Effects of Shexiang Baoxin Pill and Isosorbide Dinitrate on Angina of Coronary Heart Disease: A Meta-Analysis

ABSTRACT

Objective The aim of this study was to evaluate the evidence for Shexiang Baoxin Pill (SBP) and isosorbide dinitrate (ISDN/Xiaoxintong) use in angina of coronary heart disease. We compared their efficacy in effect rate in angina relief (included significant effect and normal effect) and electrocardiogram (ECG) improving rate.

Methods Systematically searched Randomized Control Trials (RCTs) in the Cochrane Library, EMBASE, MEDLINE, PubMed, Wanfang and CNKI databases from 2000 to 2016. According to the Cochrane Handbook for systematic reviews, quality assessment and data extraction were precise. All data were analyzed by using Review Manager 5.3.

Results 26 studies total 2,634 cases were included. In SBP groups, the effect rate and electrocardiogram improving rate are 90.0% (1223/1358) and 78.3% (799/1021), higher to the ISDN 73.6% (939/1276) and 60.2% (571/947). Both of the meta-analysis showed the SBP is the better one [Total effect: OR = 0.30; 95% CI = 0.24–0.37; ECG improved: OR = 0.30 95% CI = 0.30–0.46].

Conclusion Shexiang Baoxin Pill has a significant effect to the Isosorbide Dinitrate in angina of coronary heart disease.

KEYWORDS shexiang baoxin pill; SBP; Isosorbide dinitrate; ISDN; coronary heart disease; angina pectoris; meta-analysis; chinese traditional medicine; ECG

INTRODUCTION

Coronary heart disease (CHD) is caused by several reasons. Some of them were caused by vessel hardening, which give blood to the heart thus become harder. Sometime vessel narrow might lead an ischemic ache because of fat depositing. The superposition of multiple reasons can cause myocardial ischemia which might endanger health. Clinically, the primary symptoms of coronary heart disease are angina pectoris and myocardial infarction.

Angina pectoris is made likely by luminal stenosis or occlusion of coronary arteries. The area lack of blood supply arteries often manifests as myocardial ischemia and anoxic sign. Stable angina happens in a fixed time and fixed pain intensity. Unstable angina symptoms are usually more serious and frequently instable. Both of them might cause myocardial infarction. If the treatment cannot be in time for the acute myocardial infarction, death would suddenly happen [1,2]. All kinds of angina is common in clinic. Patients often require long-term medication. Therefore, a drug is simple to use, effective and replies diverse more factors in angina happening that can relieve pain for patients. And that, it could be the selectivity of the doctors for its improving patients’ compliance.

Nitric ester is a kind of drugs commonly used in coronary heart disease, which is a blood vessel to reduce the heart load. Nitric acid esters is the nitric oxide (NO) donor in vivo, which leads to vascular smooth muscle cell calcium decreased so as to achieve the expansion of blood vessels. Small doses can lead to decreased systolic blood pressure, decreased ventricular wall tension, preload and myocardial oxygen demand. Middle dose can lead to the redistribution of blood flow and improve the perfusion of the ischemic region.
In the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA)\(^1\), nitrates, such as the isosorbide dinitrate (ISDN/also called Xiaoxintong in Chinese), are considered as the class I recommended drugs for treating myocardial ischemia and angina pain last for several weeks. Patients may benefit after the use of nitrate. In the *diagnosis and treatment guidelines for chronic stable angina* (2007)\(^4\), isosorbide dinitrate is recommended for the prevention and relief of symptoms.

However, the nitrate esters like isosorbide dinitrate mostly have the obvious adverse reaction of the headache, which the incidence rate is of 20–30%, at the same time, ISDN may be due to the decrease of the sensitivity of the guanine nucleotide loop and makes the increase of the oxygen-free radicals caused the drug resistance of nitric oxide (NO).

Shexiang Baoxin Pill (SBP) is a traditional Chinese medicine used for treating angina pectoris, chest tightness and myocardial infarction due to myocardial ischemia. As a Chinese traditional drug, Shexiang Baoxin pill shows a faster-onset action and a lower side effects. The latest research shows, SBP can dilate coronary artery, increase besides blood supply, also protect vascular endothelial cells and inhibit intimal hyperplasia. While long-term treating for angina, patients could get the benefit in the establishment of coronary collateral circulation, reduce and delay the occurrence and development of myocardial ischemia, which improving the symptoms and prognosis\(^1\). It also showed a good effect in the case of heart failure and hypertension, hyperlipidemia and other basic diseases with coronary heart disease.

This meta-analysis study mainly uses the database, searching clinical reported for evaluating the Isosorbide Dinitrate and Shexiang Baoxin Pills in treating coronary heart disease. Through analyzing two drugs in less frequency of angina pectoris and clinical electrocardiogram improvement, we hope to evaluate the curative effect and provide an evidence-based result to improve clinical protocols.

**METHODS**

**Search strategy and inclusion criteria**

Based on the PRISMA statement guidelines for the meta analysis of RCTs\(^5\), Web of science, PubMed, EMBase were performed to identify RCTs that compared SBP and ISDN for the treatment of coronary heart disease. Otherwise, Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL were also searched. Considering SBP as a traditional Chinese medicine, the significant Chinese data, China National Knowledge Infrastructure (CNKI; http://www.cnki.net/), WangFang Data(http://www.wanfangdata.com.cn/), were included for searching. All searched articles were estimated the

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Shexiang Baoxin Pill versus Isosorbide Dinitrate in the rate of angina relief or ECG improve in English or Chinese from January 2000 to January 2016. Our search strategy used the following Medical Subject Headings (MeSH) and keywords: (coronary heart disease, OR angina, OR stenocardia, OR angina pectoris) and (isosorbide dinitrate OR ISDN OR Xiaoxintong) and (Shexiang baoxin pill OR SBP) and (random* OR clin* OR study* OR trial*). The search was restricted to clinical studies in human. The main details of search and select process are shown in Fig. 1. All studies were scanned to exclude the irrelevant ones. The reference list associated with all of the studies retrieved in the search was used to identify other potentially relevant publications. The reports in Chinese language, we translate the title in English and add the doi address in reference part. Two authors (H. G. and G. C.) first independently and manually checked the reference lists of the eligible articles or relevant review papers and then crosschecked and reached a consensus on all potentially relevant studies. Details of the selection of studies for inclusion in this meta-analysis are shown in Table 1.

**Exclusion criteria**

Studies are not standardized for measure; the intervention groups is not Shexiang Baoxin Pill and Isosorbide Dinitrate, or combined the same effect drug with SBP or ISDN; scheme design is not rigorous; study results are not clear; The original data is inconsistent with the results of the expression; in the literature, no a clear description of the duration of the drug treatment; cannot extract the outcomes; lack of detailed information for judged to be a clinical study; a patient under 18-year-old was included in study; the systematic-analysis, meta-analysis, retrospective analysis; non Chinese or English language; articles reported duplicate in English and Chinese; could not get the full text online.

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**Fig. 1** Selection process for clinical studies included in the meta-analysis.
A risk-of-bias assessment was systematically performed by two investigators (H. G. and G. C.) using instructions described in the *Cochrane Handbook for Systematic Reviews of Intervention*. And studies’ quality were assessed by Jadad Scale. Studies included in this meta-analysis were assessed the following item: random type, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. And Jadad scale will assess their assessment of frequency of endorsement, consistency, and validity through the measurement by Alejandro R. The Jadad scale is used to evaluate the quality of each independent study, scored 1 to 2 are divided into low-quality research, and 3 to 5 are high. Any disagreements were adjudicated by a third author. There were on disagreements among the assessment part.

### Data extraction and outcome measures

With the prior design, the two researchers (H. G. and G. C.) extracted the following information independently. The extracted item include: first author’s name, year of publication, the number of trial patients, number of patients in each group, type of intervention, duration of treatment, therapeutic schedule, the number of adverse events (AEs) or serious adverse events (SAEs), the number of effective cases (total effect in angina relief included significant effect cases and normal effect cases), electrocardiogram (ECG) improving cases. For
studies that reported multiple time points for the same subjects, the data from the longest period were used.

We counted the number of patients who get effective (significant effect or normal effect in angina relief) as the primary outcomes. The happen times of main adverse drug events (ADEs) such as celiacgia, nausea, headache, dizziness, were recorded and counted for the happening rate of ADEs. In addition, we counted the number of patients who get the remarkable effect or common effect in ECG improve (ECG improvement) as the secondary outcomes. As the dichotomous variables, all the studies were captured significant effect and normal effect cases as the data of the total effect in angina relief; got the significant effect and normal effect cases in ECG change as the data of ECG improvement.

State description of efficacy

Significant effect in angina relief

The times of angina attacks are reduced more than 80% than before treatment, and the cardiac function improves two levels in clinical diagnosis.

Normal effect in angina relief: The times of angina attacks are decreased by 50% to 80% than before treatment, or cardiac function improved one level in diagnosis.

Invalid in angina relief: The number of angina attacks before treatment is reduced by less than 50%, or diseases that did not improve.

Remarkable effect in ECG: After treatment, ECG switched back to normal.

Common effect in ECG: After treatment, the ST segment more than 0.05 mV, but did not reach the normal level.

Invalid in ECG: ECG similar roughly as before.

Serious in ECG: After treatment, ST decreased more than 0.05 mV than before, deepen T wave inversion.

Statistical analysis

In the present study, for the dichotomous variables, the effect sizes were expressed as the odds risk (OR), and 95% confidence intervals (95% CI) between the SBP and ISDN group as another outcome. For statistic of these trials, heterogeneity test was carried out on the included studies, used the I² measures to the inconsistency across studies. I² more or less than 50% determine the use of fixed-effect or random-effect model for statistics. Actually, the hypothesis test was considered to test the final statistics (aggregated OR), a Z value of Z(u) test less than 0.05 was considered significant. Also, we regard the study which 95% CI do not bound the middle line (where value = 1) as statistically significant.

Both of them show in the forest plots. Additionally, we evaluated the potential publication bias of the included studies with funnel plot. Two investigators (G.C. and H.G.) independently performed the statistical analysis with Review Manager (version 5.3.5 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), crosschecked and reached a consensus on all the items and outcomes. Any discrepancy was resolved by discussion or third party.

RESULTS

Characteristics of studies in the meta-analysis

In the early detection of English literatures 105, Chinese literatures 510, after duplicate removal by computer to get 77 English literatures, Chinese 169 literatures; reading the title and abstract, delete literatures not in conformity with the study, selected 26 reports in English, Chinese literatures 61. Then read the full text, in accordance with the inclusion and exclusion criteria to select the literatures, and exclude the original Chinese text for the foreign retrieval results, finally, the 26 studies consisting of 2,634 individuals were included in the meta-analysis, a process diagram shown in Fig. 1.

The efficacy of Shexiang Baoxin Pill versus Isosorbide Dinitrate on the treatment of coronary heart disease was compared in this study. The main characteristics of 26 trials included in this meta-analysis are shown in Table 1. All of the trials were published from 2000 to 2016, and all of their sample volume larger than 40. Their use duration from 14 days to 120 days, but most of them set in 14 days. Among 26 trials, only 10 trials of them mentioned the adverse drug events (ADEs) in both groups such as celiacgia, nausea, headache, dizziness during the study period, without any serious adverse events reported. ADEs happening is significant difference in two groups (shown in Table 1). The quality of the included studies was assessed by the Jadad score also shown in Table 1.

The cure effect in angina relief

In Fig 2, there are 26 studies combining the OR from fix-effects model (Mantel-Haenszel model) for the total effect in angina relief. Pooling all the 26 trials, of 1,276 patients in the ISDN group, 939 patients have got effect, compared to 1,223 out of 1,358 patients in the SBP group. But there are 10 studies of 95% CI included the invalid line. The aggregated result of the 26 papers, which OR equal to 0.30, 95% CI 0.24–0.37, suggest that SBP has a significant effect than ISDN in treating angina.

The heterogeneity test showed a significant homogeneity of the 26 studies (I² = 0%, P = 0.61). In hypothesis test, the z(u) test result (P ≤ 0.05) showed that the aggregated result of 26 studies were statistically significant.

In a funnel plot (Fig. 3) detailing publication bias in the studies, lnOR as abscissa and SE (lnOR) as ordinate, diagram is significant symmetrical, which mean publication bias made less influence in the result.

The improving effect in ECG

Fig. 4 shows the pooled results from the Mantel-Haenszel model combining the OR for the effect rate of ECG
DISCUSSION AND CONCLUSION

The results of the meta-analysis combine with the therapeutic process of SBP and Isosorbide Dinitrate against coronary heart disease such as angina pectoris. We aggregated the results suggest that SBP shown an obvious effect in angina relief and improve trouble electrocardiogram statue. The ECG improvement results can accurately describe the drug efficacy in treating coronary heart disease.

The Isosorbide Dinitrate included in this section is a medicine of nitrate drug against coronary ischemia. In the classical treatment for coronary heart disease such as stable angina, angina pectoris, nitrates were used to alleviate the symptoms or change the state of ischemia, so Isosorbide Dinitrate plays a positive role in the treatment of coronary heart disease in this kind of medicine. It can dilate coronary arteries, reduce resistance, increase the blood flow of coronary, and reduce the change of blood volume, which could release the load of the heart so as to reduce the myocardial oxygen consumption so that relieve angina pectoris and insufficient blood supply of coronary.

Isosorbide Dinitrate is one of the main active metabolites of nitrate ester, and it can quickly be absorbed in oral and its bioavailability is 100%. Isosorbide Dinitrate is commonly used in Germany firstly, and then in dozen countries’ medicine catalogue such as the United States, Netherlands. This drug works faster and better in oral compared with the early nitrate ester. Isosorbide Dinitrate works fast and short, which is suitable for resolving the cardiac sudden, used widely.

Shexiang Baoxin Pill, which made by musk, is a phytochemical drug coming from traditional Chinese medicine. Assisted by styrax and borneol, SBP enhance the effect of...
Fig. 4 The meta-analysis of the ECG improvement about Shexiang Baoxin Pill and Isosorbide Dinitrate in the treatment of coronary heart disease.

Fig. 5 The funnel plot of meta-analysis of the ECG improvement rate about Shexiang Baoxin Pill and Isosorbide Dinitrate in the treatment of coronary heart disease.

the musk, toad, venom, bezoar, cinnamon, in blood stasis removing. Basic research shows that borneol, styrax can enhance myocardial hypoxia resistance, decrease heart rate, increase the blood flow, and reduce oxygen consumption of myocardial. Toad, venom can increase the force of myocardial contraction, and expand coronary.

In the comparison result of the effect of Isosorbide Dinitrate and SBP, the statistical result of 2,634 patients in 26 articles shows that the clinical curative effect during more than 14 days of SBP is higher than Isosorbide Dinitrate under the same conditions, and its clinical total effective rate angina relief is 90.0% (1223/1358), higher than Isosorbide Dinitrate (73.6% (939/1276)). In 1,968 cases of 21 studies, Isosorbide Dinitrate made 60.2% (571/947) of patients got the common or better efficient in electrocardiogram improvement while heart disease happens, but, SBP got 78.3% (799/1021). In two sections of meta-analysis based on clinical
effectiveness and electrocardiogram improving efficiency, the aggregated statistics of studies showed that SBP is more efficient in both, and the heterogeneity test and Z test showed a statistical significance.

In the study of two groups, the reported of adverse reactions in studies included show that ADEs have happened, but the headache and dizziness of ISDN is more than SBP. There are two assumptions: SBP is different from nitrates in the mechanism of dilating blood vessels\(^{35,36}\), so, SBP might not make a headache or dizziness or while SBP as the treatment group without scientifically binding or randomizing, subjective performance bias carried out by the participants or reviewers. The two meta-analysis above show that, comparing the SBP to ISDN, SBP gave a curative effect advantage in the treatment of angina of coronary heart disease. About the side-effect reactions, while treating angor pectoris, the probability of adverse drug reaction (like celialgia, nausea, headache or dizziness) in using SBP might less than using ISDN.

REFERENCES