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Original Article

The clinical efficacy and adverse reaction of wenxin granule and amiodarone for patient with atrial fibrillation: a meta-analysis

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Abstract: Objective: To systematically evaluate the efficacy and adverse reaction of Wenxin Granule on rhythm control in patients with atrial fibrillation (AF) either as a sole or in combination with amiodarone. Method: The databases of Cochrane Central Register of Controlled Trials, PubMed, Embase, the Chinese Biomedicine Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang system database and Chongqing VIP Information (CQVIP) database were systematically searched for all relevant studies. The cut-off date for the electronic search was January 2016. All randomized controlled trials (RCTs) with enrolled patients of all ages with atrial fibrillation (AF) were included in the present study. The primary outcomes were the incidence of adverse events and the rate of rhythm control which was defined as the cardioversion and sinus rhythm maintenance in AF patients. For dichotomous outcomes, the rate of rhythm control and the incidence of adverse drug reaction were calculated as a relative risk (RR) with 95% confidence intervals (95% CI) in a fixed effects model. Result: A total of 15 trails (1,539 participants) were included in the meta-analysis. Compared with amiodarone, the group of Wenxin granule did not show statistical significance in rhythm control (RR: 0.91; 95% CI: [0.75, 1.09], P=0.30) but lower adverse events (RR: 0.54, 95% CI: [0.32, 0.90], P=0.02) while the group of Wenxin granule combined with amiodarone increased rate of sinus rhythm maintenance (RR: 1.34; 95% CI: [1.22, 1.47], P<0.01) and did not increase the incidence of adverse events (RR: 0.51, 95% CI: [0.32, 0.80], P<0.01). Trim and fill method was performed to correct the pooled effect for the funnel pot asymmetry (adjusted value of RR=1.172, 95% CI: [1.088, 1.264]). Conclusion: Wenxin granule as a sole or adjuvant agent on maintaining sinus rhythm in patients with AF was promising. However there were some methodological defects in the included studies. Further rigorously designed trials are needed to substantiate its clinical usage.

Keywords: Wenxin granule, amiodarone, atrial fibrillation, meta-analysis

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and significantly increases the risk of stroke, cardiomyopathy, and mortality. The initial therapy of AF should always include adequate antithrombotic treatment and management of the rate and rhythm. Rate or rhythm control as the treatment strategy remains an issue of considerable, ongoing debate. A multitude of clinical trials [1-3] have compared the two strategies and the results have not shown any benefit of one approach over the other. However, the trials were conducted in specific subgroups of patients. The research demonstrated a low success rate (20~50%) of maintaining sinus rhythm with antiarrhythmic drug (AAD) therapy and a high incidence of adverse AAD reactions [4]. Although radiofrequency ablation (RFA) has emerged as a relatively effective procedure for maintaining sinus rhythm, AAD is the first-line therapy for patient with AF. Improving the success rate of rhythm control and reducing the incidence of adverse drug reactions would make a better benefit than ventricular rate-control strategy in the quality of life, even disability and mortality.

Amiodarone is usually used as first-line antiarrhythmic agents for atrial fibrillation patients.

Since sodium channel blockers increase mortality in patients with reduced cardiac function, amiodarone is recommended for rhythm control in AF accompanied with structural heart disease [5]. Although amiodarone is more effective in rhythm management than sotalol, propafenone and flecainide, the benefit of amiodarone is under its toxicity profile during long-term oral administration.

Wenxin granule (WXG) is a pure Chinese herbal compound antiarrhythmic agent developed by China Academy of Chinese Medical Sciences. It contains Dangshen (Radix Codonopsis Pilosulae), Huangjing (Rhizoma Polygonati), Sanqi (Radix Notoginseng), Hupo (Succinum) and Gansong (Radix et Rhizoma Nardostachyos) et al. Recent clinical studies [6] have showed that Wenxin granule possesses potent anti-AF properties owing to its ability to depress atrial-selective I_{Na}-mediated parameters.

Currently, many clinical trials in China have reported WXG alone or combined with amiodarone have definite superiority in the efficacy and safety of rhythm control in comparison with amiodarone alone. But most of them were small sample trials and even some of the reports for the conclusion were conflicting. Therefore, this systematic review was conducted to evaluate the evidence of efficacy and safety of WXG used as a sole or adjuvant agent on rhythm control in AF patients.

Materials and methods

Search strategy

Comprehensive searches were performed-in databases of PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), Chongqing VIP Information (CQVIP) and Wanfang medical data (Wanfang), from the inceptions of the databases to January 2016. The references of published-papers were also checked to identify additional useful studies. Manual searches of relevant journals such as Traditional Chinese Medicine Journal, Chinese Journal of Integrative Medicine and Chinese Medical Journal were also performed. The Chinese Clinical Trials Registry was searched for ongoing studies. To verify unclear information and identify unpublished trails, attempts were made to contact the pharmaceutical company of Wenxin Granule via phone, email or mail. The focus of the search was randomized controlled trials (RCTs) of WXG or WXG combined with amiodarone compared to amiodarone alone for rhythm control of atrial fibrillation. The languages were limited to English and Chinese. Search terms in databases were as follows: (AF OR atrial fibrillation OR auricular fibrillation OR Paroxysmal atrial fibrillation OR Persistent atrial fibrillation OR Long-standing persistent atrial fibrillation OR Permanent atrial fibrillation) AND (Wenxin keli OR Wenxin granule OR Wenxin Granule and amiodarone OR Wenxin keli combined with amiodarone OR Wenxin granule combined with amiodarone OR Wenxin granule in combination with amiodarone OR Wenxin keli in combination with amiodarone).The article was screened based on title, abstract, and full text as needed.

Eligible studies

Studies included in the meta-analysis had to meet all of the following criterias: (1) Randomized controlled trials with atrial fibrillation patients diagnosed by electrocardiograph or dynamic electrocardiogram. (2) Oral WXG alone or in combination with oral amiodarone therapy compared with oral amiodarone therapy as controls. The oral dose of WXG was 18 g/d. The conventional oral dose of amiodarone was as follows: 0.6 g/d (1^{st} week), 0.4 g/d (2^{nd} week), 0.2 g/d (maintenance dose). (3) Outcome measurements included the rate of rhythm control and the incidence of adverse drug events. Rhythm control was defined by the success of cardioversion or sinus rhythm maintenance in AF patients, which requires to be confirmed by electrocardiogram (ECG) or Holter. (4) The patients of the study should receive basic treatments and proper anticoagulant therapy. (5) More than 8 weeks of the treatment and follow-up time are also required.

Ineligible studies

Clinical trials were excluded if they did not meet the above criteria. In addition, studies with the followings were also excluded: (1) Repetitive publications; (2) Non-original researches; (3) The data of the research was incomplete (e.g. letter to the author without respond); (4) Other antiarrhythmic drugs were used though the way of injection or oral during the treatment.

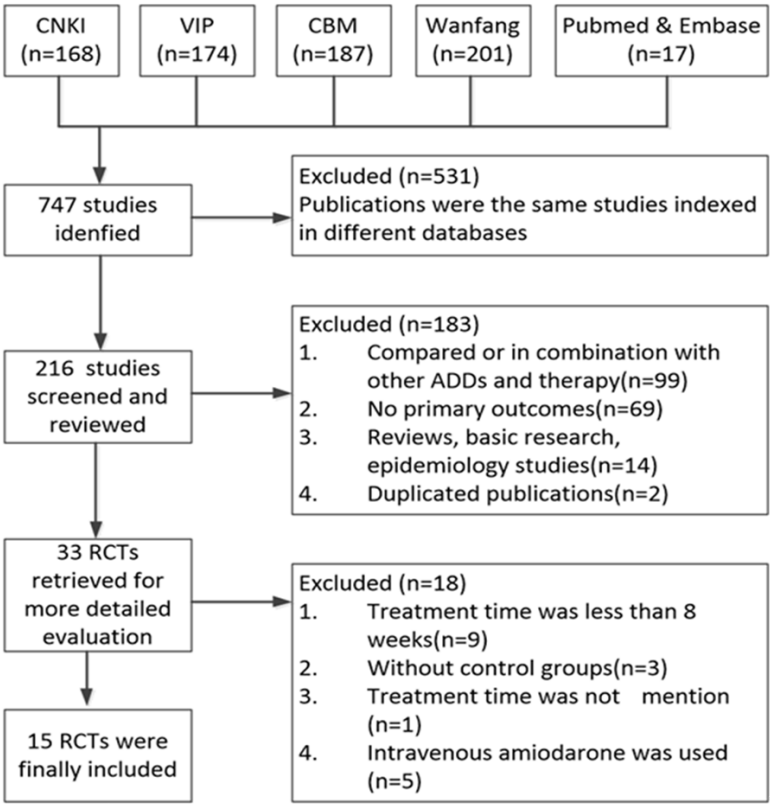

Figure 1. Flow chart of selection of randomized controlled trials (RCTs).

Data extraction

Two researchers (Nan Jiang and Chuangchang Wang) assessed studies based on the inclusion and exclusion criteria independently. Data extraction was conducted on the full-text copies of the included trials. Data on the details of source, sample size, age, sex, types of atrial fibrillation interventions, control medicine, treatment and follow-up time were extracted to a predefine form.

Risk of bias assessment

Two researchers (Lijin Qing and Rui Peng) independently assessed the quality and the risk of bias of the included studies according to Cochrane systematic review and meta-analysis handbook [7]. Disagreements were resolved by discussion and consensus by a third author (Wei Wu). Attempts were made to contact the authors of the original papers via phone and email when unclear information on data and therapy appeared. If the authors were not contactable for 3 times, we would exclude them from the study.

Statistical analyses

If the patients dropped out the clinical trails caused by adverse drug reaction or other reasons, intend-to-treat method was performed to estimate the results conservatively for the missing data. The Review Manager 5.2 and Stata 12.0 software were used to perform the data analysis. For dichotomous outcomes, the incidence of rhythm control was calculated as a relative risk (RR) with 95% confidence intervals (95% CIs). Statistical heterogeneity was assessed by Cochrane's Q test. If the analysis showed low heterogeneity ($p \geq 0.10$ and $I^2 \leq 50\%$), data were synthesized using a fixed-effects model. Otherwise, a random-effects model was applied to calculate the summary statistics. Publication bias was assessed by funnel plot analysis and Egger's test (If *p*-values >0.1, there were no publish bias). Sensitivity analyses, such as subgroup and trim-fill method were undertaken to adjust the pooled effect and examine the stability of the results as required if high heterogeneity test result appeared or funnel plot asymmetry.

Results

General characteristics of included studies

After searching the related databases, 216 potential relevant articles were screened. And 181 were excluded for not meeting the inclusion criterias after reviewing the titles and abstracts, and further 17 studies were excluded after reviewing the full text articles. In addition, there were two studies excluded for duplicated publication. Ultimately, a total of 15 [8-22] clinical trials involving 1,447 participants that meet all the selection criteria were included in this meta-analysis (**Figure 1**). All patients were diagnosed as atrial fibrillation according to electrocardiogram (ECG) or Holter. All of the studies were conducted in China and were pub-

Table 1. Characteristics of included studies (baseline data)

Source	Study type	Sample size	Age, y	Male, %	Types of atrial fibrillation (AF)	Treatment group		Control group Amiodarone (C)	Duration, mo
						Combined used (A)	Wenxin granule (B)		
Xiang 2011 [8]	RCT	90	58.5±5.19	66.7%	Paroxysmal AF	B: 3 bags/d, 9 g/bag C: Conventional oral dose#	3 bags/d, 9 g/bag	Conventional oral dose	2
Zhu 2006 [9]	RCT	168	55.94	54.2%	Not mentioned	(Ditto)	3 bags/d, 9 g/bag	Conventional oral dose	2
He 2009 [10]	RCT	118	52±13	63.56%	Paroxysmal AF	(Ditto)	3 bags/d, 9 g/bag	Conventional oral dose	6
Wang 2006 [11]	RCT	224	64.5±7.8	57.1%	Paroxysmal AF or Persistent AF	(Ditto)	NA	Conventional oral dose	6
Xia 2007 [12]	RCT	69	32~74	60.9%	(Ditto)	(Ditto)	NA	Conventional oral dose	6
Chen De 2013 [13]	RCT	100	66.5±3.82	56%	(Ditto)	(Ditto)	NA	Conventional oral dose	3
Chen Gui 2012 [14]	RCT	62	45.91±11.4	43.54%	(Ditto)	(Ditto)	NA	Conventional oral dose	6
Li 2008 [15]	RCT	62	52.9	54.9%	Paroxysmal AF	(Ditto)	NA	Conventional oral dose	6
Zheng 2013 [16]	RCT	100	61.7±8.15	61%	Paroxysmal AF	(Ditto)	NA	Conventional oral dose	12
Yan 2011 [17]	RCT	80	65.15±4.5	47.5%	Paroxysmal AF	B: 3 bags/d, 5 g/bag* C: Conventional oral dose	NA	Conventional oral dose	12
Chen Ye 2013 [18]	RCT	100	61.94±4.74	55%	Not mentioned	(Ditto)	NA	Conventional oral dose	2
Huang 2011 [19]	RCT	88	68	52.27%	Paroxysmal AF	B: 3 bags/d, 9 g/bag C: 0.2 g/d (maintenance)	NA	0.2 g/d (maintenance)	12
Cao 2011 [20]	RCT	104	60.5	69.2%	Paroxysmal AF	NA	3 bags/d, 9 g/bag	Conventional oral dose	3
Zhang D 2010 [21]	RCT	84	20~69	57.1%	Paroxysmal AF	NA	3 bags/d, 9 g/bag	Conventional oral dose	12
Zhang 2011 [22]	RCT	90	67.5	54.4%	Paroxysmal AF	NA	3 bags/d, 5 g/bag	Conventional oral dose	2

*There are two types of standard Wenxin Granule: 9 g/bag and 5 g/bag (Sugar free). The effectiveness of these two types of Wenxin Granule are the same. #The Conventional oral dose of amiodarone: 0.6 g/d (1st week), 0.4 g/d (2nd week), 0.2 g/d (maintenance dose). NA, Not available; RCT, Randomized controlled trials.

Table 2. Characteristics of included studies (etiology of atrial fibrillation)

Study	Etiology of atrial fibrillation							
	Coronary heart disease	Hyper-tension	Pulmonary heart disease	Lone AF	Heart Failure	Cardio-myopathy	Valvular heart disease	Post-cardiac surgery
Wang 2006	102	118	42	16	35	--	--	--
Xia 2007	32	12	--	--	69	18	7	--
Xiang 2011	20	15	--	--	--	--	9	--
Chen De 2013	--	100	--	--	--	--	--	--
Li 2008#	Unclear	Unclear	Unclear	--	Unclear	Unclear	Unclear	Unclear
Cao 2011#	Unclear	Unclear	Unclear	--	Unclear	Unclear	Unclear	Unclear
Zhu 2006	34	19	13	6	--	8	32	--
Zhang D 2010#	Unclear	Unclear	Unclear	--	Unclear	Unclear	Unclear	Unclear
Yan 2011#	Unclear	Unclear	Unclear	--	Unclear	Unclear	Unclear	Unclear
Zheng 2013	44	21	15	20	--	--	--	--
Huang 2011	40	38	--	--	--	3	5	--
Zhang 2011	43	10	--	--	--	7	30	--
Chen Ye 2013#	Unclear	Unclear	Unclear	--	Unclear	Unclear	Unclear	Unclear
Chen Gui 2012	--	--	--	--	--	--	--	62
He 2009#	Unclear	Unclear	Unclear	--	Unclear	Unclear	Unclear	Unclear

#Six studies were lack of a detail description of the definite etiology in the patients with AF. It was indicated that the etiology of all the six trials were nonvalvular heart diseases after reading the full articles.

lished in Chinese. Fifteen studies were divided into two groups: Group A contains twelve studies [8-19] (1,136 participants) which compared Wenxin granule (3 bags/d, 9 g/bag) plus amiodarone with amiodarone (0.6 g/d×1 week, 0.4 g/d×1 week, followed by 0.2 g/d as a maintenance dose). Group B contains six studies [8-10, 20-22] (528 participants) which compared Wenxin granule with amiodarone. (Three studies compared the efficacy of rhythm control among Wenxin granule combined with amiodarone, Wenxin granule and amiodarone). One trail [19] with 88 participants initial administered oral dose of amiodarone of 0.2 g/d. There are two types of standard Wenxin Granule with the same effectiveness: 9 g/bag and 5 g/bag (Sugar free). The duration of treatment varied form 2 months to 12 months. The characteristics of the included studies were summarized in **Tables 1** and **2**.

Risk of bias of the included studies

"Randomly allocating of the patients" was mentioned in all the studies, but the randomization method was mentioned in seven trails [8, 11, 14-16, 19, 20]. Eight studies reported a total of 26 participants dropped out the clinical trails for the adverse drug reaction or withdrawals. After contacting the corresponding author, we found allocation concealment method in six studies [8, 11, 14-16, 20]. However, none of the included trials reported whether they had used intention-to-treat analysis (ITT) or not. ITT was performed to estimate the results conservatively for the missing data in the meta-analysis. None of the trials had a registered or published protocol, the judgment of selective outcome reporting was based on description of the method and outcome measures in the study. Most of the trials were lack of detail description of the methodological research and at high risk of bias. The results of the risk of bias are presented in **Figure 2.**

Meta-analysis

WXG versus amiodarone: Six studies with a total of 528 patients directly compared the efficacy and adverse events of WXG with amiodarone for the sinus rhythm control of atrial fibrillation. The sinus rhythm maintenance rate was 41.6% of the patients taking WXG and 45.6% of the patients taking amiodarone (RR 0.91, 95%; CI: 0.75, 1.09, P=0.30, **Figure 3**), with a non-significant difference. There was no statistical heterogeneity among the six studies (P=0.92, I^2=0%). All of the included studies reported adverse events in both WXG and amiodarone groups. Most of the adverse drug events in the

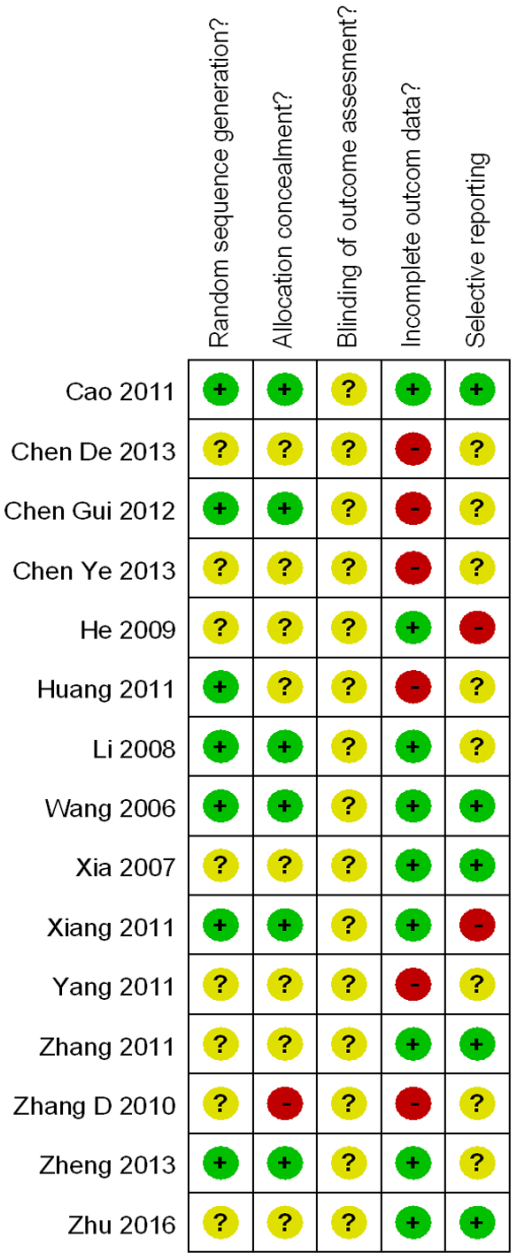

Figure 2. Summary of assessment of risk of bias for the included studies. (Eight studies reported a total of 26 participants dropped out the clinical trails for the adverse drug reaction or withdrawals, although no trials reported whether they had used intention-to-treat analysis (ITT), ITT was performed to estimate the results conservatively for the missing data in this meta-analysis).

amiodarone group (37 cases) were cardiac toxic reaction such as sinus bradycardia (8 cases), Q-T interval prolongation (2 cases), II AVB (1 case), and other organ toxic reaction, for instance stomach discomfort (16 cases), thyroid dysfunction (7 cases), pulmonary fibrosis (2 cases), liver dysfunction (1 case), whereas the common side effects of Wenxin granule (20 cases) were stomach discomfort, dizziness and sinus bradycardic. There were 2 patients dropped out of the trials in the amiodarone group for the adverse events of pulmonary fibrosis. The total incidence of adverse drug events was lower in the WXG group than in amiodarone group (RR 0.54, 95% CI: [0.32, 0.90], P=0.02, I^2=16%, **Figure 4**).

WXG combination with amiodaroneversus amiodarone alone: The pooled relative risk (RR) of 12 studies (1,136 patients), by the fixed effects model, showed that combination of WXG and amiodarone (66%) significantly increased rate of sinus rhythm maintenance in the AF patients verse amiodarone (49%) alone (RR 1.34, 95%, CI: [1.22, 1.47], P<0.05, **Figure 5**) and no statistical heterogeneity was found (P=0.16, I^2= 29%). After contacting the authors of original papers through phone and e-mail, 2 [17-18] of the included trials lacked a detailed description of adverse events. Ten out of the 12 included studies described adverse effects in both groups, and the result indicated that the combination with WXG and amiodarone do not increase the incidence of adverse events in the treatment duration when compared with amiodarone. (RR 0.51, 95%, CI: [0.32,0.80], P=0.003, I^2=34%, **Figure 6**).

Publication bias, sensitivity analysis and subgroup analysis: The publication bias was evaluated by egger's test and funnel plot (**Figure 7**). It indicated that the publication bias across the included studies was not statistical significant (t=0.26, 95%, CI: [1.87, 2.25], p=0.81). For the group of WXG in combination with amiodarone versus amiodarone alone, in addition to funnel plot, Trim and Fill method was performed to correct the pooled effect and examine the stability of the results as sensitivity analysis. There were some evidences of asymmetry (six studies trimmed) which may be related to publication bias or to clinical difference. Given that, the overall effect was unchanged after trimming missing studies, the result was considered to be steady (adjusted value of RR=1.172, 95%, CI: [1.088, 1.264] with fixed model, **Figure 6**). It was indicated that the minor heterogeneity may attribute to the different treatment duration. According, a subgroup analysis in the group of WXG combined with amiodarone versus amiodarone alone was performed for heterogeneity

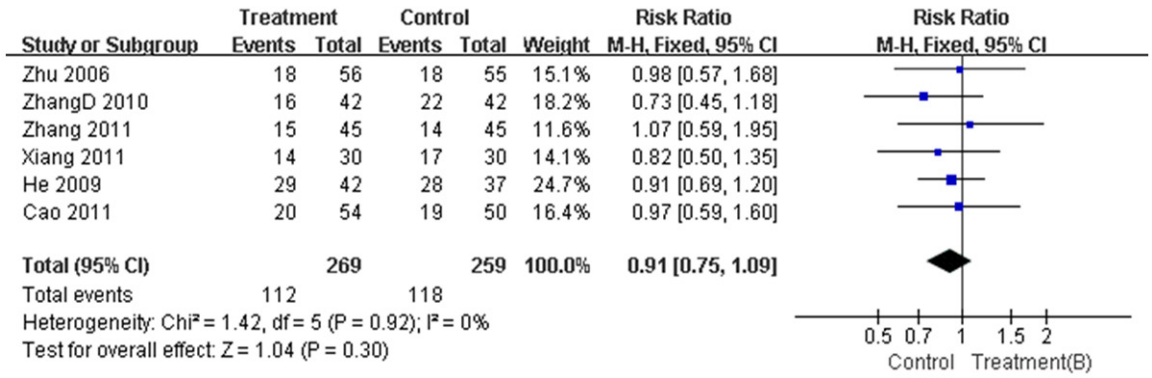

Figure 3. Forest plot of the comparison Wenxin granule versus amiodarone in sinus rhythm maintenance.

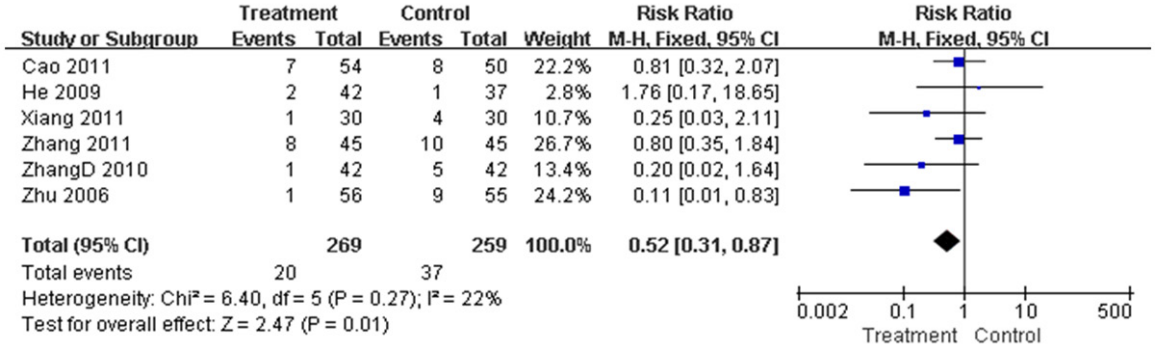

Figure 4. Forest plot of the comparison Wenxin granule versus amiodarone in adverse events.

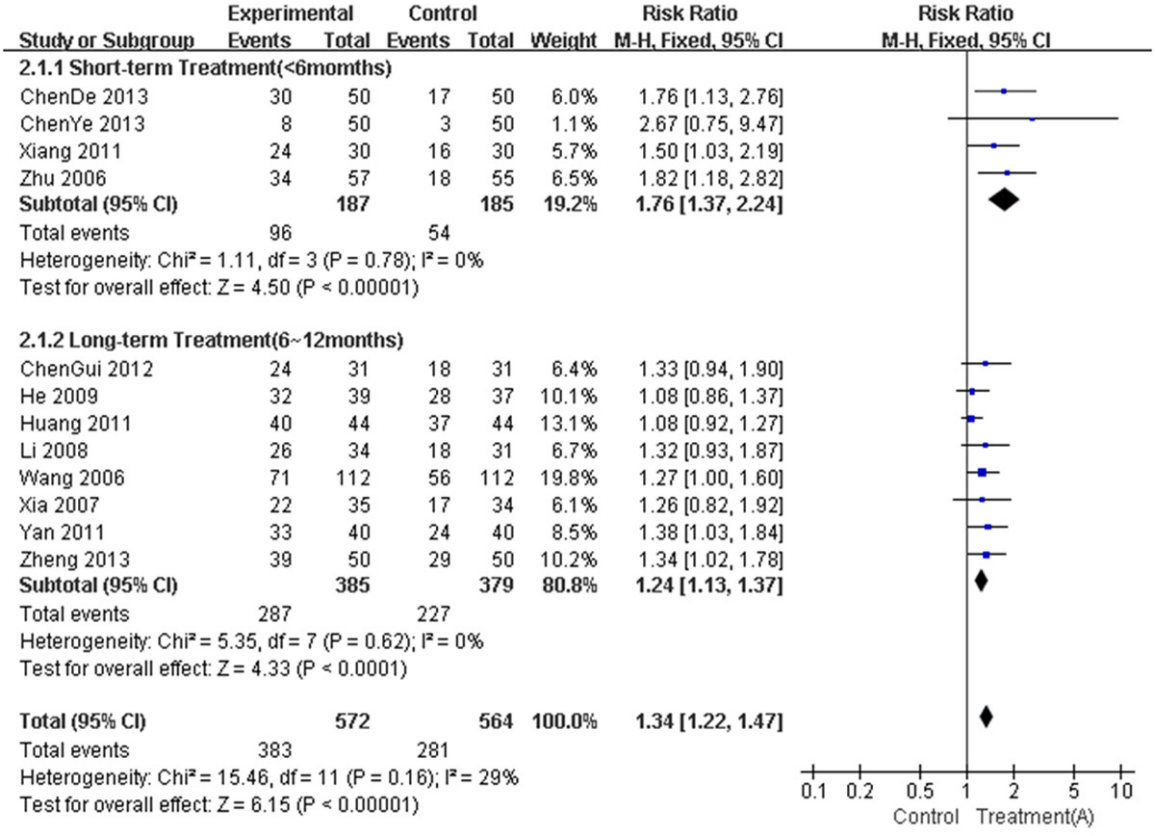

Figure 5. Forest plot of the comparison Wenxin granule combined with amiodarone versus amiodarone in sinus rhythm maintenance.

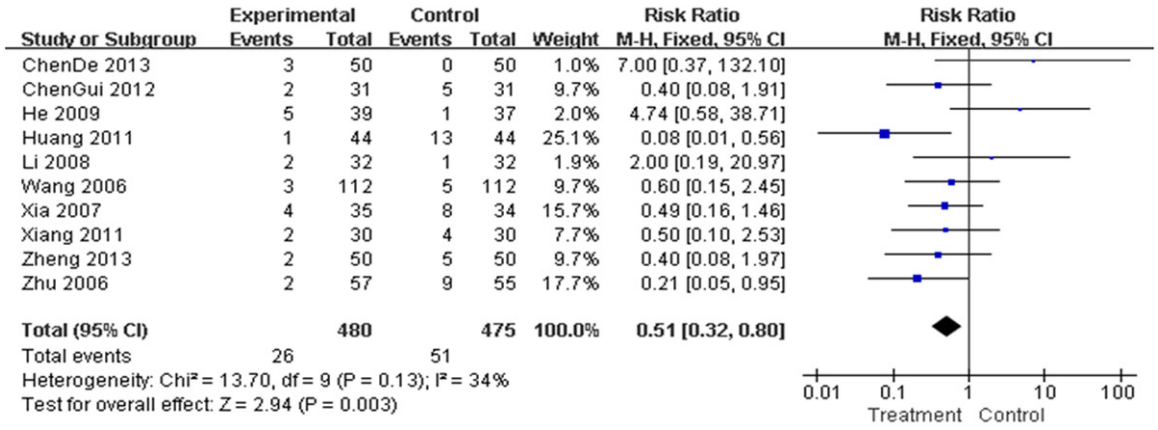

Figure 6. Forest plot of the comparison Wenxin granule combined with amiodarone versus amiodarone in adverse events.

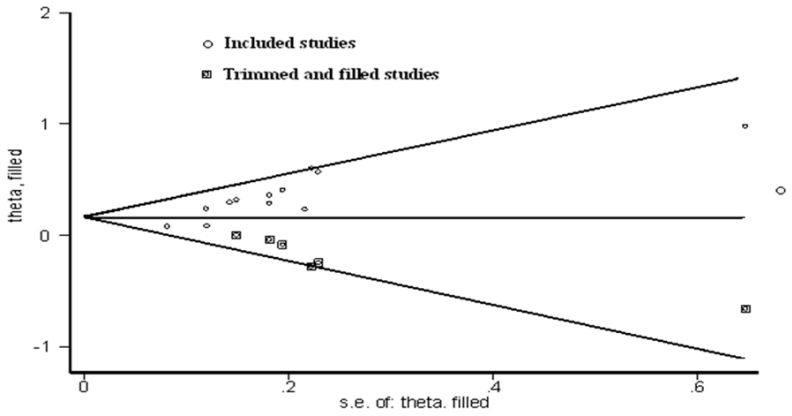

Figure 7. Funnel plot with trim and fill in studies for evaluation the publication bias in patients with AF.

test according to treatment duration of short-term (<6 months) and long-term (6~12 months). Both the short-term group (4 studies, 372 patients) and longg-term group (8 studies, 764 patients) showed a significant increase in the sinus rhythm maintenance compared to amiodarone in AF patients with little heterogeneity (RR 1.76, 95% CI: [1.37, 2.24], I^2=0%; RR 1.24, 95% CI: [1.13, 1.37], I^2=0%. **Figure 5**).

Discussion

All of the included studies suggested some methodological deficiencies which may result in potential risks of bias and false-positive findings. Eight studies reported participants dropped out the clinical trails for the adverse drug reaction or withdrawals. Only one trial described the procedure of random sequence generation, no study reported the allocation concealment and blinding. In addition, all of the trials were lack of register or publication of protocols which may lead to selective reporting of outcome. Although the evidence were insufficient to obtain a definite conclusion of the efficacy of WXG alone or in combination with amiodarone for the poor methodological quality, it was promising that WXG was used as a sole or adjuvant agent in the sinus rhythm control for patients with AF. Although trim and fill method had been performed to prove the stability of the results, potential publication bias and clinical difference may be the explanations for the funnel plot asymmetry. The included trials were conducted in China and published in Chinese, most of which were small sample with positive results and lack of the negative findings, and it was not possible to include the unpublished studies with negative results although comprehensive research of database had been conducted. However, there are two clinical factors that could have resulted in clinical difference. Firstly, the treatment duration of each study was not the same. Six studies [8, 9, 13, 18, 20, 22] reported the pri-

mary outcome in a short-term treatment course (<6 months), while nine studies [10-12, 14-17, 19, 21] reported in a long-term treatment course (6~12 months). The analysis of subgroup based on treatment duration revealed that the effect size of long-term and short-term duration was different. In addition, the basic etiology and clinical types of AF were the important factors that could affect the clinical efficacy of cardioversion. Most of the trails [8, 10-17, 19-22] included the participants with paroxysmal types while four trails [11-14] including persistent types, and the basic etiology in the patients with AF were more likely related to hypertension and coronary heart disease.

Wenxin Granule is the first antiarrhythmic Chinese herb extract reported to be of benefit in the treatment of cardiac arrhythmias. A fundamental research [6] showed that WXG causes potent atrial-selective depression of I_{Na}-mediated parameters in canine isolated coronary, thus preventing induction of AF and terminate persistent AF. Unlike amiodarone selectively prolong action potential duration (APD_{90}), WXG abbreviates APD_{90} much more in atrial versus ventricular cells, with minimal effects on ventricular electrophysiology. ECG P-Wave Dispersion (PD) is a predictor of the risk of developing AF [23], the longer of the PD interval, the higher occurrence of developing paroxysmal AF, and a system review and meta-analysis [24] have demonstrated that Wenxin granule, alone or combined with Western medicine can lower the PD than Western medicine treatment.

There are some limitations for this system review. Firstly, although trim and fill method had been performed to examine the results, without negative findings studies, the publication bias may play a major issue which could affect the results. However, there are other potential bias because of methodological deficiencies and insufficient reporting statement. We suggest that the further RCTs conducted and published in China should register or publish protocols in the Cochrane Central Register of Controlled Trials (CENTRAL), design the study in a rigorously way and report the clinical observation following a CONSORT statement. Secondly, our research only concentrate on efficacy and safety of WXG alone or combined with amiodarone on the sinus rhythm maintenance. However, a multitude of clinical trials [1-3] proved that rhythm control do not decrease the mortality compared to ventricular rate control. So, it is necessary performing systematic studies to prove whether WXG used as rhythm control strategy can reduce the mortality in the patients with AF or not when comparing to other antiarrhythmia drugs such as amiodarone and β-blocker. Thirdly, most of the trials are focus on the efficacy between WXG in combination with amiodarone versus amiodarone alone. However, the benefits of WXG in suppressing atrial fibrillation are promising, although the total sample size (528 patients) are not large, we provide some evidence of the potential effect of WXG used as a sole agent in sinus rhythm maintenance for the patients with AF in this system review, further rigorously and large designed studies are encouraging to substantiate its use.

In conclusion, this systematic review including 15 RCTs indicated WXG may have a potential effect with less adverse events in sinus rhythm control for patients with AF. WXG in combination with amiodarone can significantly increase the rate of sinus rhythm maintenance and reduce the incidence of adverse events compared to amiodarone alone with a treatment duration of 2-12 months.

Disclosure of conflict of interest

None.

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