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Wenxin Keli for Ventricular premature complexes with Heart failure: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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ABSTRACT

Objective: To evaluate the efficacy and safety of Wenxin Keli (WXKL) alone or combined with Western medicine in treating ventricular premature complexes (VPCs) with heart failure (HF).

Methods: We searched five databases to identify relevant randomized controlled trials (RCTs) published before May 2016. Two review authors independently searched and screened the literature, extracted the data as well as assessed the methodological quality of the included studies by using criteria from the Cochrane Handbook, and analyzed via using Review Manager 5.3 software.

Results: Eight studies of WXKL were included. The results of the Meta-analysis showed that WXKL was more significant on the frequency of VPCs (MD = −427.08, 95% CI: −526.73 ~ −327.43, $P < 0.01$), left ventricular ejection fraction (LVEF) (MD = −4.12, 95% CI: 2.97 ~ 5.27, $P < 0.01$), the total effect of VPCs (RR = 0.48, 95% CI: 0.34 ~ 0.69, $P < 0.01$) and 6-min walking test (MD = 28.05, 95% CI: 19.56 ~ 36.54, $P < 0.01$). The treatment group presented a significant reduction at left ventricular end-diastolic diameter (LVED) (MD = −3.94, 95% CI: −6.57 ~ −1.31, $P < 0.01$) when treatment time was 12 weeks, however, there was no statistical difference at 8 weeks. In addition, the included trials generally showed low methodological quality.

Conclusions: Wenxin Keli may be effective and safe for treating VPCs and HF. However, further RCTs of larger scale, multi-center/country, longer follow-up periods, and higher quality are still required to verify the efficacy of Wenxin Keli in ventricular premature beat with heart failure.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of premature death throughout the world. An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths.[1] As a sort of the abnormalities in heart rate or rhythm, cardiac arrhythmia is one of the serious CVDs, which affects the pump function of the heart [2,3] Ventricular premature complexes (VPCs), a type of cardiac arrhythmia with premature contractions of the heart ventricle, is prevalent in the general population and it is characterized by the premature QRS complex on ECG that is of abnormal shape and great duration (generally > 129 msec). Studies have shown a higher frequency of VPCs was associated with LVEF decline, the damage of cardiac function, and it also reduced the quality of life and increased the risk of heart failure (HF) or mortality according to some population-based samples.[4,5]

Heart failure (HF) is a major and growing public health issue with an estimated prevalence of > 37.7 million individuals globally.[6,7] In the USA, the total medical costs for patients with HF are expected to rise from US $20.9 billion in 2012 to $53.1 billion by 2030.[8] HF is a terminal stage of various heart disease in which the heart is unable to pump out sufficient blood to meet the metabolic need of the body, leading to reduced blood flow, congestion of blood in the veins and lungs, and other changes that may further weaken the heart. Patients with HF experience numerous symptoms that affect their quality of life, including fatigue, dyspnea, poor exercise tolerance, fluid retention, etc. [9] HF is associated with increased morbidity and mortality, and confers a substantial burden to the health-care system worldwide.[10]

Arrhythmias are a common and fatal complication of HF, with

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estimates 50% to 70% cardiac deaths due to tachyarrhythmic mechanisms.[11] The failing heart plays a critical role in disturbances in cardiac rhythm, leading to cardiac remodeling, bringing out structural and/or electro-physiological abnormalities. In addition, ventricular arrhythmias are widely perceived as contributing to HF.[12] In a population-based cohort of more than 1100 participants, a higher frequency of VPCs resulted in an increase in incident CHF incident, a decrease in LVEF and increased mortality.[13] Therefore, the control of VPCs and HF is the main therapeutic principle.

Currently, as for frequent VPCs or HF, drug therapy may be the preferred therapeutic method to improve survival and the drug of choice is the one that interferes least with health-related well-being, otherwise known as the quality of life.[14,15] Unfortunately, efficacy of the drugs remains limited due to the complex remodeling processes underlying heart failure. And a problem in the treatment of frequent VPCs is that almost all western antiarrhythmic drugs have notable adverse effects, and some drugs might be proarrhythmic,[16] confirmed by the Cardiac Arrhythmia Suppression Trial (CAST).[17] Owing to the limitations of the current available treatments, complementary and/or alternative medicine (CAM) is increasingly sought to treat cardiac arrhythmia. Traditional Chinese medicine (TCM), as a form of CAM, has been used in patients with cardiac arrhythmia for thousands of years and is still being commonly used in modern times in both China and elsewhere worldwide.[18,19] However, there is still a lack for the mechanism study of TCM in the treatment of cardiac arrhythmia, and thus further exploration is greatly needed.

Wenxin Keli (WXKL), a formally classical Chinese patent medicine, is the first Chinese-developed anti-arrhythmic medicine approved by the China Food and Drug Administration and has been increasingly used as an alternative approach for cardiovascular diseases (CVDs) in both China and elsewhere worldwide.[20] WXKL is composed of five main components: *Codonopsis pilosula, Rhizoma polygonatum, Panax notoginseng, Spikenard* and *Amber*, which can tonify qi, supply yin, promote blood circulation and remove blood stasis according to the TCM theory. Developed in various forms over the past 2000 years, it is used by millions today for the treatment of a variety of cardiac diseases. Several experimental and clinical researches demonstrated WXKL is useful in the treatment of atrial fibrillation,[21] ventricular arrhythmia,[22] myocardial infarction,[23] heart failure,[24] Brugada syndrome,[25] and so forth. Currently, a large number of studies indicated WXKL had good curative effects on patients who suffer from ventricular premature and heart failure, but there is no full systematic evaluation about its effectiveness and safety. Therefore, in this work, we conducted a preclinical systematic review to evaluate the cardioprotective and antiarrhythmic effects of WXKL in RCTs, and provided some clues for researchers to develop new antiarrhythmic drugs based on WXKL.

2. Objective

The purpose of this study is to evaluate the effectiveness and safety of WXKL alone or combined with Western medicine in treating VPCs with HF.

3. Methods

3.1. Criteria for considering studies for this review

3.1.1. Types of studies

Randomized controlled trials (RCTs) with blind method or not and no limit of publishing language were included. We excluded quasi-randomized controlled trials (quasi-RCTs) and non-randomized controlled trials. The course of treatment was not less than 4 weeks, and the number of patients, not only the treatment group but also the control group, was more than 30. In addition, the outcomes of studies must involve left ventricular ejection fraction (LVEF) or Brain Natriuretic Peptide (BNP).

3.1.2. Types of participants

Patients diagnosed with VPCs and HF were included, not including those with severe liver and kidney dysfunction. Age and race were not limited.

3.1.3. Types of interventions

Based on the conventional western medicine treatment, the treatment group was given WXKL alone or combined with western medicine, and the control group was given nothing or only western medicine.

3.1.4. Types of outcome measures

3.1.4.1. Primary outcomes. The frequency of VPCs, LVEF, BNP.

3.1.4.2. Secondary outcomes. The total effect of VPCs, left ventricular end-diastolic diameter (LVED), 6-min walking test before and after treatment. Safety was calculated as follows: peripheral hemogram, liver function, renal function, adverse events (gastrointestinal reaction, allergic reaction), and so forth.

3.1.5. Effective criteria

According to the guiding principle of vascular system drugs clinical research by Ministry of Health,[4] the effective criteria of VPCs was as follows: Remarkable effect: VPCs disappeared or decreased by 90% or more, and there was an obvious improvement in the clinical symptom. Effect: VPCs decreased by 50% ~ 90%, and the clinical symptom improved partly. Non-effect: VPCs decreased by 50% or less, and the clinical symptom had no improvement even exacerbation. The total effect = Remarkable effect plus Effect.

3.2. Search methods for identification of studies

The search was applied to PubMed, The Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, and Chinese Scientific Journal Database (VIP) (publishing time was before May 2016). The search strategy used the following general terms individually or combined: “Wenxin Keli”, “WXKL”, “Wenxin granule”, “Ventricular arrhythmias”, “Ventricular premature complexes”, “Ventricular premature beat”, “Ventricular extrasystole”, “Premature ventricular contraction”, “Heart failure”, “Cardiac failure”, “Myocardial failure”, “Heart decompensation”. The detail search strategy was shown in Appendix A.

3.3. Data extraction and management

3.3.1. Data extraction and management

Two investigators independently conducted the literature searching, study selection, and data extraction. The extracted data of included studies was filled in a standardized form prepared for this review. The extracted data include study name, the type of experiment, intervention, dose, group, random, outcome and so on. Disagreements were discussed and resolved in a consensus meeting with the corresponding author.

3.3.2. Unit of analysis issues

Subgroups were divided according to intervention or course of treatment and analyzed individually.

3.3.3. Assessment of risk of bias in included studies

According to Cochrane Reviewer’s Handbook, 6 evaluation criteria of the quality of RCTs were used, which involved the generation of random sequence, randomization concealment, blind method, integrity of outcome data, selective reporting and other bias.

3.3.4. Measures of treatment effect

Revman 5.3 software provided by the Cochrane Collaboration was used for data analyses. Continuous outcomes were presented as