Meta-analysis

Efficacy and safety of Mahuang Fuzi Xixin Decoction on sick sinus syndrome: A meta – analysis

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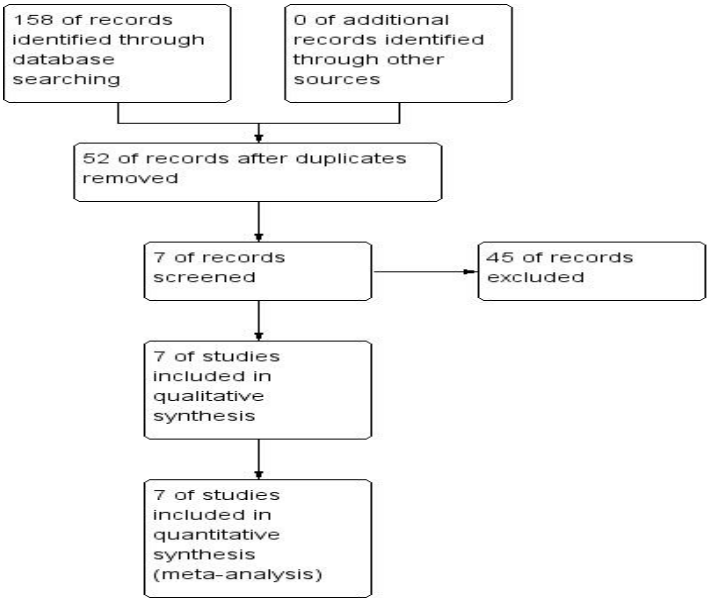
Highlights：
To evaluate the efficacy and safety of Mahuang Fuzi Xixin Decoction on sick sinus syndrome and provide evidence for clinical practice, a meta-analysis was performed. Meta analysis showed that the treatment (86.9%) was more effective than the control (70.1%), the difference was statistically significant (RR = 1.25, 95% CI:(1.15-1.37), $P < 0.001$); the treatment (17.0%) was safer than the control (49.8%), the difference was statistically significant (RR = 0.23, 95% CI:(0.06-0.93), $P = 0.04$).



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Abstract

Objective: To evaluate the efficacy and safety of Mahuang Fuzi Xixin Decoction on sick sinus syndrome and provide evidence for clinical practice. **Methods:** Randomized controlled trials of all the languages of Mahuang Fuzi Xixin Decoction on sick sinus syndrome were collected by computer search and manual retrieval. The retrieval time was from January 2000 to January 2017. According to the inclusion and exclusion criteria, 2 reviewers independently selected and extracted data, then evaluated the quality, cross-checked the information and evaluated the quality of menthodology. Through discussion or third reviewer to help solve the divergence, RevMan 5.3 software was used to perform meta analysis. **Results:** A total of 7 documents (n = 612) were finally enrolled, with 358 in Mahuang Fuzi Xixin Decoction group (treatment group) and 254 in control group. Meta analysis showed that the treatment (86.9%) was more effective than the control (70.1%), the difference was statistically significant (RR = 1.25, 95% CI:(1.15-1.37), $P < 0.001$); the treatment (17.0%) was safer than the control (49.8%), the difference was statistically significant (RR=0.23,95% CI:(0.06-0.93), P =0.04). **Conclusion:** The existing clinical studies suggest that Mahuang Fuzi Xixin Decoction on sick sinus syndrome is effective and safe; due to the limited quality of the enrolled documents, the above conclusions need more high-quality randomized controlled trials to be verified.

Key words: Mahuang Fuzi Xixin Decoction, Sick sinus syndrome, Meta - analysis

摘要

目的：评价麻黄附子细辛汤治疗病态窦房结综合征的疗效与安全性，为临床实践提供循证参考。
方法：采用 Cochrane 系统评价方法，通过计算机检索和手工检索，全面收集麻黄附子细辛汤治疗病态窦房结综合征的所有语种随机对照试验，检索时间为 2000 年至 2017 年 01 月，由 2 名评价者按照纳入和排除标准独立选择文献、提取资料、评价质量、交叉核对并进行方法学质量评估，若遇分歧，通过讨论或者第三名研究者协助解决，对纳入文献采用 RevMan 5.3 软件进行 meta 分析。
结果：共纳入 7 篇文献，共 612 例患者，麻黄附子细辛汤（治疗组）358 例，对照组 254 例。纳入的 7 篇文献均报告了有效率，治疗组有效率（86.9%）高于对照组（70.1%），差异具有统计学意义［RR=1.25, 95%CI (1.15,1.37), P<0.00001］；纳入的文献中有 5 篇报告了不良反应，治疗组不良反应发生率（17.0%）明显低于对照组（49.8%），差异具有统计学意义[RR=0.23, 95%CI (0.06,0.93), P=0.04］。
结论：现有临床研究提示，麻黄附子细辛汤治疗病态窦房结综合征疗效明显且未见明显不良反应；受纳入文献质量限制，以上结论有待开展更多高质量随机对照试验予以验证。

关键词：麻黄附子细辛汤；病态窦房结综合征；meta 分析

Abbreviations: SSS, Sick sinus syndrome; RCTs, randomized controlled trials; RR, risk ratio; CI, confidence interval; MD, mean difference.
Competing interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

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Introduction

Sick sinus syndrome (SSS) is caused by the sinus node dysfunction, resulting in the general performance of a variety of arrhythmias. Patients at different times appear more than one arrhythmia, often accompanied by atrial abnormalities, some patients also have atrioventricular conduction dysfunction. With the thriving and development of traditional Chinese medicine, the curative effect of Mahuang Fuzi Xixin Decoction in the treatment of SSS has been achieved. However, all of them are of small sample size and the reliability and extendibility of the formula have not been systematically evaluated for lacking large sample multi-centre randomized controlled trials. The purpose of this study is to evaluate and analyze the existing randomized controlled trials of Mahuang Fuzi Xixin Decoction for the treatment of SSS, to make an objective systematic evaluation of its clinical efficacy and safety, and to provide evidence-based reference for clinical practice.

Materials and Methods

Inclusion criteria

Study design All randomized controlled trials (RCTs) on the efficacy and safety of "Mahuang Fuzi Xixin Decoction" in the treatment of SSS were included in the study, including the study designed to be blind or not, and regardless of the language and type of publication.

Object of study The subjects met the diagnosis of sick sinus syndrome: there exists a clear correlation between the clinical manifestations and electrocardiographic changes, based on the typical ECG findings[1] . Main ECG findings include: 1) persistent and significant sinus bradycardia (below 50 bpm) and not due to medication; 2) sinus arrest and sinoatrial block; and 3) sinoatrial block accompanying atrioventricular block; 4) bradycardia-tachycardia syndrome, which refers to alternating seizures of bradycardia and atrial tachyarrhythmia (atrial flutter, atrial fibrillation or atrial tachycardia). Other ECG changes were: 1) slow ventricular rate of atrial fibrillation in the absence of antiarrhythmic drugs, or sinus bradycardia and/or first degree atrioventricular block before or after the episode, 2) chronotropic incompetence, manifesting as not significant increase in heart rate after exercise; 3) atrioventricular junctional escape rhythm and so on. Not subject to gender, race, age restrictions.

Intervention The treatment group was employed with Mahuang Fuzi Xixin Decoction, and the control group was employed with other drugs or non-drug treatment (including the blank control).

Outcome indicator One or more of the following outcome indicators are included: improvement in major symptoms, change in heart rate, relapse rate after drug withdrawal, drug response, gastrointestinal reaction, and so on.

Exclusion criteria

1) No clear diagnostic criteria, inclusion criteria or exclusion criteria of the study
2) Treatment course intra-group has inconsistencies or data reported exist errors in the study;
3) Animal experimental research.
4) Full conference document cannot be achieved.
5) Research with only abstract or unable to extract relevant data.

Search strategy The databases of Cochrane Library, PubMed, SinoMed, Ovid, CBM, Embase, CNKI, Wanfang and VIP were searched by computer, and references and related journals were searched by manual searching, such as “Chinese Journal of Cardiology”, “Chinese Journal of Cardiac Arrhythmias”, “China Circulation Magazine”, “Circulation”, etc. At the same time, the ongoing research trials were searched on websites such as Clinical Trials, BioMed Central and the China Clinical Trial Register, and the lack of information was supplemented with phone calls or e-mail contacts. The retrieve time was from January 2000 to January 2017. English database search terms were: “sick sinus syndrome, sinus node dysfunction, amd Mahuang Fuzi Xixin Decoction”, different words and form differ in different databases. The search is mainly focused on keywords and extensions, text words, titles, abstracts, etc.

Screening and data extraction Two researchers read the literature topics and abstracts independently for preliminary screening, and the final reading of the text is based on the inclusion and exclusion criteria for final confirmation of the entry document. Information extraction includes general information (first author’s name, the year of publish, the country), patient characteristics (sex, age, examples), intervention measures and end indicators, methodology (random method, blind) etc. Firstly, the two researchers read literatures subjectly and independently eliminate the researches which obviously do not meet the inclusion criteria. Then, they selected literatures according to the inclusion criteria and exclusion criteria. The uncertainty literatures were selected through discussion or through a third party.

Methodology quality assessment All entries were assessed using the RCT test-leaning risk assessment tool provided by the Cochrane manuals by two researchers independently, and to evaluate the

controversial document by discussing or assisting the third researcher, and create Risk of Bias Chart and Bias Risk Summary Chart.

Statistical methods

The data were analyzed using the RevMan 5.3 provided by Cochrane collaboration network. The original count data were analyzed using risk ratio (RR) and 95% confidence interval (CI), and The original measurement data used mean difference (MD) and 95% confidence intervals (CI) as efficacy analysis statistics. If there are difference in the measurement method of metric system or fundamental unit in methodology, SMD was used to merger effect analysis. "Mantel-Haenszel"test was used for heterogeneity analysis, and the differences in the heterogeneity of the literature are expressed by the statistics I^2, testing standard is $\alpha = 0.1$. If $I^2 <$ 50%, a fixed-effects model was used for meta analysis, if $I^2 \geqslant 50\%$, taking a subsection analysis according to the factors which lead to heterogeneity. If there is no clear reason, random model was used. If the heterogeneity of group is too large, descriptive analysis was used. Sensitivity analysis was used to test the stability of the results if necessary. Funnel diagrams was used to analyze the bias of published studies

Results

Literature search results and methodological quality assessment

Results of literature search

A total of 158 articles were retrieved according to the search strategy, 52 articles were removed after removing duplicate studies (106 articles), and 7 articles were read carefully[2-8]. (Figure 1)

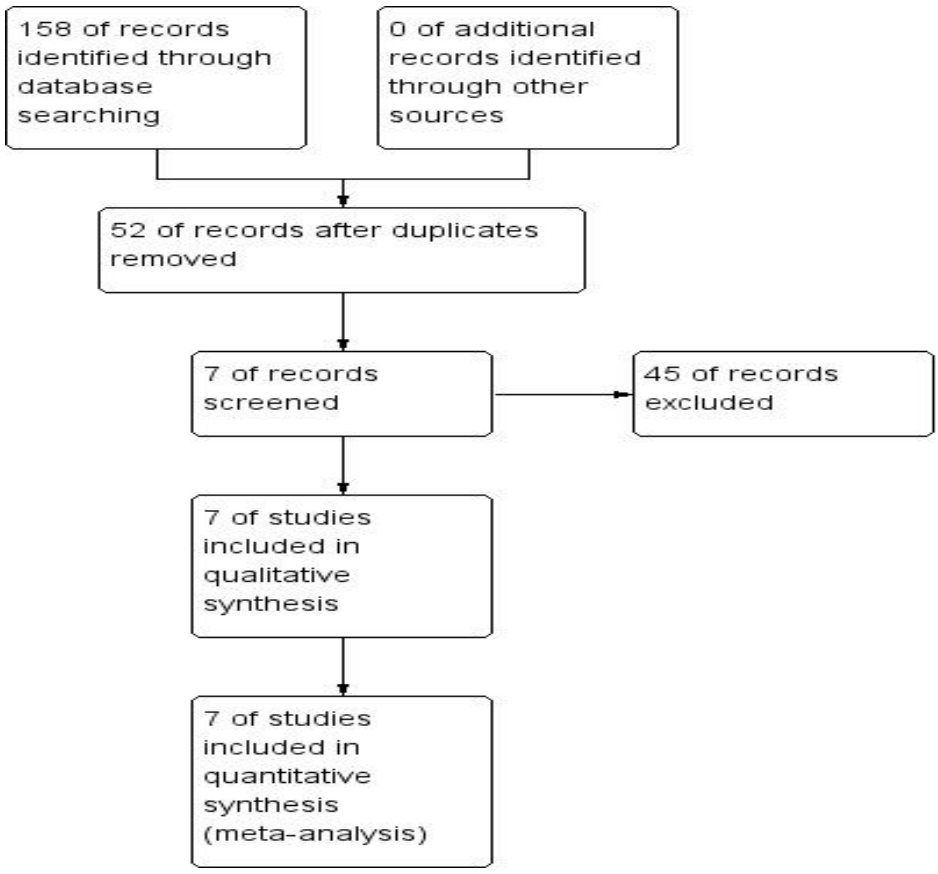

Figure 1 Flow chart showing the process of literature search and selection algorithm

The basic features of the included literature

The 7 included studies are domestic, the basic characteristics of the situation shown in Table 1. The seven articles included were published after 2000,

one of which [7]was conference paper, and the remaining [2-6, 8] are journal articles. A total of 612 patients were enrolled, including 358 patients in the treatment group and 254 patients in the control group. The treatment course of 4 studies [2, 5-7] were 30 days, one [3] was 2 months and the remaining two [4, 8] did not mention; Interventions in the treatment group of 1 study [2] was Mahuang Fuzi Xixin Decoction combined with ginseng needles (the first to the fourth day), and the treatment for the remaining 6 [3-8] was Mahuang Fuzi Xixin Decoction; The atropine tablets 0.6mg tid combined with ephedrine 12.5mg bid was used in the control group of 3 studies [2, 6, 7]. Xin Bao Wan 5-10 pills tid was used in the control group of 2 studies [3, 5], Atropine 2 mg tid, was used in the control group of 1 study [4]; Outcome measures are involved in the improvement of the main symptoms and heart rate changes, 2 sudies [6,7]reported the drug reactions and gastrointestinal reactions, 1 study reported [3]the relapse rate after stopping and gastrointestinal reactions.

Methodological Quality Assessments Included in Literature

The methodology was double-blinded for method quality assessment for the included seven articles and the results were presented as a offset risk map (Figure 2).

Efficacy analysis

All the seven articles included in the literature were reported to be effective, and were examined by heterogeneity, the literature is homogeneous(P = 1.00, I^2 = 0%), fixed effect model was used to meta analysis. The results showed that the efficiency of the treatment (86.9%) was better than the control (70.1%), the difference was statistically significant (RR = 1.25, 95% CI (1.15, 1.15), P < 0.001].（Figure. 2）

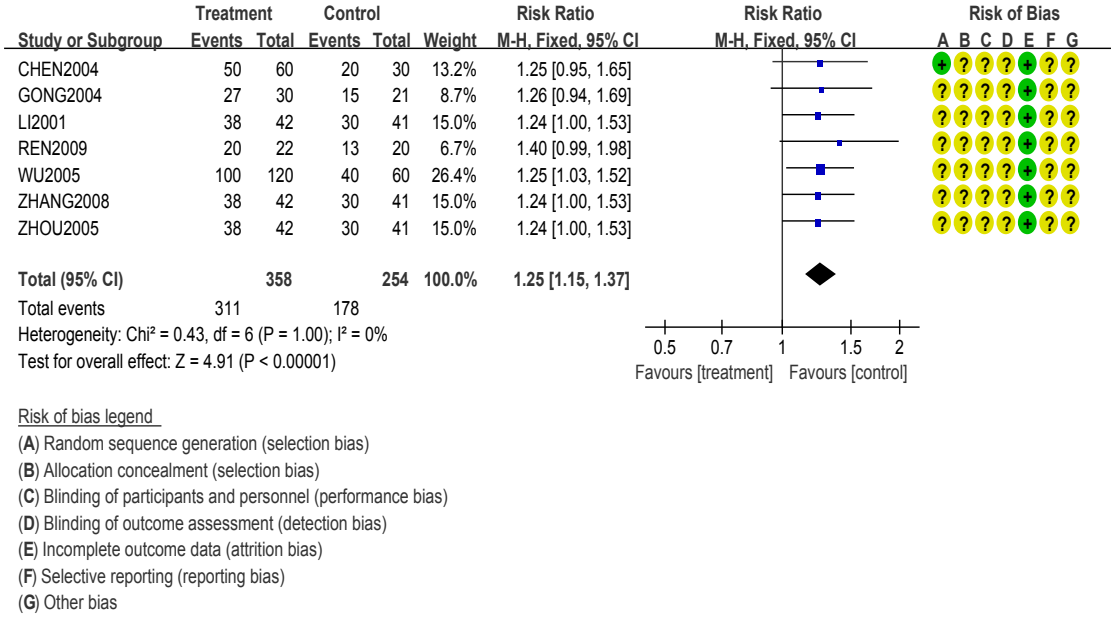

Figure 2 Efficacy of Mahuang Fuzi Xixin Decoction on SSS and risk of bias

Subgroup analysis were carried out according to different interventions of treatment groups. The results showed that the 95% CI overlaps between the Mahuang Fuzi Xixin Decoction subgroup and the subgroup of the combination of Mahuang Fuzi Xixin Decoction and ginseng needles, which means that there was no interaction between the two subgroups (P < 0.001) (Figure 3).

Subgroup analysis were further carried out according to the difference of the control group; the results showed that the 95% CI overlaped among the combination of atropine and Mahuang subgroup [RR=1.24, 95%CI (1.10,1.40)], xinbao pills [RR = 1.25, 95% CI (1.07, 1.47)], the atropine subgroup[RR=1.26, 95%CI (0.94,1.69)] and the blank control group [RR = 1.40, 95% CI (0.99,1.98)].Thus there was no interaction among the subgroups (P<0.001) (Figure 4).

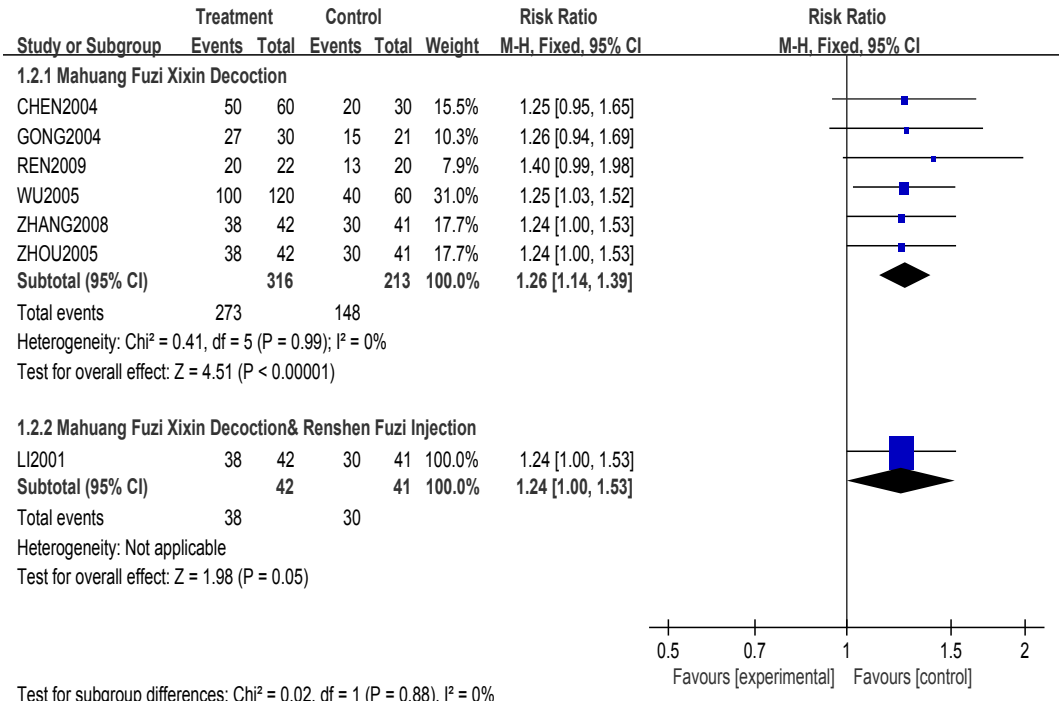

Figure 3 Subgroup analysis of effect of Mahuang Fuzi Xixin Decoction on SSS

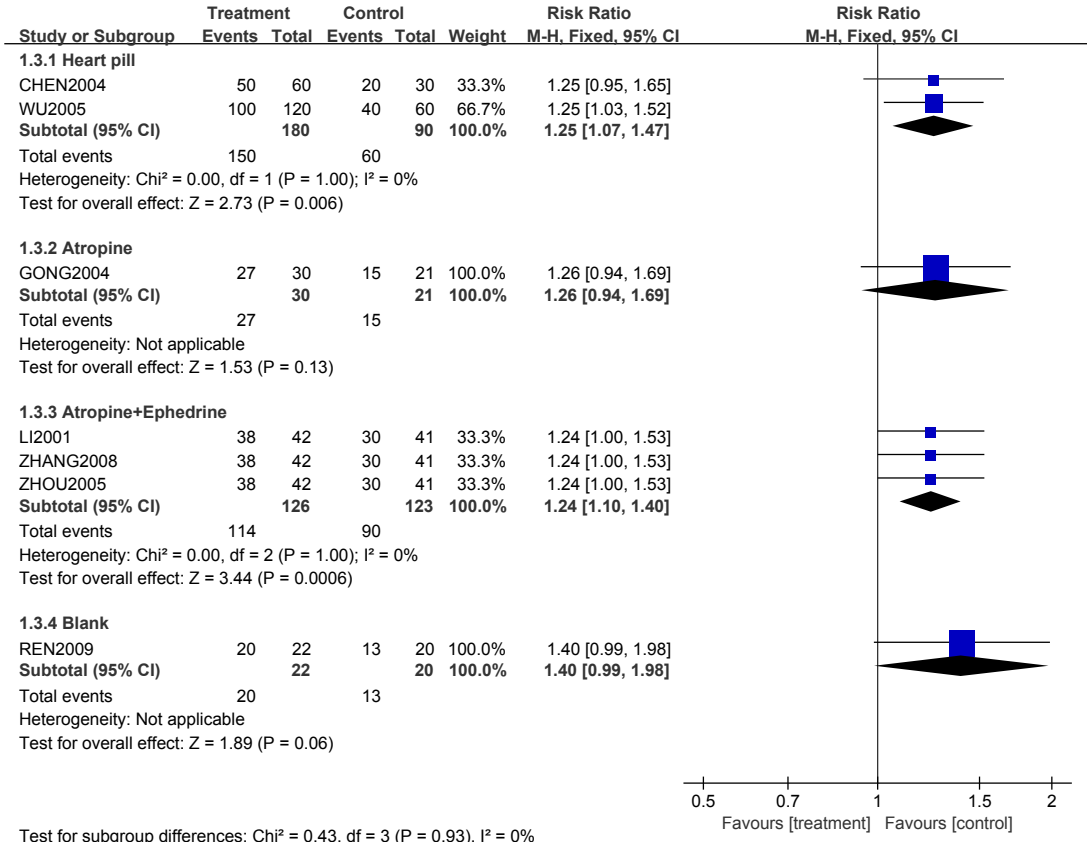

Figure 4 Subgroup analysis of effect of Mahuang Fuzi Xixin Decoction on SSS

Security Analysis

Adverse reactions were reported in the included literature of five articles. Heterogeneity was not observed among the 5 literatures (P < 0.001, I^2 = 90%). A random-effect model was used and showed that the incidence of adverse reactions in the treatment group was 17.0%, which was significantly lower than that of the control group (49.8%). The difference was statistically significant [RR = 0.23, 95% CI (0.06, 0.93), P = 0.04] (Figure 5). All five articles involved in liver and kidney function, and have no adverse effects on liver and kidney function.

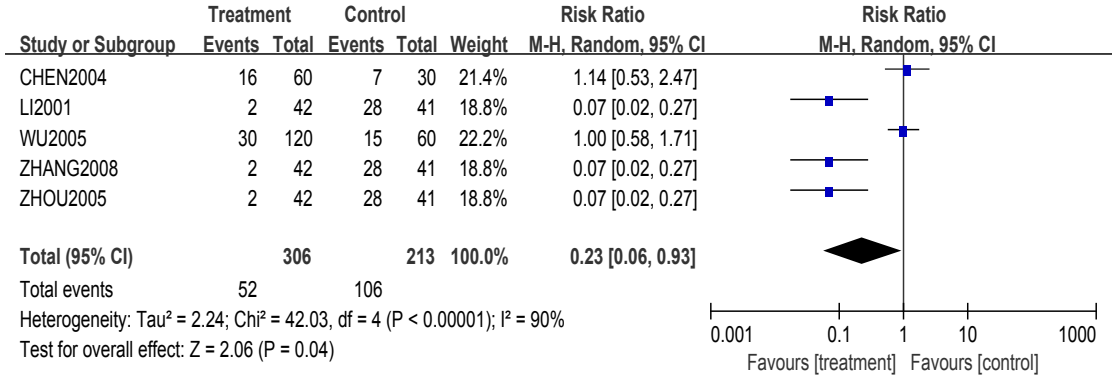

Figure 5 Safety of Mahuang Fuzi Xixin Decoction on SSS

Subgroup analysis on adverse events showed the 95% CI overlaped between the face flushing subgroup [RR = 0.39, 95% CI (0.16, 0.97)] and the subgroup of dry mouth, abdominal fullness and loss of appetite [RR = 1.00, 95% CI (0.61, 1.63)], suggesting there was no interaction between the two subgroups (P <0.001) (Figure 6).

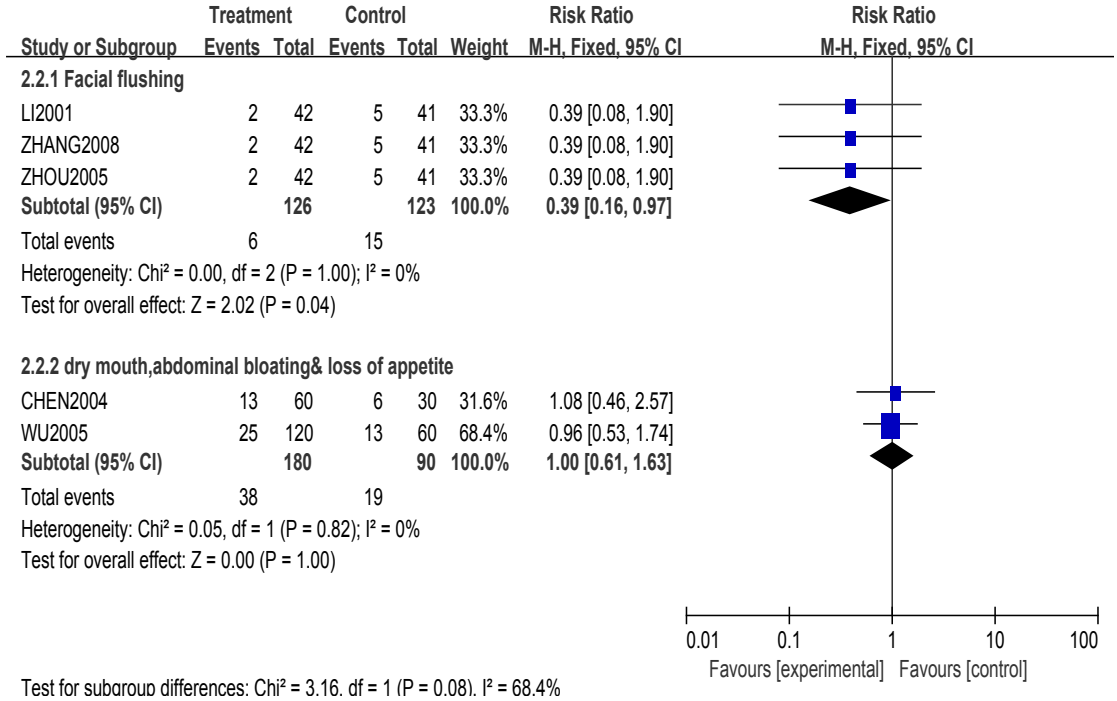

Figure 6 Subgroup analysis of safety of Mahuang Fuzi Xixin Decoction on SSS

Publication bias

As showed in the funnel chart (Figure 7), the distribution of the studies were symmetry, like a funnel, indicated that the bias of the inclusion publications were small.

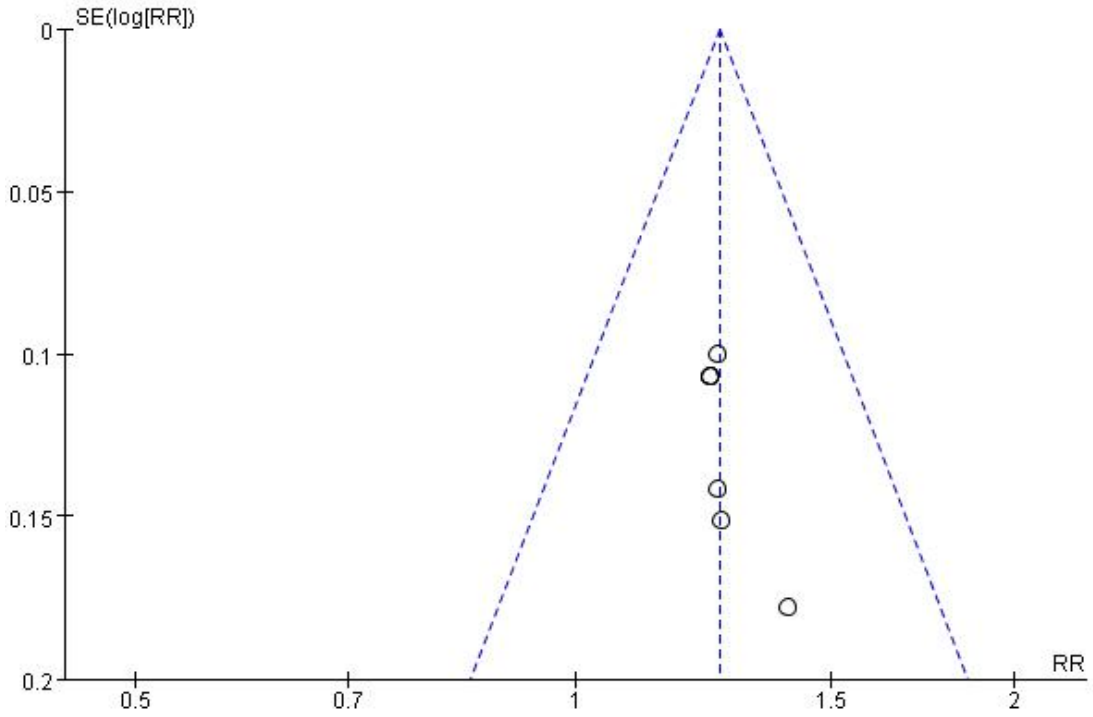

Figure 7 Funnel plot

Discussion

Mahuang Fuzi Xixin Decoction found in the "Shang Han Lun" which reported that" Mahuang Fuzi Xixin Decoction should be used in the beginning of Shaoyin disease accompanied by fever and deep pulse." As a exterior-interior concurrent disease, we should develop a treatment plan according to specific circumstances. In the original, Shaoyin disease with deep pulse means deficiency of yang. There is no diarrhea with undigested food in the stool and cold hands and feet, means the deficiency of yang is not very much. The abnormal fever is a result of exogenous cold. When the exterior-interior concurrent disease and the certificate is not clear, we should treat from both exterior and interior and warm the surface using Mahuang Fuzi Xixin Decoction. Ephedra could relieve exterior syndrome and cold, monkshood could warm the yang of kidney. Asarum hot and penetrating which could assist ephedra and monkshood in the treatment [9]. Combination of three drugs warmed Shaoyin, relieved exterior syndrome, warmed yang and restored deficiency. Mahuang Fuzi Xixin Decoction was designed for the treatment of Tai and Shao, but its main role is warming yang and activating meridian. Its clinical application is not limited to Tai Shao two syndromes. Its effective as long as suitable for the pathogenesis. Sick sinus syndrome is a combination of dysfunction and arrhythmia caused by sinus node lesions, which attributed to angina pectoris, palpitation, dizziness in Chinese medicine. Its pathogenesis is the deficiency of yang in heart, kidney and spleen together with yin excess cold in interior. The deficiency of yang lead to phlegmatic hygrosis and blood stasis, which classified into four groups: heart-yang deficiency, deficiency of both qi and yin, heart-kidney yang deficiency with or without spleen deficiency. According to dialectical classification of Chinese medicine. SSS was caused by the deficiency of yang which is suitable for Mahuang Fuzi Xixin Decoction. So Mahuang Fuzi Xixin Decoction could be used to treat sick sinus syndrome.

The results of this analysis showed that the treatment of sick sinus syndrome with Mahuang Fuzi Xixin Decoction better than placebo or other treatment, the difference was statistically significant. The incidence of adverse reactions is low, but the difference was not statistically significant. Mahuang

Fuzi Xixin Decoction treatment of SSS has clear effect, but lack of high-quality randomized controlled trials to support.

Its safety and effectiveness needed to design rigorous multicenter, large sample clinical trials to confirm. According to the results of the funnel chart analysis, the bias of publication publication included in this analysis is acceptable. The evaluation results are stable with certain credibility, but the possibility of unpublished negative results cannot be ruled out and the exaggerated efficacy cannot be excluded. Through the analysis, it is found that there are no high-quality randomized, controlled and double-blind trials in the present study. There are also many deficiencies in the experimental design. The main findings are as follows: 1) the diagnostic criteria and evaluation criteria of sick sinus syndrome was not unitary, some without the source. The lack of objective and specific evaluation index affected the evaluation results. 2) Inclusive criteria seldom describe the stochastic method, stochastic allocation of the program blind and blind method result in the quality of the method is poor. 3) Sample size is small. There are no multi-center and large sample clinical trials. Part of the test group and the control group sample size was different. The distribution cannot be randomized. 4) Treatment course in the literature included is not uniform, which may affect the treatment efficiency and safety. 5) The literature involved did not describe all the adverse reactions which mean no good evaluation of safety. 6) Follow-up information is incomplete in the literature included.

In summary, Mahuang Fuzi Xixin Decoction treatment of SSS curative effect was significant, but cannot be considered safe and different with placebo or other treatment. This conclusion needs to be proved by rigorous, multicenter and large sample clinical trials.

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