Amiodarone and acupuncture for cardiac arrhythmia
Study protocol for a systematic review
Xiang-Dong Meng, MM, Wei-Qin Gao, MM*†, Ze Sun, MM

Abstract
Background: Amiodarone and acupuncture (AA) are commonly used to treat cardiac arrhythmia (CA). The objective of this systematic review is to assess the efficacy and safety of AA for patients with CA.

Methods: Randomized controlled trials (RCTs) of AA for CA will be searched from 9 databases including PubMed, EMBASE, Cochrane Library, Web of Science, Scopus, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, VIP Information, and Wanfang Data from inception to February 1, 2019 without any limitations. Two reviewers will independently screen the relevant papers, extract data, and evaluate the risk of bias for each included study. RevMan 5.3 software will be used for meta-analysis. The primary outcome includes arrhythmic episodes (including time and frequency domain parameters). The secondary outcomes consist of health-related quality of life, oxygen saturation, and safety.

Results: The protocol of this proposed study will provide evidence to judge whether AA is an effective treatment for patients with CA.

Conclusion: The findings of this proposed study will summarize the up-to-date evidence of AA for CA.

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Abbreviations: AA = amiodarone and acupuncture, CA = cardiac arrhythmia, RCTs = randomized controlled trials.

Keywords: acupuncture, amiodarone, cardiac arrhythmia, efficacy, randomized controlled trial, safety

1. Introduction
Cardiac arrhythmia (CA) is a very common disorder for patients with cardiovascular disease, which is often characterized as any change from the normal sequence of electrical impulses.[1–3] Many factors are account for this disorder, such as smoking, high blood pressure, diabetes, high cholesterol, obesity, a high-fat diet, drug abuse, stress, family history, and so on.[4–10] It has been reported that about 2% to 3% of the population in Europe and North America experienced such condition in 2014.[11] Further studies found that approximately 30% deaths resulted from cardiovascular disease and 15% of all these deaths occurred because of the sudden cardiac death.[12] Moreover, of these sudden cardiac deaths, about 80% of them are caused by CA.[12] Thus, it is very important and very necessary to prevent and treat CA.

A variety of clinical studies have reported that the amiodarone, acupuncture, and combination of amiodarone and acupuncture (AA) are used to treat CA effectively.[13–26] However, no systematic review and meta-analysis have been conducted to assess the efficacy and safety of AA for the treatment of CA. Thus, in this systematic review, we will explore the efficacy and safety of AA for the treatment of patients with CA.

2. Methods and materials
2.1. Inclusion and exclusion criteria
2.1.1. Study types. This proposed systematic review will include randomized controlled trials (RCTs) that have evaluated all types of AA for CA. However, any other studies, such as non-clinical trials, case studies, non-RCTs, and quasi-RCTs will not be included.

2.1.2. Participants. All participants of clinically diagnosed with CA will be included without restrictions of race, gender, and age.

2.1.3. Interventions. The patients in the experimental group must receive any forms of AA, and will not combine with other treatments. The patients in the control group can receive any types of treatments, but not any forms of AA.

*W-Q G and X-D M contributed equally to this study.
No research ethics approval is needed for this study because it will not analyze individual patient data.
The findings of this systematic review will be planned to publish at a peer-reviewed journal.
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2.1.4. Outcomes. The primary outcome includes arrhythmic episodes (including time and frequency domain parameters). The secondary outcomes are health-related quality of life, oxygen saturation, and safety.

2.2. Literature search strategy

Nine databases will be searched from inception to February 1, 2019 without any restrictions. These databases include PubMed, EMBASE, Cochrane Library, Web of Science, Scopus, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, VIP Information, and Wanfang Database. All relevant RCTs of AA for CC will be fully considered in this study. Moreover, the websites of clinical registration and reference lists of included trials will also be searched to avoid missing any potential trials. The details of the search strategy are shown in Table 1, and a similar strategy will be performed to other databases.

2.3. Study selection

Two independent authors will select studies by scanning titles and abstracts initially, and then full-texts will be further read if it is necessary. Any potential studies will be fully considered. The whole procedure of study selection is shown in Figure 1. The disagreements regarding the study selection will be solved through discussion with a third author.

2.4. Data extraction and management

All data will be extracted by 2 independent authors following predefined standard form of data extraction. Any divergences will be resolved by consulting a third author. The form consists of the following information.

(1) General information: title, first author, country, year of publication;

(2) Basic characteristics: sample size, gender, age, eligibility criteria of diagnosis, inclusion and exclusion, and other specific details;

(3) Methods: study design, sample size, sequence generation, allocation and concealment, blinding, and any other bias;

(4) Treatment details: details of experimental and controls, dose, duration, and frequency of interventions;

(5) Outcomes: All primary and secondary outcomes, and any other reporting information.

2.5. Dealing with missing data

We will contact primary authors if any insufficient or missing data will happen during the data extraction period. If those missing data are not available, we will only analyze the available data, and will discuss their potential effects.

2.6. Methodological quality assessment

Cochrane Risk of Bias Tool will be used to assess the methodological quality by 2 independent authors. This tool includes 7 fields, and each aspect will be judged as high risk of bias, or unclear risk of bias, or low risk of bias. Any divisions will be resolved by consulting a third author for the methodological quality assessment.

2.7. Statistical analysis

ReMan 5.3 software will be utilized for statistical analysis. All the extracted data will be categorized into continuous variables, presented as the mean difference or standardized mean difference with 95% confidence intervals; or dichotomous variables, as showed with risk ratio and 95% confidence intervals.

Heterogeneity among trials is determined by using $I^2$ test. A fixed-effects model will be used to pool the data for assessing the effects of AA for CA if $I^2 \leq 50\%$. Otherwise, a random-effects model will be utilized to pool the data. Where significant heterogeneity is detected, subgroup analysis will be carried out based on the different study characteristics, experimental therapies, control treatments, and outcome measurements. A narrative summary will be elaborated if substantial heterogeneity is still detected after the subgroup analysis, and data will not be
pooled. In addition, sensitivity analysis will be performed to check the robustness of pooled data by removing low-quality trials. Moreover, funnel plot[27] and Egg regression[28] will be conducted to detect the reporting biases if more than 10 trials are included.

3. Discussion

Amiodarone has been used to treat CA for a long time. However, it still has limited efficacy and also accompanies lots of adverse events for long term treatment. Thus, adjunctive therapy with more exciting efficacy and fewer adverse events to amiodarone is urgently needed for the treatment of CA. Fortunately, many CA patients in China are seeking traditional Chinese medicine for their alternative treatments, and have achieved promising outcome results. For example, acupuncture, as one of the most important parts of traditional Chinese medicine has long been used for the treatment of CA condition in China. However, no systematic review has investigated the efficacy and safety of AA for CA. Thus, in this systematic review, we first assessed the efficacy and safety of AA for the treatment of CA. The results of this study will provide the first rigorous summary evidence of AA for CA across all published RCTs.

The data pooled will provide a better understanding of the efficacy and safety of AA for patients with CA. Its findings will inform our understanding of the value of AA in treating CA outcomes. Additionally, it may also provide helpful evidence for clinical practice and future studies.

Author contributions

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References

[1] Singh BN. Overview of trends in the control of cardiac arrhythmia: past and future. Am J Cardiol 1999;84:3R–10R.
[2] Andrade JG, Rivard L, Macle L. The past, the present, and the future of cardiac arrhythmia ablation. Can J Cardiol 2014;30(12 Suppl):S431–41.
[3] Nattel S, Andrade J, Macle L, et al. New directions in cardiac arrhythmia management: present challenges and future solutions. Can J Cardiol 2014;30(12 Suppl):S420–30.
[4] Haefeli WE, Schoenenberger RA, Weiss P, et al. Possible risk for cardiac arrhythmia related to intravenous erythromycin. Intensive Care Med 1992;18:469–73.
[5] Conte G, Lauro S, Lazzarin M, et al. Evaluation of hyperkinetic cardiac arrhythmia in chronic obstructive bronchopneumopathy. Minerva Cardioangiol 1997;45:29–33.
[6] Lagrutta AA, Trepakova ES, Salata JJ. The hERG channel and risk of drug-acquired cardiac arrhythmia: an overview. Curr Top Med Chem 2008;8:1102–12.
[7] D’Alessandro A, Boseckelmann I, Hammwhiner M, et al. Nicotine, cigarette smoking and cardiac arrhythmia: an overview. Eur J Prev Cardiol 2012;19:297–305.
[8] Langrish JP, Watts SJ, Hunter AJ, et al. Controlled exposures to air pollutants and risk of cardiac arrhythmia. Environ Health Perspect 2014;122:747–53.
[9] Abuelo JG. Low dialysate potassium concentration: an overrated risk factor for cardiac arrhythmia? Semin Dial 2015;28:266–75.
[10] Pathak RK, Mahajan R, Lau DH, et al. The implications of obesity for cardiac arrhythmia mechanisms and management. Can J Cardiol 2015;31:203–10.
[11] Zoni-Berisso M, Lencari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol 2014;6:213–20.
[12] Mehra R. Global public health problem of sudden cardiac death. J Electrocardiol 2007;40(6 Suppl):S118–22.
[13] Darkner S, Chen X, Hansen J, et al. Recurrence of arrhythmia following short-term oral AMIODarone after CATHeter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). Eur Heart J 2014;35:3356–64.
[14] Li HS, He BB, Huang GH. Therapeutic effects of amiodarone and metoprolol on chronic heart failure complicated by ventricular arrhythmia. Nan Fang Yi Ke Da Xue Xue Bao 2009;29:1240–2.
[15] Crystal E, Kahn S, Roberts R, et al. Long-term amiodarone therapy and the risk of complications after cardiac surgery: results from the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT). J Thorac Cardiovasc Surg 2003;125:635–7.
[16] Rokicki W, Durnala J, Nowakowska E. Amiodarone for long term treatment of arrhythmia in children. Wiad Lek 2001;54:45–50.
[17] Chuang SF, Liao CC, Yeh CC, et al. Reduced risk of stroke in patients with cardiac arrhythmia receiving traditional Chinese medicine: a nationwide matched retrospective cohort study. Complement Ther Med 2016;25:34–8.
[18] Zou M. Clinical observation on therapeutic effect of combination of acupuncture and ginger-partition moxibustion for treatment of patients with cardiac arrhythmia. Zhongguo Zhen Jiu 2009;29:876–8.
[19] Liu LY, Li ZP. Observation on the clinical curative effect of propafenone with acupuncture Neiguan on frequent ventricular premature beat. Chin J Integr Tradit West Med Intens Crit Care (Chin) 1999;6:65–6.
[20] Li H. The transient effect of acupoint selection of Linggu Bafa on sinus tachycardia. Chin Acupunct Moxibust (Chin) 2003;23:132–4.
[21] Dong SJ. 32 cases of paroxysmal supraventricular tachycardia in acupuncture Neiguan. J Henan Univ Tradit Chin Med (Chin) 2006;21:69–70.
[22] Xu HK, Zhang YF. Comparison between therapeutic effects of acupuncture and intravenous injection of amiodarone in the treatment of paroxysmal atrial fibrillation and atrial flutter. Chin J Acupunct Moxibust (Chin) 2007;27:96–8.
[23] Zhong CH. Observations on the efficacy of combined acupuncture and medicine in treating ventricular premature beat without organic heart disease. Shanghai J Acupunct Moxibust (Chin) 2008;27:15–6.
[24] Wang F, Zhou L, Xia LM, et al. Clinical observations on acupuncture point injection plus medication for the treatment of coronary heart disease-caused ventricular premature beats. Shanghai J Acupunct Moxibust (Chin) 2012;31:96–7.
[25] Han BD. Clinical observation on 62 cases of paroxysmal rapid atrial fibrillation treated by acupuncture combined with drug therapy. J Emerg Tradit Chin Med (Chin) 2012;21:303.
[26] Alberto L, Sebastiano B, Maria BP, et al. Efficacy of acupuncture in preventing atrial fibrillation recurrence after electrical cardioversion. J Cardiovasc Electrophysiol 2011;22:241–7.
[27] Sutton AJ, Duval SJ, Tweedie RL, et al. Empirical assessment of effect of publication bias on meta-analyses. BMJ 2000;320:1574–7.
[28] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.