A Meta-analysis of Effectiveness Evaluation between Shexiang Baoxin Pill and Isosorbide Mononitrate Tablet

ABSTRACT

Objective To compare the efficacy of Shexiang Baoxin Pill (SBP) with isosorbide mononitrate tablet (ISM) in the clinical treatment of angina pectoris of coronary heart disease and the ratio of electrocardiogram (ECG) improvement in patients.

Methods Systematically searched EMBASE, MEDLINE, PubMed, CBM, VIP, Wanfang and CNKI databases from 2000 to 2016 to collect all relevant studies. According to the Cochrane Handbook for systematic reviews, quality assessment and data extraction were precise. All data were analyzed by using Review Manager 5.2.

Results The results showed that SBP had a significant effect on the total effective rate (7 trials, n = 874, OR = 0.31, 95% CI: 0.21–0.46, P < 0.05) and on the ECG improving rate (4 trials, n = 437, OR = 0.39, 95% CI: 0.20–0.49, P < 0.05), which compared with ISM in the clinical treatment of angina pectoris of coronary heart disease.

Conclusion SBP had a better effect than the ISM in the treatment of angina pectoris of coronary heart disease in terms of total effective rate and ECG improving rate.

KEYWORDS Shexiang Baoxin Pill, isosorbide mononitrat tablet, angina pectoris, coronary heart disease, meta-analysis

INTRODUCTION

Acute heart disease (AHD) is one of the coronary heart diseases (CHD), which has already been the potent killer of human health. In the 21st century, with the growing life pressure, the sharp social contradictions, and the aggravating environment, AHD has been listed in the top several acute lethal diseases. Most of the AHDs cause injury by angina or myocardial infarction or, as we know, the heart attack. Also, most of them present acute, manifest seriously, non-predictable, which lead a high fatality rate. Even through the slight symptom, the angina would also lead an unacceptable heartache. CHD or AHD has made a rigorous trouble in our life.

CHD or AHD may be caused by several reasons. Some were caused by vessels hardening. The peripheral blood is hard to pass narrowly to get into heart, then, the angina occurred. And some fat deposit in vascular endothelium could also make an ischemic heart ache. Angina and myocardial infarction, as the main symptoms of CHD in clinic, could make endanger in health as superposition of multiple reasons. Either angina or angina pectoris was made likely by luminal stenosis or occlusion of coronary arteries. The artery area lacking of blood supply to arteries often manifests as myocardial ischemia and anoxic sign. Angina has several presentations, the stable angina (SA), unstable angina (UA) and mix angina. Stable angina happens in a predictable time and pain intensity. And unstable angina symptoms are usually more serious and frequently instability. Both might cause myocardial infarction. Death might suddenly happen without in time treatment. For the angina happening commonly in CHD patients, they usually were required to take a drug for long periods. Nitric ester is a kind of drug commonly used in CHD, which is a blood vessel to reduce the heart load. Isosorbide mononitrate tablet (ISM), one of the nitric oxide (NO) drugs, can cause
some relaxation in vascular smooth muscle. 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), ISM could be the top five recommended drugs for treating myocardial ischemia and angina pain last for several weeks. And in the diagnostic and treatment guidelines for chronic stable angina (2007), nitrates, such as ISM is recommended for the prevention and relief of symptoms.

In another way, the nitrates like isosorbide dinitrate mostly have the obvious adverse reaction of the headache. The incidence rate is in 20–30%, at the same time, ISD may be due to the decrease of the sensitivity of the guanine nucleotide loop and makes increase of the oxygen-free radicals, which caused the drug resistance of NO.

Shexiang Baoxin Pill (SBP) is a traditional Chinese medicine used for treating angina pectoris, chest tightness or due to another heart ache like CHD. As a Chinese traditional drug, SBP, which uses moschus as its main component, showed a faster-onset action and a lower side effects. In some latest research shown, SBP dilates coronary artery, increases besides blood supply, also protects vascular endothelial cells and inhibits intimal hyperplasia. While long-term using for angina, less headache would the patient fell. SBP might have a good performance in the case of heart failure and hypertension, so it could have a larger stage in cardiovascular disease.

This study mainly used the database in clinical studies as a meta-analysis, by searching clinical reports. We had compared the ISM and SBP in treatment effect in patients with CHD. Through analyzing two drugs in occurrence, reduction of angina and clinical electrocardiogram (ECG) improvement. This research evaluated the curative effect and expected to provide an evidence-based results for clinical decision-making.

METHODS

Search objects and contents

Since 2000, the reported studies published on SBP and ISM for the treatment of patients with several common CHD and angina pectoris, which were the objects of study. Compared SBP with ISM, the control group was ISM: each 20 mg, 3 times/day; The test group was SBP: every time the sublingual administration 2 tablets, 3 times a day. The two groups were treated for 4 weeks as the cycle course of study, and the therapeutic effect was compared between the courses of treatments. According to reference guide, drug manuals, and the studies frequently reported, set above course of medication use and treatment.

Inclusion & exclusion criteria

In this study, the inclusion measures were set as follows: raw materials were the literatures published in the regular journals; the original studies were randomized controlled trials or clinical controlled trials or case control studies or cohort studies or retrospective studies; the patients aged between 18 and 65; the patients reported in the studies were consistent with the criteria of WHO angina pectoris; the object of study and treatment group was the comparison of SBP and ISMs.

The exclusion measures included these: original information was not published or published in the magazine was not standardized; the control group of original study was not clear; the scheme design in the original data was not rigorous; the results were not clear or the results did not meet the statistical difference ($P > 0.05$) in the raw data; the original data were inconsistent with the results of the expression; in the studies, there was no clear description of the duration of the drug treatment; lack of detailed information could not be judged as a research study; studies on the basis of the in vitro study of drug mechanism and toxicology; studies on the systematic analysis, meta-analysis, etc.; non-Chinese or English language; studies that could not get the full text of the information.

Outcome measures

Outcome measures were divided into main outcome measures and secondary outcome measures.

The number of patients got effective treatment including significant effect and normal effect in angina relief was counted as main outcomes. The evaluation index of significant effect was that the number of angina attacked after treatment reduced more than 80%, and the heart function improved more than two levels. The evaluation index of normal effect was the number of angina attacks before treatment decreased by 50% to 80%, or heart function improved one level. At last, the number of angina attacked before treatment reduced by less than 50%, or heart function without improvement was regarded as invalid outcome.

In addition, the number of patients who got the obvious effect or common effect in ECG improvement after the treatment was considered to be secondary outcome measures. The distinguishing standards in ECG improvement were as follows:

Obvious effect meant the ECG recovered to “roughly normal level” or “normal level” after treatment. A common effect represented the ST segment recovered more than 0.05 mV, but did not reach the normal level after treatment. When ECG was roughly similar before and after treatment, it was regarded as invalid outcome. Moreover, if the decrease of ST segment more than 0.05 mV than before and T wave inversion deepen, it was a part of serious outcome.
Search strategy

Searched the Cochrane library database, PubMed database, EMBase database and domestic CNKI, CBM, Wanfang, VIP and the search time limit was set from database building to January 2016. Search keywords included (coronary heart disease OR stenocardia or stenocardia or coronary syndrome or unstable angina or stable angina pectoris) and (Shexiang Baoxin Pill) and (xinkang or isosorbide mononitrate tablet or isosorbide-5-nitrate tablet or isosorbide-5-nitrate tablet), due to the need of therapeutic evaluation between Shexiang Baoxin Pill and ISM in the clinical treatment of angina pectoris of coronary heart disease and the ratio of ECG improvement in patients. At the same time, referred to the reference documents included in the study and manually retrieved related research, in order to supplement the research might be missing.

Data extraction

With the prior designed table, the two researchers independently completed the extraction of relevant information. The extracted data contained the following information: the first author’s name, year of publication, topic, study patients, drug administration program (drug treatment), the number of trial patients, the number of effective cases, the number of adverse drug reactions (ADR), clinical manifestations of specific adverse reactions and the corresponding number of cases, etc. If there were differences between the two researchers in the data extraction process, the two jointly reviewed and consulted the solution, or reviewed by third researcher.

Study quality evaluation

The risk of bias was used to evaluate the quality of each independent study. The risk of bias legend included the 7 parts as follows: (A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel (performance bias); (D) Blinging of outcome assessment (detection bias); (E) Incomplete outcome data(attrition bias); (F) Selective reporting (reporting bias); (G) Other bias. The red meant high risk and green expressed low risk, meanwhile, the blank is not detailed.

Statistical analysis

Data results for the two component variables were expressed with the odds ratio (OR) as the effect and 95% CI. The calculation method adopted the Mantel-Haenszel method. Heterogeneity between studies was assessed by the Cochrane Q test with a significance level set at 0.10. The P statistic was also examined, and $P > 0.50$ was considered to have heterogeneity. If the $P \leq 0.10$ and $I^2 \geq 50\%$, that could be considered homogeneity to a number of similar studies, using fixed-effect model for statistics; If $P \leq 0.10$ and $I^2 \geq 50\%$, meant that much research had heterogeneity, analyzed the sources of heterogeneity. After excluding the differences in the research design quality, data extraction and so on, if there were still more heterogeneity between the studies, the subgroup analysis was applied to analyze results, and carefully interpreted research results. Hypothesis test method for test of combined statistics, Z(U) test for all of the combined studies, according to the $Z(U)$ value calculating the probability ($P$) value, there was statistical significance only with $P \leq 0.05$. The publication bias was expressed by inverted funnel chart. The total effect carried out meta-analysis with RevMan 5.2 software, $P \leq 0.05$ meant the difference with statistical significance, according to the PRISMA statement undertaking the meta-analysis.

RESULTS

Results of study collection

Documents retrieved and extracted from the main database of Chinese and foreign languages by using the retrieval strategy. The foreign language database included Web of knowledge, Pubmed, Library Cochrance, EMBase, the Chinese database included Wanfang, CNKI and Chinese biomedical studies database. The specific retrieval process and the number of retrieved documents were as follows. In the early detection of English articles 8, Chinese articles 20, after duplicate removal by computer to get English 12; reading the title and abstract, deleted articles not in conformity with the study, selected 10 papers. Then read the full text, in accordance with the specified inclusion and exclusion criteria to select the articles, the final 7 studies included in the meta-analysis, shown in Fig. 1.

In the final 7 studies, the efficacy of SBP and ISM on the treatment of CHD was compared. Characteristics of the 7 studies included in this meta-analysis were
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indicated in Table 1. All studies were published from 2003 to 2015, and their sample volume were almost larger than 30. The drug administration program last 28 to 56 days, and most of them were 28 days.

The total effective rate

The data in Fig. 2 show that in the included 7 articles on the treatment of CHD of SBP and ISM, extracted the total effective rate including significant effect and normal effect for the treatment of patients. A total of 874 cases in the two groups were studied. In the ISM group of total 410 patients, 311 patients got effect, compared to 419 out of 464 patients in the SBP group. The aggregated result of the 7 studies showed that SBP had better effect with OR = 0.31, 95% CI: 0.21–0.46 on the treatment of CHD.

In the heterogeneity test of the combined documents, $I^2 = 2\%$, $P = 0.41$, the results of the studies combining statistics had significant homogeneity, so could undertake statistic consolidation.

In hypothesis test, the Z(U) test result with $P < 0.05$, showed that the combined statistics was statistically significant, and there were significant differences between SBP and ISM in the curative effect on the treatment of CHD.

A funnel plot (Fig. 3) was used to express the publication bias in the studies. It indicated there were good symmetry of the sample and the total efficacy in the included 7 articles and less bias within the group.
The effect in ECG improvement

The data in Fig. 4 show that in the included 7 articles on the treatment of CHD of SBP and ISM, there were 4 papers describing the patient’s ECG improvement. Extracted total efficiency contained obvious effect and common effect describing in the papers for the treatment of patients with the ECG improvement. A total of 437 cases were studied in the two groups. In the ISM group of total 195 patients, 116 patients got effective ECG improvement, compared to 195 out of 242 patients in the SBP group. The aggregated result of the 4 studies showed that SBP had better ECG improvement with OR = 0.31, 95% CI: 0.20–0.49 on the treatment of CHD.

In the heterogeneity test of the combined documents, $I^2 = 31\%$, $P = 0.23$, within the acceptable range. The results of the studies combining statistics had significant homogeneity, so could undertake statistic consolidation.

$Z(U)$ test with $P < 0.05$, expressed that the combined statistics had statistical significance, which indicated the significant differences of SBP and ISM in the curative effect of patients, ECG improvement.

A funnel plot evaluated the publication bias of the 4 studies like the Fig. 5, InOR as abscissa and SE (lnOR) as ordinate, the diagram had significant symmetry, which showed less publication bias within the group.

DISCUSSION AND CONCLUSION

The results of the meta-analysis combined with the therapeutic process and ECG improvement of SBP and ISM for against CHD, and the meta-analysis suggested that SBP had more obvious clinical effect of angina while using at less 28 days. With the patient ECG detection, the ECG results also showed a similar conclusion in their comparison. Through an ECG detect, we evaluated an effect accurately.

The ISM belongs to chemical medicine of nitrate. In the classic medicine treatment for CHD stable angina, nitrate or calcium antagonists can be used to alleviate the symptoms or change the state of ischemia, as they can dilate coronary arteries, reduce resistance, increase the blood flow of coronary to reduce the change of blood volume. Single isosorbide nitrate ester, ISM, can quickly be absorbed in oral and its bioavailability is 100%. One of the single isosorbide nitrate ester, ISM belongs to a short-acting agents in nitrate. Because of fast work, it is often used in the process of rapid nursing in order to...
quickly relieve angina, and as a standing medicine for CHD patients.

Assisted by moschus and borneol, SBP enhanced the effect of removing blood stasis. Basic research showed that SBP could return myocardial hypoxia, slowed heart rate, increased the blood flow and reduced oxygen consumption of myocardial. In the comparison result of the effect of ISM and SBP, the merger of the statistical result of 874 patients in 7 articles showed that the clinical curative effect of more than one treatment (28 days) of SBP was higher than ISM under the same conditions, and its average clinical total effective rate was 92.56%, which was 16.42% higher than ISM. In 437 cases of 4 articles, ISM had 61.92% efficient to improve ECG for patients with CHD, and SBP had 82.75%. In two groups of meta-analysis based on clinical effectiveness and ECG improving efficiency, the merged statistics of studies showed that SBP was useful, and the heterogeneity of combined results and Z test had statistical significance.

In some studies of two objects, they reported that SBP had shown less adverse drug reactions (ADR) in headache, nausea, dizzy, than the ISM. And in the ISM-using patients, the ADR not only, as headache and dizziness, happened more, but also various. Why the ADR of SBP happened less. There were two assumptions: the first, SBP was different from nitrates in the mechanism of the role to dilate blood vessels. The moschus played a different way in releasing myocardial ischemia or cardiovascular stenosis, so a headache or dizziness happened less. And the second, SBP was made by multiple composition of natural crude drug, which contained moschus or the anther medicinal composition not in pure, leading the ADR slighter.

Basing on the above results, comparing the ISM and the SBP, SBP had a curative effect advantage in the treatment of CHD in the long-term using. And in the report mentioning patients with ECG detection, the probability of ECG improvement of ISM was less than SBP. Both of the results implied the SBP had better effectiveness in CHD.

However, caution should be taken during the interpretation of the results due to the relatively low score according to the quality assessment. More high quality clinical trials are needed to provide stronger evidence for our decision making on treatment of CHD.

REFERENCES