A meta-analysis of wenxin granule and metoprolol for the treatment of coronary heart disease and arrhythmia

Ling-Li Meng, MMa, Wei Huang, MBa,*

Abstract

Background: This meta-analysis aimed to systematically and comprehensively assess the effectiveness and safety of wenxin granule (WXG) and metoprolol in the treatment of elderly patients with coronary heart disease (CHD) and arrhythmia.

Methods: We searched the electronic databases of the Cochrane Library, PUBMED, EMBASE, CNKI, Wangfang, and CBM from initiation to May 1, 2022, and selected a set of clinical indicators for WXG and metoprolol for CHD and arrhythmia. The methodological quality of the included studies was analyzed using the Cochrane risk-of-bias tool. Data were pooled using a fixed-effects or random-effects model, and a meta-analysis was conducted.

Results: Eight randomized controlled trials involving 722 patients with CHD and arrhythmia were included. Our findings showed that WXG and metoprolol showed better effects than metoprolol alone on electrocardiogram change (odds ratio [OR] = 7.21, 95% confidence interval [CI] [1.48, 35.07]), clinical symptom improvement (OR = 5.83, 95% CI [1.52, 22.35]), overall clinical effect (OR = 5.51, 95% CI [2.65, 11.44], P < .001), atrial premature beat (mean difference [MD] = −109.85, 95% CI [−171.25, −48.46], P < .001), ventricular premature beat (MD = −195.43, 95% CI [−334.09, −56.77], P < .001), borderline premature beat (MD = −42.92, 95% CI [−77.18, −8.67], P = .01), short-burst ventricular tachycardia (MD = −35.98, 95% CI [−39.66, −32.30], P < .001), ST segment reduction (MD = −0.47, 95% CI [−0.54, −0.40], P < .001), ST segment decrease duration (MD = −0.76, 95% CI [−0.95, −0.57], P < .001). However, no significant differences were observed in adverse reactions (OR = 0.54, 95% CI [0.27, 1.09], P = .09).

Conclusion: Compared to metoprolol alone, WXG and metoprolol can more effectively manage patients with CHD and arrhythmia. However, additional large-scale, multicenter, rigorous, and high-quality randomized controlled trials are warranted to verify the present findings.

Abbreviations: APB = atrial premature beat, ARs = adverse reactions, BPB = borderline premature beat, CHD = coronary heart disease, CI = confidence interval, CYI = clinical symptom improvement, ECG-C = electrocardiogram change, MD = mean difference, OCE = overall clinical effect, OR = odds ratio, RCTs = randomized controlled trials, STSD = ST segment decrease duration, STSR = ST segment reduction, STVT = short-burst ventricular tachycardia, VPB = ventricular premature beat, WXG = wenxin granule.

Keywords: arrhythmia, coronary heart disease, meta-analysis, metoprolol, wenxin granule

1. Introduction

Coronary heart disease (CHD) is characterized by occlusion or vascular stenosis leading to myocardial ischemia, hypoxia, and necrosis. It is one of the most common risk factors for cardiovascular diseases and a major public health problem worldwide. It has been reported that CHD primarily leads to cardiovascular-related mortality, with approximately 7.3 million annual deaths, and China has contributed about 130,000 deaths. Together with arrhythmia, it is responsible for the largest number of cardiac-associated mortality and morbidity worldwide. Thus, it is important to manage patients with CHD and arrhythmia.

Metoprolol, a class II antiarrhythmic agent, is currently utilized clinically for the management of arrhythmias and CHD. According to previous experimental and clinical studies, it can significantly decrease the occurrence of CHD and arrhythmia. Studies have reported that it can slow heart rate, inhibit cardiac contractility by blocking β-adrenoceptors, and enhance cardiac autonomic function. However, its efficacy remains unsatisfactory and is accompanied by a variety of adverse events, such as nausea, dizziness, headache, and bradycardia.

Fortunately, the traditional Chinese herbal medicine, wenxin granule (WXG), has also been reported to manage such conditions with promising outcomes. WXG comprises of 5
2. Methods

We reported this meta-analysis based on the PRISMA statement.

2.1. Ethic approval statement

This study did not require ethical approval because it analyzed secondary data from potential publications.

2.2. Eligibility criteria

We included the following trials: randomized controlled trial (RCT); patients aged >60 years; diagnosed with CHD and arrhythmia; experimental group treated with WXG and metoprolol and the control group treated with metoprolol alone; and no gender, race, or nationality limitations.

We excluded the following studies: duplicate records; irrelevant studies, including animal studies, experimental studies, reviews, conference summaries, case reports, case series, non-controlled clinical studies, and retrospective studies; and not RCT, combined therapies, wrong comparisons, quasi-RCTs, and studies with incomplete data.

2.3. Search strategy for eligible records

Six electronic databases were searched from initiation to May 1, 2022: Cochrane Library, PUBMED, EMBASE, CNKI, Wangfang, and CBM. There were no limitations to the language of the search results. Keywords used to search were: “Wenxin granule,” “Wenxin keli,” “Betaloc,” “metoprolol,” “coronary heart disease,” “arrhythmia,” “cardiac arrhythmia,” “clinical trial,” “RCT,” “randomized controlled trial.” The search strategy of PUBMED is given in Table 1. This study included RCT that investigated the effectiveness and safety of WXG as adjunctive therapy to metoprolol in elderly patients with CHD and arrhythmia.

2.4. Outcome measurement

The outcomes were electrocardiogram change (ECG-C), clinical symptom improvement (CYI), overall clinical effect, atrial premature beat (APB), ventricular premature beat (VPB), borderline premature beat (BPB), short-burst ventricular tachycardia (STVT), ST segment reduction (STSR), ST segment decrease duration (STSD), and adverse reactions (ARs).

2.5. Study selection, data extraction, and risk of bias assessment

Record screening, data extraction, and risk of bias assessment was independently performed by 2 authors and cross-checked. Any disagreement was resolved through consultation or discussion with the third author. All records were selected based on eligibility criteria. Data from the included trials were extracted using a previously designed data collection form, including general data summary (e.g., title, first author, year of publication), basic patient and study information (e.g., age, gender, sample size, details of intervention and comparison), and outcomes. The methodological quality of all the included trials was evaluated using the Cochrane risk-of-bias tool in 7 domains. Each study was assessed through 7 domains, and each was rated as having a low, unclear, or high risk of bias.

2.6. Statistical analysis

This study analyzed data and conducted a meta-analysis using RevMan 5.3 software (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration). Continuous data were calculated using the mean difference (MD) and 95% confidence interval (CI), and dichotomous data were calculated using odds ratios (OR) and 95% CI. Statistical heterogeneity across the included studies was checked using I² index. A fixed-effects model was used to synthesize the data if I² was <50%, and a random-effects model was used to pool the data if I² was ≥50%.

3. Results

3.1. Study characteristics

In total, 938 records were identified in this study (Fig. 1). A total of 930 citations were excluded because of duplication, irrelevant studies, non-RCT, combined therapy, wrong comparison, quasi-RCT, and trials with incomplete data (Fig. 1). Finally, 8 eligible studies involving 722 patients focusing on WXG and metoprolol for CHD and arrhythmia were included, and the data were analyzed (Fig. 1). The sample sizes varied from 60 to 148 and all were prospective studies. The general characteristics of the 8 eligible studies are summarized in Table 2.

| Table 1 |
|---------|
| **Number** | **Search terms** |
| 1 | Coronary heart disease |
| 2 | Cardiac arrhythmia |
| 3 | Arhythmia |
| 4 | Or 1–3 |
| 5 | Chinese medicine |
| 6 | Herbal medicine |
| 7 | Chinese herbal medicine |
| 8 | Wenxin granule |
| 9 | Wenxin keli |
| 10 | Betaloc |
| 11 | Metoprolol |
| 12 | Or 5–11 |
| 13 | Clinical trial |
| 14 | Controlled clinical trial |
| 15 | Randomized controlled trial |
| 16 | Case-control study |
| 17 | Observational study |
| 18 | Or 13–17 |
| 19 | 4 AND 12 AND 18 |
3.2. Study quality assessment

The Cochrane risk-of-bias tool was used to assess the quality of the 8 included trials (Fig. 2). All 8 studies reported details of random sequence generation. However, none of the included trials provided insufficient information on allocation concealment and blinding to participants, investigators, and outcome assessors (Fig. 2). Regarding incomplete outcome data, all studies reported sufficient data, except for 3 studies with insufficient outcome indicators. All trials reported selective reporting and other biases with sufficient information (Fig. 2).

Table 2

| Study | No. of patients (T/C) | Age (yr, T/C) | Intervention | Outcomes |
|-------|-----------------------|---------------|--------------|----------|
| Gu 2019 | 40/40 | 69.7 ± 3.4; 69.5 ± 3.5 | Metoprolol + WXG | ECG-C, OCE, STVT, STSR, STSD, ARs |
| Guo 2018 | 50/50 | 68.3 ± 4.6; 69.1 ± 4.7 | Metoprolol + WXG | OCE, APB, VPB, ARs |
| Luo 2018 | 40/40 | 70.5 ± 1.1; 71.5 ± 1.3 | Metoprolol + WXG | OCE |
| Tan 2021 | 30/30 | 72.6 ± 2.4; 72.1 ± 2.3 | Metoprolol + WXG | OCE, APB, VPB, BPB |
| Wang 2017 | 42/42 | 71.0 ± 2.6; 71.0 ± 2.4 | Metoprolol + WXG | CYI, APB, VPB, BPB |
| Wang 2019 | 46/46 | 71.1 ± 2.4; 70.5 ± 2.6 | Metoprolol + WXG | OCE, ARs |
| Zhang 2019 | 39/39 | 63.3 ± 3.1; 63.2 ± 3.1 | Metoprolol + WXG | APB, BPB, ARs |
| Zhu 2019 | 74/74 | 74.3 ± 9.1; 74.3 ± 9.1 | Metoprolol + WXG | APB, VPB, ARs |

APB = atrial premature beat, ARs = adverse reactions, BPB = borderline premature beat, C = control group, CYI = clinical improvement, ECG-C = electrocardiogram change, OCE = overall clinical effect, STSD = ST segment decrease duration, STSR = ST segment reduction, STVT = short-burst ventricular tachycardia, T = treatment group, VPB = ventricular premature beat, WXG = wenxin granule.
3.3. ECG-C and CYI

One study involving 80 patients evaluated the ECG-C (OR = 7.21, 95% CI [1.48, 35.07], Table 3)[28] and another study investigated CYI (OR = 5.83, 95% CI [1.52, 22.35], Table 3).[32]

3.4. Meta-analysis of OCE

Four trials involving 332 patients assessed the OCE. Its results showed that WXG and metoprolol showed better effects than metoprolol alone on OCE (OR = 5.51, 95% CI [2.65, 11.44], I² = 0%, P < .001, Table 3, Fig. 3).[29–31,33]

3.5. Meta-analysis of APB and VPB

Four studies with 370 patients explored APB and VPB (Table 3). Statistically significant differences were found in APB (MD = −109.85, 95% CI [−171.25, −48.46], I² = 97%, P < .001; Table 3, Fig. 4), and VPB (MD = −195.43, 95% CI [−334.09, −56.77], I² = 99%, P < .001; Table 3, Fig. 5).
Figure 3. Meta-analysis of overall clinical effect.

Figure 4. Meta-analysis of atrial premature beat.

Figure 5. Meta-analysis of ventricular premature beat.

Figure 6. Meta-analysis of borderline premature beat.

Figure 7. Meta-analysis of short-burst ventricular tachycardia.
3.6. Meta-analysis of BPB

Two studies involving 162 patients evaluated BPB, and the results showed a statistically significant difference on BPB (MD = −42.92, 95% CI [−77.18, −8.67], I² = 89%, P = .01; Table 3, Fig. 6).

3.7. Meta-analysis of STVT, STSR, and STSD

Two trials with 178 participants examined STVT, STSR, and STSD[29,34] (Table 3). There were significant differences between 2 groups on STVT (MD = −35.98, 95% CI [−39.66, −32.30], I² = 23%, P < .001; Fig. 7), STSR (MD = 0.47, 95% CI [0.38, 0.56], P = .001; Fig. 8), and STSD (MD = 0.76, 95% CI [0.65, 0.86], P = .001; Fig. 9).

3.8. Meta-analysis of ARs

A total of 4 studies with 400 patients explored ARs[29,31,34,35] (Table 3). No significant difference was observed in ARs (OR = 0.54, 95% CI [0.27, 1.09], P = .33, P = .09; Fig. 10).

4. Discussion

CHD is still one of the most significant risk factors that can result in major public health problems or even cardiovascular-related deaths worldwide.[6–9] In addition to arrhythmia, previous studies have reported that such conditions account for more cardiac-associated mortality and morbidity.[10–12] Metoprolol has been reported to relieve both CHD and arrhythmia symptoms.[13–15] Furthermore, a variety of clinical trials have explored the effects and safety of WXG and metoprolol in the treatment of elderly patients with CHD and arrhythmia. However, there is limited evidence supporting this hypothesis.

This meta-analysis included a total of 8 trials involving 722 patients. This study comprehensively and systematically investigated the effects and safety of WXG and metoprolol in the treatment of elderly patients with CHD and arrhythmia. The results showed that patients who received WXG and metoprolol had better outcomes than those who received metoprolol alone. Effectiveness of WXG and metoprolol on ECG-C, CYI, OCE, APB, VPB, BPB, STVT, STSR, and STSD indicates that the effects of WXG and metoprolol are superior to those of metoprolol alone for the management of CHD and arrhythmia.

In addition, 4 trials involving 400 participants reported adverse events. There were no significant differences in the ARs when the data were pooled. This indicates that both modalities have similar safety profiles.

The present study has certain limitations as follows: there were certain risk of bias in the included trials, and all included studies did not fully describe the procedures of allocation and blind implementation; the sample size of some of the included studies was small, and their effectiveness tests were restricted; all studies were conducted in China and were published in Chinese journals, which may have caused bias. Therefore, further studies with larger sample sizes and multicenter designs are needed to validate the current findings.

5. Conclusion

The findings of this study showed that WXG and metoprolol was more effective than metoprolol for the treatment of elderly patients with CHD and arrhythmia.
Author contributions
Conceptualization: Ling-Li Meng and Wei Huang.
Data curation: Ling-Li Meng and Wei Huang.
Formal analysis: Ling-Li Meng.
Investigation: Wei Huang.
Methodology: Ling-Li Meng.
Supervision: Wei Huang.
Validation: Wei Huang.
Writing–original draft: Ling-Li Meng and Wei Huang.
Writing–review & editing: Ling-Li Meng and Wei Huang.

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