adverse cardiovascular events were significantly lower in the FDD plus aspirin group after one-year follow-up; in total, there were 6 cases of adverse cardiovascular events in the FDD plus aspirin treatment group and 26 cases in aspirin monotherapy group [13, 20].

Discussion

Coronary heart disease (CHD) is the single leading cause of death and disability in the world [21-25]. In Western medicine, lifelong aspirin and clopidogrel therapy has been found to be effective in reducing cardiac-related death, myocardial infarction and stroke [26]. However, dual Western medical antiplatelet therapy also has limitations, as stopping prematurely significantly increases the risk of myocardial infarction and death [27]. In China, traditional Chinese medicines such as FDD have a long history of integration with routine Western or conventional medical interventions. However, their effectiveness is controversial worldwide due to the absence of systematic overviews summarizing the existing evidence. The present meta-analyses suggest that the Chinese medicine formula FDD plus aspirin is an effective and safe therapy for patients with coronary heart disease. However, the included studies were of poor quality.

Fourteen studies involving 703 coronary heart diseases patients evaluated FDD in combination with aspirin. The results of the meta-analysis showed that the FDD plus aspirin was associated with better outcomes than aspirin monotherapy, as evidenced by overall effects of combination treatment that were significantly greater in the experimental group than the control group for markedly effective (OR = 2.45; 95% CI 1.95–3.08) and total effective (OR = 3.92; 95% CI 2.87–5.36) rates. In addition, four studies involving 222 coronary

heart diseases patients found that the efficacy of combination FDD and aspirin therapy was significantly better than aspirin as monotherapy in improving blood lipid levels, reflected by reductions in TC level (SMD -1.12 ; 95% CI -1.49 to -0.76), TG level (SMD -0.94 ; 95% CI -1.15 to -0.74), and LDL level (SMD -0.68 ; 95% CI -0.88 to -0.48) and improvement in HDL level (SMD 0.52 ; 95% CI 0.04 to 0.99). These results are broadly encouraging and suggest that combining FDD with aspirin might be beneficial. The robust effects could be, at least in part, supported by the better outcomes of coronary heart diseases treatment observed using integrated traditional medicine and western medicine. However, the results were only based on information regarding short-term effectiveness. No data on the long-term effectiveness of treatment was provided for analysis.

These results of our present meta-analysis are in accordance with previous reports describing the mechanisms by which FDD might reduce CHD risk. FDD can reduce CHD risk by improving biochemical indices in CHD patients, including reductions in the levels of TG, TC, LDL-C, lipoprotein (a), gamma-glutamyl transpeptidase, direct bilirubin, uric acid, and homocysteine. In contrast, FDD has also been associated with increases in levels of HDL-C, apolipoprotein (Apo) A, ApoB, ApoE, total bilirubin, and indirect bilirubin [28].

There was heterogeneity ($p < 0.1$, $I^2 > 50\%$) in both TC and HDL level analyses (Figs. 4 and 7). One of the primary reasons may have been that the dosage of aspirin was different in one of the trials [12]. This trial used a modified dosage of aspirin, which made the effect of FDD difficult to assess. Thus, standardization of dosage may be required. Another probable reason for presence of heterogeneity might have been the course of treatment between trials.

There are several limitations in the study. Most of the trials did not include a clearly described method of randomization and were not placebo-controlled, and none of the trials reported blinding of outcomes assessors. There was also no clear description of dropouts and withdrawals. The determination of treatment effect was performed based on the included studies, which had very low Jadad scores (Jadad score ≤ 3). The poor evidence does not allow any conclusions regarding the effectiveness of FDD, and none of the included studies were ideally suited to investigate the effectiveness of FDD in treating coronary heart disease. There is an obvious need to conduct a full-scale randomized clinical trial addressing these limitations and comparing the efficacy of FDD with placebo and pharmacotherapy in the same study.

Conclusion

In conclusion, the results of this meta-analysis including fourteen randomized controlled trials, and comparing Chinese medicinal formula FDD combination with aspirin to aspirin alone support the efficacy of a combination of FDD and aspirin, finding that combined therapy was significantly better than aspirin as monotherapy in treating patients with coronary heart diseases. However, the trials conducted to date have been of relatively low quality. More full-scale randomized clinical trials with reliable designs are recommended to further evaluate the clinical benefit and long-term effectiveness of FDD combined with aspirin for the treatment of coronary heart disease.

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Disclosure Statement

The authors declare no conflicts of interest.

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