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Original Article

The protective effect of suxiaojiuxin pill on coronary heart disease: a meta-analysis of randomized controlled trials

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Abstract: The traditional Chinese medicine suxiaojiuxin pill is having the protective efficacy on the coronary heart disease (CHD) patients. However, the efficacy has never been accurate assessed. This meta-analysis is performed to evaluate the effects of suxiaojiuxin pill based on randomized control studies. Randomized controlled trials (RCTs) were identified in the PubMed, Cochrane, Embase, Wanfang, CNKI, VIP database using the index words. The latest research was done in the December 2016. Relative risks (RR), mean difference (MD) along with 95% confidence interval (95% CI) were using to analysis the main outcomes. Thirty-nine studies were involved in the meta-analysis with 3560 patients in the treatment group and 2347 patients in the control group. Suxiaojiuxin pill could significant decrease the value of Whole Blood Low Shear Viscosity (WBLSV) (WMD = 1.43, 95% CI = 0.21-2.66), Whole Blood High Shear Viscosity (WBHSV) (WMD = 0.57, 95% CI = 0.28-0.85) when compared with standard therapy. Suxiaojiuxin pill could significant improve the Electrocardiogram efficient (RR = 1.30, 95% CI = 1.21-1.41). No significant difference was found in the level of Fibrinogen (WMD = 0.48, 95% CI = -0.14-1.10), Plasma Viscosity (WMD = 0.03, 95% CI = -0.02-0.07) and Packed Cell Volume (WMD = 2.97, 95% CI = -3.30-9.25). In conclusion, suxiaojiuxin pill showed better effect on Electrocardiogram efficient and significant decreased the value of WBLSV, WBHSV when compared with standard therapy. However, during to the low quality of included studies, there still need large sample and high quality studies to verify the clinical efficacy of suxiaojiuxin pill on CHD.

Keywords: Suxiaojiuxin pill, coronary heart disease (CHD), randomized controlled trial (RCT), meta-analysis

Introduction

Coronary Heart Disease (CHD) is a disease that caused by coronary atherosclerosis and makes the myocardial cells producing ischemia, anoxia and necrosis. According to the MONICA research in China, the morbidity and mortality of CHD has obviously increased in recently years. Otherwise, WHO estimated there will be four millions people died from CHD in China at 2020. The majority of CHD related death occurred in persons older than 65 years [1-3]. The spectrum of CHD includes subclinical CHD, chronic stable angina pectoris, unstable angina and acute myocardial infarction. Besides, large numbers of elderly patients have asymptomatic heart disease, so the prevalence of CHD may be underestimated [4]. Several large prospective clinical studies demonstrated that CHD was significantly associated with atrial fibrillation, congestive heart failure, stroke and several serious diseases. Therefore, effectively prevent angina, reduce the cardiovascular mortality and reduce the disease burden are the big challenge for the cardiovascular disease prevention in global [5-7].

Traditional Chinese were first documented by Confucian scholars about 2500 years ago. Nowadays, more than 100000 Chinese medicinal recipes have been applied in clinical practice [8, 9]. Suxiaojiuxin pill was made of Borneol and Ligusticum chuanxiong Hort. Several small clinical studies have been conducted the effect of suxiaojiuxin pill on CHD patients, but the result was not consistent. Therefore, we performed this meta-analysis to evaluate the benefits of suxiaojiuxin pill for CHD patients.

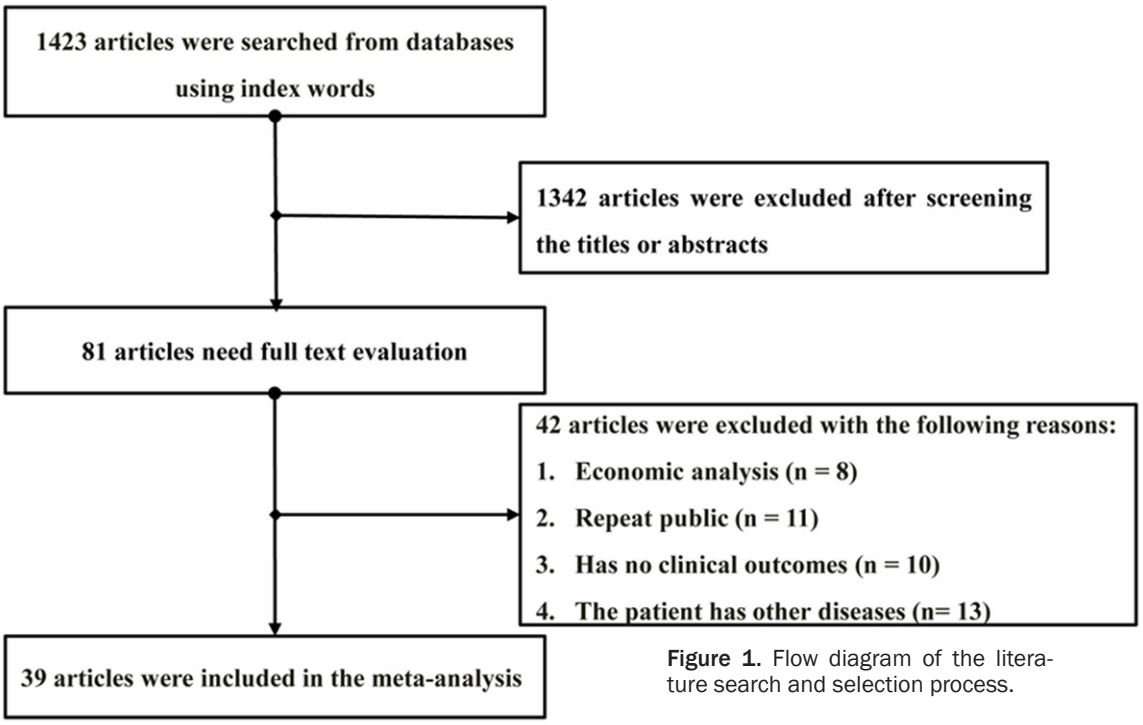

Figure 1. Flow diagram of the literature search and selection process.

Materials and methods

Literature search

The Cochrane, Pubmed, Embase, CNKI (China National Knowledge Infrastructure), WangFang and Weipu (VIP) were searched for all trials assessing the effect of suxiaojiuxin pill in the treatment of patients with CHD. Other related articles and reference materials were also searched and the latest research was performed on December 2016. Two investigators performed the literature search independently, a third investigator was involved when an agreement occurred.

Inclusion and exclusion criteria

A study was included if it was: 1) randomized control trial (RCT); 2) the research objects are patients with coronary heart disease and without others serious diseases; 3) the outcomes including electrocardiogram curative effect or blood rheology indexes; 4) the invention of treatment group is suxiaojiuxin pill without any others treatments, the invention of control group is standard therapy or others relative medicine.

A study was extracted if it was: 1) repeat published articles, or the content and result are same; 2) data are wrong, or has no outcomes that we need; 3) case report, conference report, systematic review, meta-analysis, expert comment; 4) the studies are chemical component analysis, pharmacological investigation, or animal experiment and so on.

Two reviewers independently screened all the studies to determine whether they satisfied the inclusion and exclusion criteria. Discrepancies were resolved by involved a third reviewer.

Data extraction and quality assessment

The data were extracted from included studies and consisted of two parts. The first part were about the basic information: the author name, publish time, the interventions of treatment group and control group, the sample size, the percentage of male, the main age. The second part were the clinical outcomes: the hemorrheology measurements including whole blood low shear viscosity (WBLSV), whole blood high shear viscosity (WBHSV), plasma viscosity (PV), packed cell volume (PCV), fibrinogen; the electrocardiogram (ECG). The Jadad scoring checklist was used to appraise the quality of involved studies. We evaluated all the RCTs from the five items: statement of randomization; appropriateness of generating randomized sequence; use of double blind; description of double blind-

Table 1. The basic characteristics description of the thirty-nine included studies

Study	No. of patients		Therapy		Gender (male)		Age		Jadad score
	T	C	T	C	T	C	T	C	
Guanhua He [25]	26	22	Suxiaojiuxin pill	Compound Salvia Tablet	18	15	42-60	40-57	1
Zhijin Song [23]	102	82	Suxiaojiuxin pill	Compound Salvia Tablet	72	51	55±7.2	56±6.9	1
Dongping Wang [29]	24	36	Suxiaojiuxin pill	Heart-protecting musk pill	-	-	-	-	1
Kefu Ji [14]	36	36	Suxiaojiuxin pill	Nitroglycerin Tablet	21	22	45-79	46-78	1
Yuchu Gao [11]	105	42	Suxiaojiuxin pill	Nitroglycerin Tablet	58	42	36-85	35-84	1
Yunyuan Guo [36]	161	157	suxiaojiuxin pill	Isosorbide Dinitrate	85	78	44-76	44-75	1
Li An [34]	103	51	Suxiaojiuxin pill	Isosorbide Dinitrate	56	28	58.93±10.91	59.25±10.12	1
Ling Feng [17]	430	70	Suxiaojiuxin pill	Compound Salvia Tablet	234	36	56±4.24	55±4.36	1
Mei Hu [37]	68	60	Suxiaojiuxin pill	Isosorbide Dinitrate	-	-	-	-	1
Xiaochun Liu [39]	78	60	Suxiaojiuxin pill	Isosorbide Dinitrate	-	-	-	-	1
Rubao Jia [19]	60	30	Suxiaojiuxin pill	Compound Salvia Tablet	38	22	-	-	1
Shudong Yang [45]	50	30	Suxiaojiuxin pill	Isosorbide Dinitrate	28	20	58.3±7.24	57.2±8.27	2
Guoping Yang [20]	46	40	Suxiaojiuxin pill	Isosorbide Dinitrate	30	26	50±13	53±15	1
Shaomin Li [33]	30	26	Suxiaojiuxin pill	Isosorbide Dinitrate	21	16	58±7	59±5	2
Yongjin Hou [12]	84	64	Suxiaojiuxin pill	Isosorbide Dinitrate	53	46	45-72	47-70	1
Guangyu Tang [43]	124	124	Suxiaojiuxin pill	Isosorbide Dinitrate	-	-	-	-	1
Lijun Zhou [16]	124	42	Suxiaojiuxin pill	Nitroglycerin Tablet	90	32	-	-	1
Yuping Li [38]	148	100	Suxiaojiuxin pill	Isosorbide Dinitrate	103	-	-	-	1
Yaxiong Zhan [15]	31	29	Suxiaojiuxin pill	Isosorbide Dinitrate	24	24	60-84	61-84	1
Jingxian Yuan [32]	52	50	Suxiaojiuxin pill	Pill for promoting coronary circulation	24	26	61.68±4.71	59.53±5.62	1
Kejie Duan [26]	40	40	Suxiaojiuxin pill	Xinkeshu capsule	25	22	42-79	41-75	1
Hai Shi [41]	40	30	Suxiaojiuxin pill	Isosorbide Dinitrate	21	16	57±7	59±6	1
Buce Sun [42]	50	50	Suxiaojiuxin pill	Isosorbide Dinitrate	31	-	32-72	-	1
Jin Gao [35]	98	80	Suxiaojiuxin pill	Isosorbide Dinitrate	-	-	-	-	1
Xianzhen Ma [21]	83	33	Suxiaojiuxin pill	Compound Salvia Tablet	50	20	63.4±6.74	62.9±7.84	1
Peifen Chang [10]	60	40	Suxiaojiuxin pill	Xinkeshu capsule	19	12	57.5±10.2	63.1±7.9	1
Yuesheng Zhao [31]	40	38	Suxiaojiuxin pill	Xinkeshu capsule	28	21	52-75	55-74	1
Gang Hu [13]	40	40	Suxiaojiuxin pill	Nitroglycerin Tablet	24	23	51.56±11.69	50.89±11.02	1
Wei Wan [28]	32	32	Suxiaojiuxin pill	Guanxinsuhe Pills	-	-	-	-	1
Shuixiang Wan [24]	46	27	Suxiaojiuxin pill	Compound Salvia Tablet	27	18	43-78	45-76	1
Shenghai Cao [8]	105	82	Suxiaojiuxin pill	Compound Salvia Tablet	59	45	57.15±5.38	58.77±5.01	1
Runlian Tang [44]	45	45	Suxiaojiuxin pill	Isosorbide Dinitrate	-	-	-	-	2
Fei Wang [30]	24	36	Suxiaojiuxin pill	Heart-protecting musk pill	15	20	63.9±12.1	64.1±11.2	1
Wen Luo [40]	46	42	Suxiaojiuxin pill	Isosorbide Dinitrate	29	27	56.7	56.8	1
Fenghua Song [22]	600	300	Suxiaojiuxin pill	Compound Salvia Tablet	421	165	-	-	1
Wensheng Li [27]	19	31	Suxiaojiuxin pill	Tongxinluo capsule	-	-	-	-	2
Weiqin Guo [18]	30	30	Suxiaojiuxin pill	Compound Salvia Tablet	17	16	42-70	43-73	1
Qiaokun Xu [9]	180	120	Suxiaojiuxin pill	Compound Salvia Tablet	100	70	39-82	40-81	1
Xiaojing Li [46]	100	100	Suxiaojiuxin pill	Compound Salvia Tablet	60	61	44-75	45-76	2

ing method; detail of withdrawals and dropouts. Studies with a score of less than 3 represented a low-quality and high bias risks, studies got a score exceed 3 were indicated as high-quality trail. All the above process was done by two reviewers independently. Disagreements between reviewers were resolved by discussion until a consensus was reached.

Statistical analysis

Chi-squared and I^2 tests were used to test the heterogeneity of clinical trial results. When the Chi-squared test *P*-value of ≤ 0.05 and I^2 tests-value > 50%, we defined it was acceptable heterogeneity and analysis by random-effects model. When the Chi-squared test *P*-value of > 0.05 and I^2 tests-value ≤ 50%, it was defined as homogeneous data and assessed by fixed-effects model. The continuous variables are expressed as the mean ± standard deviation. The categorical data are presented as frequencies and percentages. Relative risk (RR) along with 95% CI was used to analysis the ECG efficient. WBLSV, WBHSV, PV, PCV and fibrinogen were analysed by mean difference (MD) and

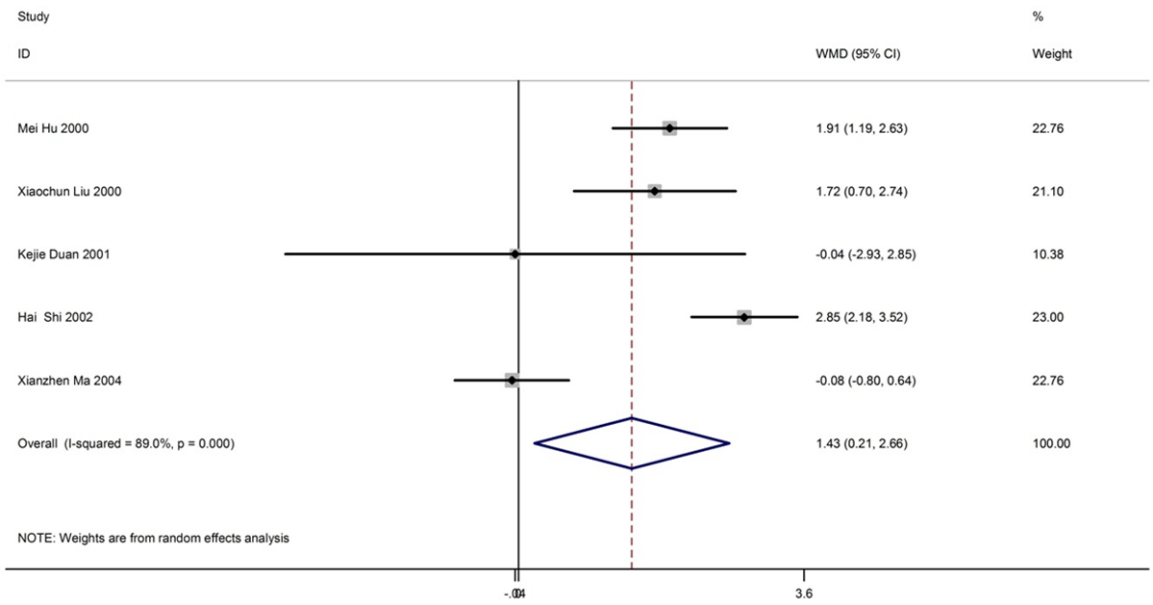

Figure 2. The forest figure of comparison between suxiaojiuxin pill and standard therapy in WBLSV.

95% CI. All statistical analyses were performed with the STATA 10.0 (TX, USA).

Results

The basic characteristics of included studies

The search strategy revealed 1423 potentially eligible articles. After screening the titles or abstracts, 1342 articles were removed. When the abstracts were reviewed in terms of the inclusion and exclusion criteria, 81 studies need further review. Among these, 42 studies were excluded for the reasons: economic analysis, repeat public, no clinical outcomes, the patients has others diseases. At last 39 studies [4, 8, 10-46] were all included in the meta-analysis (**Figure 1**). The basic characteristics of included studies were listed in **Table 1**. All the studies were conducted in china and designed as RCT. This analysis included 5907 patients, with 3560 patients in the treatment group and 2347 patients in the control group. There was 1881 male (52.70%) in the treatment group and 1020 male (43.46%) in the control group. The basic characteristics were balanced in the two groups. All the included studies were evaluated by the Jadad Scale, and the mean score is 1.13, so all the studies were low-qualities and high bias risks. In the control groups, 11 studies were treated by Compound Salvia Tablet, 1 study was treated by Compound Salvia Tablet, 2 studies were treated by Heart-protecting musk pill, 16 studies were treated by Isosorbide Dinitrate, 4 studies were treated by Nitroglycerin Tablet, 1 study was treated by pill for promoting coronary circulation, 1 study was treated by Tongxinluo capsule, 3 studies were treated by Xinkeshu capsule. All the treatment groups were treated by suxiaojiuxin pill.

Hemorrheology measurement

Five studies reported the change of whole blood low shear viscosity (WBLSV) (**Figure 2**) after treatment, based on the Chi-squared test *P*-value = 0.00 < 0.05 and I^2 tests-value = 89.0% > 50.0%, we chose random-effect model to analysis the WBLSV, the results showed that the decreased value of treatment group was significant higher (WMD 1.43, 95% CI 0.21-2.66) than the control group. Five studies reported the value of whole blood high shear viscosity (WBHSV) (**Figure 3**), random-effect model was chose for the Chi-squared test *P*-value = 0.012 < 0.05 and I^2 tests-value = 68.8% > 50.0%, the analysis showed that suxiaojiuxin pill could significant decrease the value of WBHSV when compared with the standard therapy. Five studies reported the value of plasma viscosity (PV) (**Figure 4**), the value of packed cell volume (PCV) (**Figure 5**) and fibrinogen (**Figure 6**) are separately provided by three articles, there has no significant difference (PV:

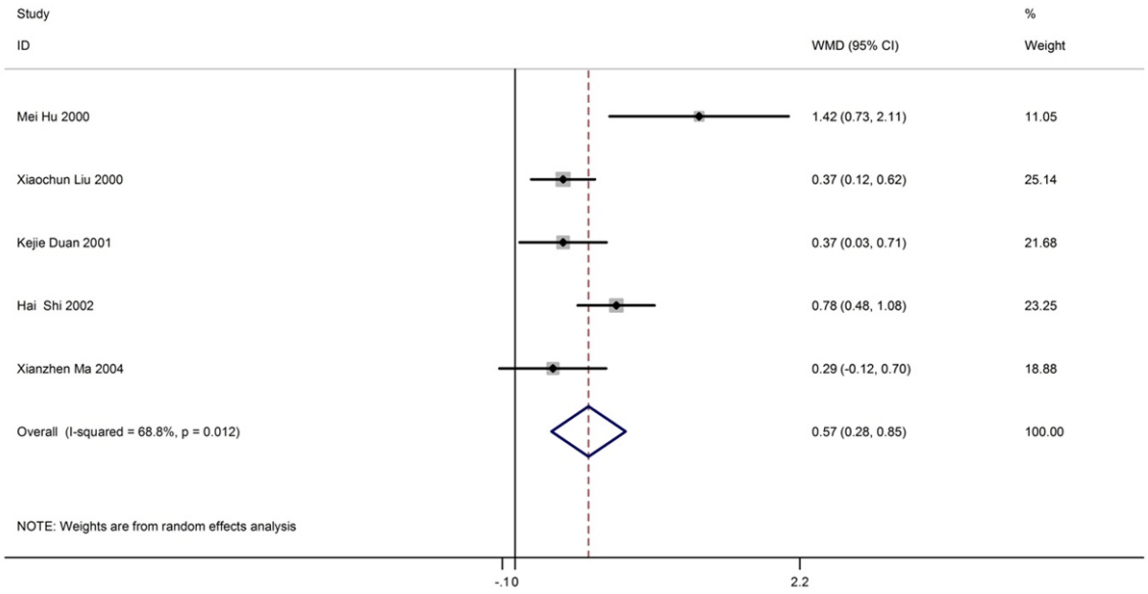

Figure 3. The forest figure of comparison between suxiaojiuxin pill and standard therapy in WBHSV.

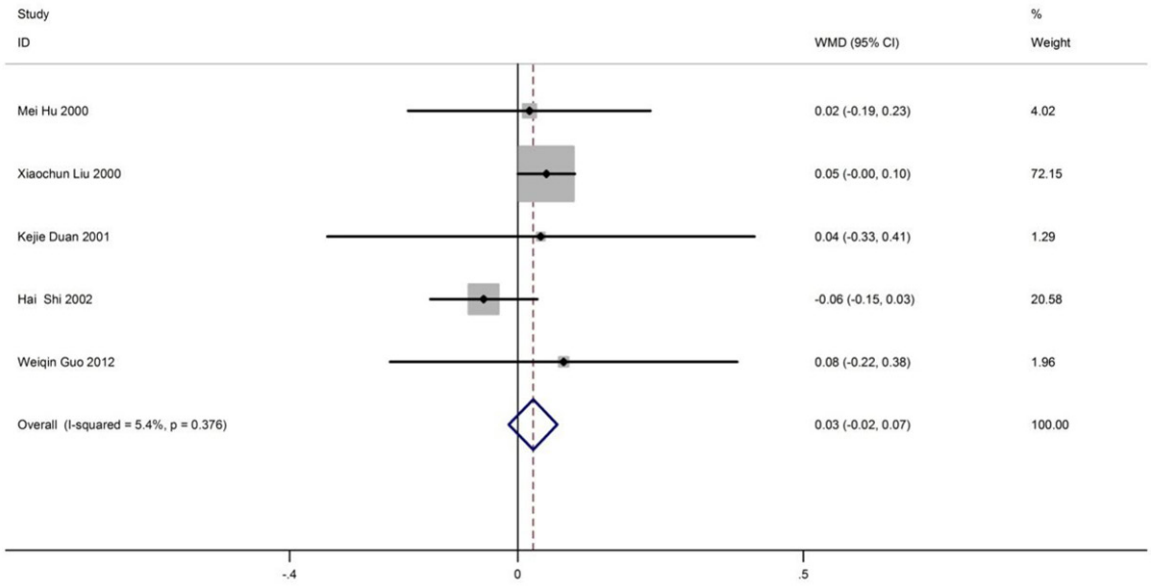

Figure 4. The forest figure of comparison between suxiaojiuxin pill and standard therapy in PV.

WMD = 0.03, 95% CI = -0.02-0.07; PCV: WMD = 2.97, 95% CI = -3.30-9.25; Fibrinogen: WMD = 0.48, 95% CI = -0.14-1.10) between the two group in above three indexes.

Electrocardiogram (ECG) curative effect

36 studies reported the curative effect of Electrocardiogram. Based on the Chi-squared test *P*-value = 0.00 < 0.05 and I^2 tests-value = 62.4% > 50.0%, random-effect model was chose. Polled analysis indicated that suxiaojiuxin pill could significant improved the ECG curative effect (RR = 1.30; 95% CI = 1.21-1.41) when compared with the standard therapy (**Figure 7**).

Publication bias

The publication bias of this meta-analysis was assessed using funnel plot and Egger's test. All the included indexes were analyzed the publi-

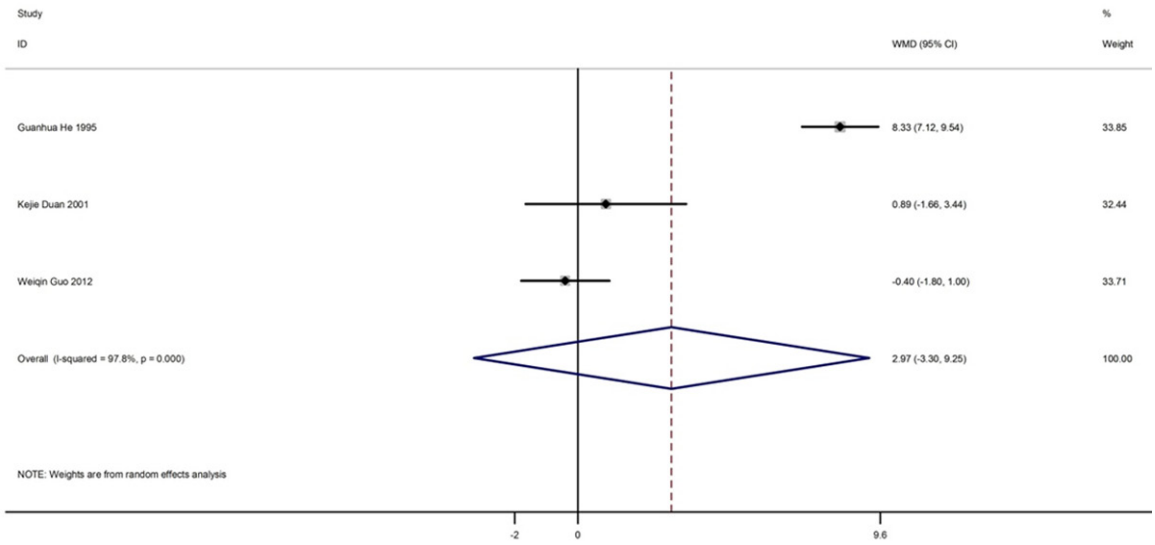

Figure 5. The forest figure of comparison between suxiaojiuxin pill and standard therapy in PCV.

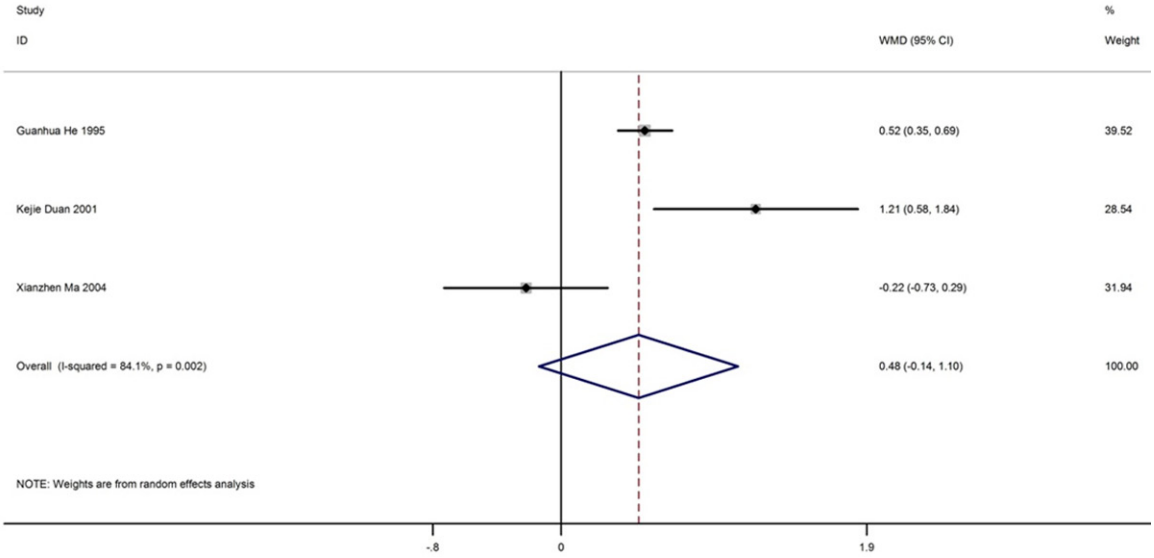

Figure 6. The forest figure of comparison between suxiaojiuxin pill and standard therapy in Fibrinogen.

cation bias. The results of publication bias were shown in **Figure 8**. No evidence of significant publication was found by inspection of statistical test in WBLSV (Egger's test, P = 0.722), WBHSV (Egger's test, P = 0.338), PV (Egger's test, P = 0.759), PCV (Egger's test, P = 0.681), Fibrinogen (Egger's test, P = 0.959), ECG efficient (Egger's test, P = 0.128).

Discussion

There were few meta-analyses about the positive effect of suxiaojiuxin pill on CHD patients. In previous studies, Wang et al. [47] suggested that the overall incidence of symptom alleviation was significantly higher in patients taking suxiaojiuxin pill than isosorbide dinitrate, and significant difference was also found in the ECG improvement. Wang et al. [48] found that suxiaojiuxin pill could significantly reduce the incidence of angina, improve the ECG curative effect and decrease the adverse reactions. Ruan et al. [49] suggested that compared with the routine treatment, additional use of suxiaojiuxin pill could improve the Traditional Chinese Medicine syndrome efficacy, the angina symptoms and ECG efficacy, and decrease the level of CRP.

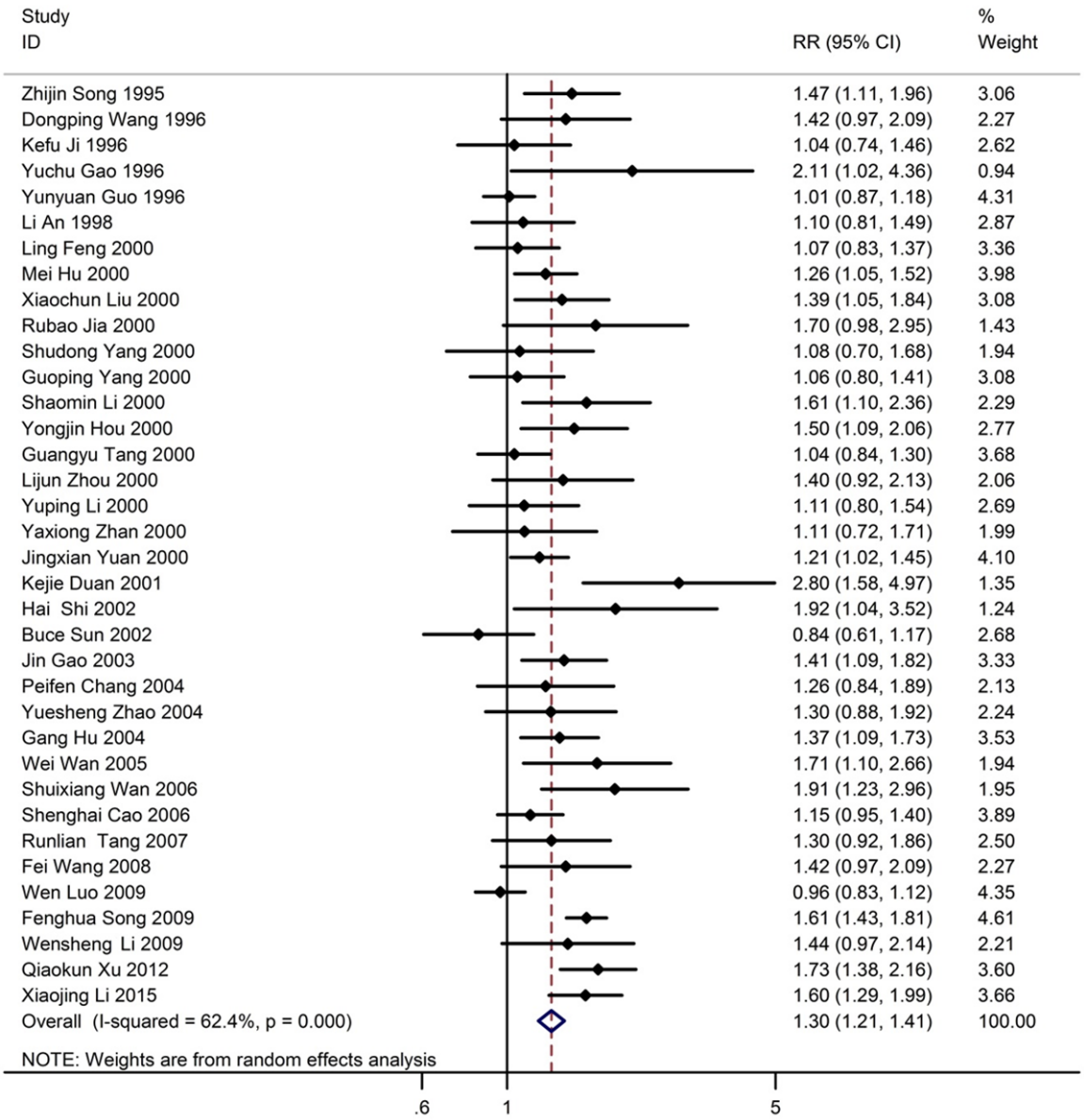

Figure 7. The forest figure of comparison between suxiaojiuxin pill and standard therapy in ECG efficient.

In this meta-analysis, we found that suxiaojiuxin pill could significant improve ECG efficient and this find was consisted with the previous studies. Besides, suxiaojiuxin pill could also decrease the levels of WBLSV, WBHSV. Other hemorheology related parameters such as plasma viscosity, fibrinogen and packed cell volume showed the same tendency, but they didn't reach statistical significance.

In China, suxiaojiuxin pill has been widely used for treating patients with CHD and angina pectoris. In clinical, suxiaojiuxin pill could effectively improve blood supply of the cardiac muscle, cure atherosclerosis in some degree, anticoagulant and decrease the risk of thrombosis. The major components of suxiaojiuxin pill is Borneol and Ligusticum chuanxiong Hort. Lower lipid profile and improve the hemorheology by the effect of LC and Bornenol which could improve the coronary artery circulation and ECG [50].

Ligusticum chuanxiong Hort (LC) [51-54] is mainly located in Sichuan province and first recorded in the Divine Husbandman's Classic of the Materia Medica. LC has long been regarded as a traditional Chinese medicine and widely applied in food as a way of health protec-

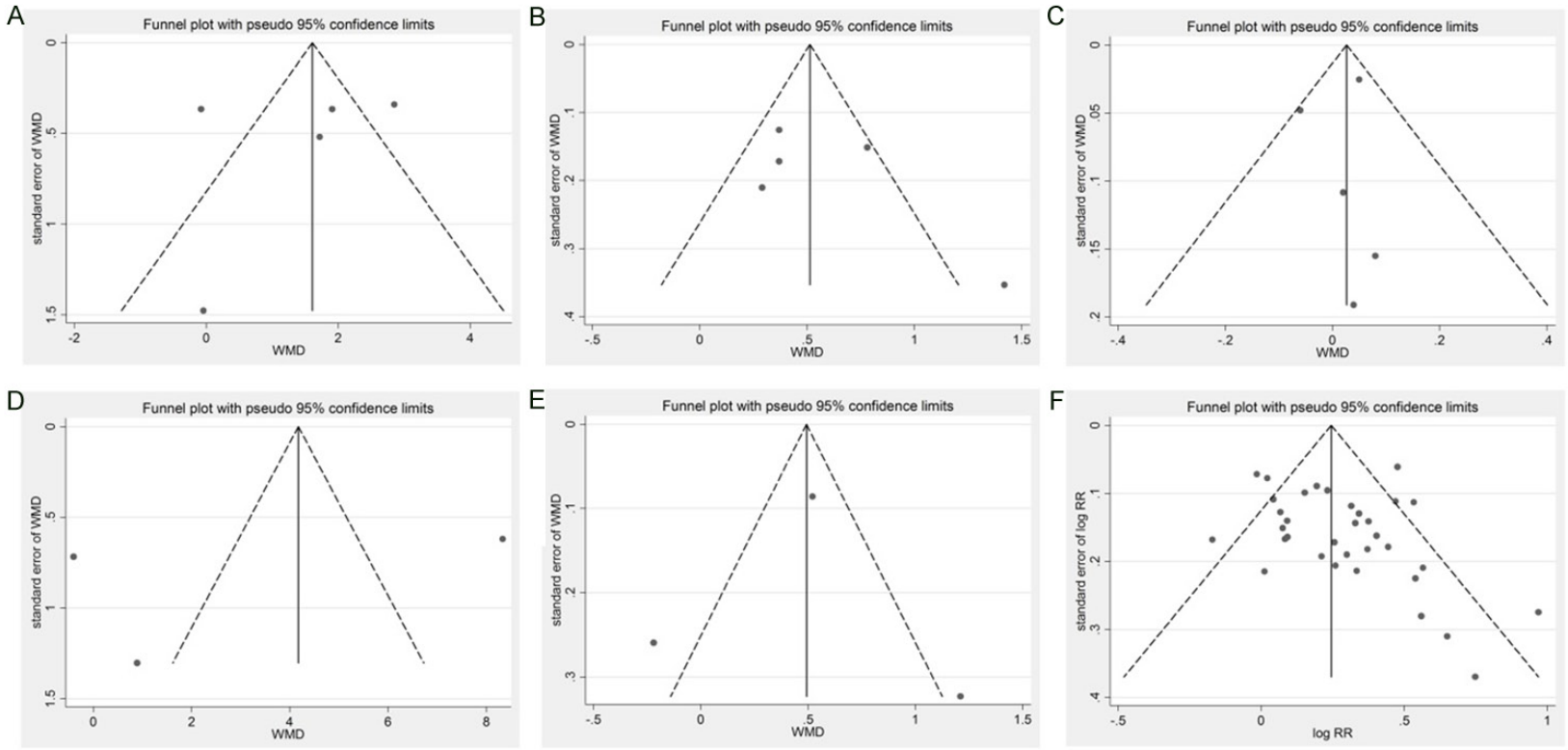

Figure 8. Funnel plot for WBLSV (A), WBHSV (B), PV (C), PCV (D), Fibrinogen (E), and ECG efficient (F).

tion. The mainly chemical components include essential oil, phenolic acids, phthalide lactones. Some researchers found that LC could decrease the levels of serum cholesterol, lower lipoprotein, reduce the red blood cell deformability and relive angiotensin II, which induces vascular smooth muscle cell proliferation. These unique roles may be guided by the increase of nitric oxide and repression of nuclear factor-κB activation. Besides, LC has a direct vasodilatation effect on isolated aortic rings in rats. The mechanisms of this effect were related to the opening of SK (Ca) and ATP_K channels and reduced ET-1 as well as ROS formation. Recently, LC has been confirmed the effect of inhibiting platelet thrombus formation and LC possibly exerts antiplatelet effects by inhibiting the vWF-mediated process of platelet thrombus formation.

Bornenol [55, 56] is a fragrance ingredient used in decorative cosmetics and it's widely regarded as an adjuvant in Chinese herbs. Several animal experiments demonstrated that Bornenol could dilate the coronary artery and improve the coronary circulation. Besides, several other studies showed Bornenol could inhibit the inflammatory response on animal models. As a result, Bornenol has been widely used in clinical practice on CHD patients.

However, there are some limitations in this analysis. The limitations are as follows: 1) randomized case-control studies were included; 2) differences in the inclusion criteria and exclusion criteria for patients; 3) different patients with previous disease and treatments were unavailable; 4) most trials with low quality and low Jadad score were included in our study; 5) all the included studies were from Chinese articles and this may be the source of bias; 6) pooled date were used for analysis, and individual patients' data were unavailable, so it limited us to make more comprehensive analysis.

In this updated meta-analysis, suxiaojiuxin pill showed better effect on ECG efficient improvement and some hemorheology related parameters. But there still need large samples, high quality studies to verify the clinical efficacy of suxiaojiuxin pill on patients with CHD.

Disclosure of conflict of interest

None.

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