Acupuncture versus pharmacological conversation in treatment of atrial fibrillation in a randomized controlled trial: a systemic review and meta-analysis

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Abstract

Objective: This study aimed to investigate the effect of conventional drugs combined with acupuncture therapy on the conversion of sinus rhythm in patients with atrial fibrillation.

Methods: We searched databases, such as PubMed, Embase, WOS, Cochrane, CNKI (China National Knowledge Infrastructure), Wan fang Data, VIP, and CBM to collect data in randomized controlled trials of acupuncture included patients with atrial fibrillation. Publication time was limited from the beginning to May 15, 2021. The primary outcome is the number of participants who converted successfully.

Results: A total of 11 papers were included in this study. The combined effect indicated that acupuncture significantly effectively benefitted the patients with atrial fibrillation (RR = 1.208, 95% CI 1.123, 1.298, \( P < 0.001 \)). Further subgroup analysis of persistent and paroxysmal atrial fibrillation and the timing of acupuncture suggested that the addition of acupuncture was not statistically significant in the treatment of persistent AF compared to the control group (RR = 1.147, 95% CI 0.811, 1.623 \( P = 0.147 \)). The combination of acupuncture was more effective in paroxysmal AF RR = 1.148 (95% CI 1.064, 1.239) \( P < 0.001 \). In addition, when the acupuncture time was limited to 20 min, it had the best treatment effect (RR = 1.510, 95% CI 1.25, 1.82).

Conclusions: The combination of pharmacological resuscitation with acupuncture significantly improved the conversion of paroxysmal atrial fibrillation compared to pharmacological resuscitation only. The most significant benefit was achieved with an acupuncture duration of < 20 min. Thus, the combination of acupuncture could be considered in clinical practice for the resuscitation of patients with atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia associated with atrial enlargement, myocardial damage, heart failure, and other organic heart diseases. In China, the prevalence of AF has been found to be approximately 0.77% [1] and is known to increase with age; it has also been reported to be more prevalent in men than in women of all age groups [2, 3]. In addition, AF has been shown to cause many other serious complications. Patients with AF are known to be at a 4–5 times higher risk of ischemic stroke compared to patients...
without AF, resulting in a mortality rate of approximately 20% and a disability rate of 60%. Asian patients with AF have a higher risk of ischemic stroke and hemorrhagic stroke than non-Asian patients [4]. In addition, AF triples the prevalence and exacerbates the symptoms of heart failure [5], increases the risk of myocardial infarction by twofold [6], and increases the risk of dementia, cognitive decline, and renal insufficiency [7, 8].

As an economical green therapy in traditional medicine, acupuncture has been used for the clinical treatment of AF [9, 10], and has been shown to safely and effectively relieve the symptoms of AF and reduce the recurrence rate after early RFCA (radiofrequency catheter ablation) and after electrical cardioversion. Acupuncture can also improve sleep and relieve anxiety and depression in patients with AF [11], improving their quality of life.

Although some studies have shown the effectiveness of acupuncture in the treatment of AF, these studies lack systematic analysis to verify the effectiveness and heterogeneity of acupuncture in AF. Here, we studied the effectiveness and safety of acupuncture for the treatment of AF as well as investigated the effects of different durations of acupuncture on the treatment efficacy.

Research method
This study followed the international guidelines for reporting meta-analyses for the selection and use of research methods. This study protocol was registered with INPLASY (202150108).

Literature inclusion and exclusion criteria

Study design
We used Randomized controlled trials (RCTs) and studies related to acupuncture for AF for this meta-analysis.

Inclusion criteria of the literature
(1) The study population included patients with AF, and the diagnostic criteria for AF followed the European Society of Cardiology Guidelines for the Management of AF 2020 [12]; (2) patients who had been treated with acupuncture; (3) the type of study was a randomized controlled trial.

Exclusion criteria of the literature
(1) The studies that were conducted in patients without AF; (2) the studies without a comfort group; (3) the article was repeatedly published.

Literature search strategy
Eight databases, including PubMed, web of science, Cochrane, Embase, China Biomedical Literature System, CNKI, VIP database, and Wan fang database, were searched for RCTs based on acupuncture for AF. The search period ran from the start date of each database to May 16, 2021. The search strategy was based on the principles of PICOS (overall, intervention, comparison, outcome, and study design), and was done using a combination of subject terms and free words, identified by repeated pre-searching, and supplemented by manual searches and reference tracking. Chinese search terms included atrial fibrillation, paroxysmal atrial fibrillation, persistent atrial fibrillation, acupuncture, electroacupuncture, acupuncture points, meridians, clinical studies, clinical trials, controlled clinical trials, randomized controlled trials, and pragmatic clinical trials. The English search terms for WOS were as follows:

#1 TS = (Acupuncture Treatment or Acupuncture or Acupunctor Treatment or Treatment, Acupuncture or Therapy, Acupuncture or Pharmacoacupuncture Treatment or Treatment, Pharmacoacupuncture or Pharmacoacupuncture Therapy or Therapy, Pharmacoacupuncture or Acupuncture or Needling or Electroacupuncture).

#2 TS = (Atrial Fibrillations or Fibrillation, Atrial or Fibrillations, Atrial or Auricular Fibrillation or Auricular Fibrillations, Auricular or Persistent Atrial Fibrillation or Atrial Fibrillation, Persistent or Atrial Fibrillations, Persistent or Fibrillation, Persistent Atrial or Fibrillations, Atrial Fibrillation, Familial or Atrial Fibrillations, Familial or Familial Atrial Fibrillations or Fibrillation, Familial Atrial or Fibrillations, Familial Atrial or Paroxysmal Atrial Fibrillation or Atrial Fibrillation, Paroxysmal or Atrial Fibrillations, Paroxysmal or Fibrillation, Paroxysmal Atrial or Fibrillations, Paroxysmal Atrial or Paroxysmal Atrial Fibrillations or AF).

#3 TS = (Clinical Study or Clinical Trial or Controlled Clinical Trial or Randomized Controlled Trial) #4 #1 AND #2 AND #3.

Interventions
The test group received acupuncture plus pharmacological resuscitation, while the control group received pharmacological resuscitation alone.

Outcome indicators
Patients with AF after surgery were observed to determine the rate of AF recurrence. Patients without surgery were studied to observe the rate of conversion of paroxysmal AF or persistent AF to sinus rhythm after acupuncture.
Literature screening, data extraction, and quality assessment

Literature search
Two investigators screened the literature and extracted relevant data using an independent double-blind method based on the inclusion and exclusion criteria. If there is disagreement at the mutual review, screening, and data extraction stages, a third researcher joined the discussion on whether to include these data.

Data extraction
Data extracted from the literature included mainly author names, year of publication, sample size, age, gender, and time of needling. The results extracted from the study were indicators of outcomes included in the literature. Based on the extracted data, the needling time was categorized as <20 min, 20–30 min, and > 30 min (Table 1).

Quality assessment
The risk of bias criteria was based on the Cochrane Collaboration Network’s RCT criteria to qualitatively evaluate seven aspects of random sequence generation, distribution concealment, subject and investigator blinding, blinding of outcome assessors, incomplete outcome data, and selective reporting, and were evaluated as “low risk of bias,” “uncertain risk of bias,” and” (Table 2).

Statistical analysis
The literature data were processed using Stata (v15.1); combined effect sizes and heterogeneity tests were performed, and forest plots were drawn. The literature outcome indicators were dichotomous variables, and the effect size was chosen as relative risk (RR) with an effect size of 95% of the confidence interval (95% CI). The meta-analysis followed strict PRISMA guidelines (Table 2).

Results
A total of 597 articles was retrieved from the database, of which 78 duplicate papers were excluded. After browsing through the titles and abstracts, 474 papers were excluded. After reading the full text, 34 articles were excluded, of which 14 were reviews, 7 were non-RCTs, 1 was a single-arm trial, 2 included patients with sinus bradycardia after modified maze surgery for AF, 8 had unclear outcome indicators or did not fit the current study, 1 was a duplicate publication, and 1 could not be accessed in full text. We identified 11 potentially eligible trials. We included 11 trials of acupuncture for AF (1234 patients) [13–23] (Fig. 1).

Eleven papers investigated the therapeutic effects of acupuncture on the resetting of AF. The combined effect size RR = 1.19 (95% CI 1.06, 1.34) and heterogeneity analysis showed $I^2 = 55.7\%$, $P = 0.01$ (Fig. 2). Therefore, further searching for heterogeneity, regression analysis showed (Fig. 3) that heterogeneity was caused by differences in acupuncture point coefficient = −1.30, standard error = 0.39, $P < 0.001$, 95% CI (−2.18, −0.42), excluding the following literature for analysis, $I^2 = 0.0$, $P = 0.619$, no significant heterogeneity. The combined effect size was 1.21, 95% CI (1.123, 1.298), $P < 0.001$, which showed a significant improvement in the test group with the addition of acupuncture treatment (Fig. 4).

Further subgroup and regression analyses were performed for other factors. Regression analysis of disease type into persistent and paroxysmal AF showed no statistically significant correlation (Fig. 5) (coefficient = 0.24, SD = 0.33, $P = 0.492$; 95% CI 0.51, 0.98). Subgroup analysis (Fig. 6) showed persistent AF group $I^2 = 52.5\%$, $P = 0.15$, combined effect size using the D + L method, showing an RR = 1.147 (95% CI 0.81, 1.62) $P = 0.15$. Paroxysmal AF $I^2 = 0.0\%$, $P = 0.68$, combined effect size using the M–H method, showing an RR = 1.15 (95% CI 1.064, 1.239) $P = 0.001$. These results showed that for paroxysmal AF, the addition of acupuncture was more effective, with a statistically significant difference between the test and the control groups, and a less significant effect for persistent AF, possibly related to the number of studies.

Regression analysis (Fig. 7) was performed by dividing the duration of needling into four groups: (1) within 20 min, (2) 20–30 min, and (3) > 30 min. The results showed a coefficient = 0.26, Std. Err. = 0.16, $P = 0.16$ (95% CI −0.12, 0.63). It was possible that there was no significant positive association between the duration of needling and the effect of treating AF. However, subgroup analysis (Fig. 8) showed that the best RR = 1.44 (95% CI 0.89, 2.32) was within 20 min of needling time, the next best RR = 1.23 (95% CI 1.04, 1.47) was between 20 and 30 min and the worst RR = 1.11 (95% CI 1.02, 1.21) was >30 min. Considering that the duration of treatment for persistent AF was all within 20 min, it was presumed that needling within 20 min was more effective for the treatment of AF.
| Study | Junkui Yin | Albert Lomuscio | Baozhen Xu | Ying Jiao | Baode Han | Yuanzeng Zhang | Yuanshi Xia | Yahong Yan | Li Chen | Hongke Xu | Xuhai Wang |
|-------|------------|-----------------|------------|-----------|------------|----------------|------------|------------|---------|-----------|-------------|
| Age (mean ± SD) | 61.6 ± 10.6 | 63.7 ± 10.6 | 64 ± 10.6 | 63 ± 7 | 64.50 ± 6.7 | 62.3 ± 6.7 | 52.1 ± 6.7 | 34.26 ± 6.4 | 52.28 ± 10.5 | 62.3 ± 5.4 | 58.9 ± 10.5 |
| Gender (male:female) | 53:32 | 58:50 | 243:189 | 64:50 | 58:50 | 58:50 | 64:50 | 32:28 | 52:28 | 58:50 | 58:50 |
| Classification | Persistent | Persistent | Persistent | Paroxysm | Paroxysm | Paroxysm | Paroxysm | Paroxysm | Paroxysm | Paroxysm | Paroxysm |
| Duration of treatment | 20 min | 15–20 min | 30 min | 24 h | 30 min | 20 min | 30 min | 24 h | 1 h | 24 h | 1 h |
| Intervention | Needle prick & Amiodarone | Needle prick & Wenxin Granules | Needle prick & Digilanid C | Needle prick & Cardiox | Needle prick & Anticoagulation | Needle prick & Digilanid C | Needle prick & Cardiox | Needle prick & Amiodarone | Needle prick & Digilanid C | Needle prick & Cardiox |
| Participants | 85 | 90 | 108 | 108 | 108 | 108 | 108 | 108 | 108 | 108 | 108 |
| Study design | Randomized; parallel-group clinical study | Randomized; parallel-group clinical study | Randomized; parallel-group clinical study | Randomized; parallel-group clinical study | Randomized; parallel-group clinical study | Randomized; parallel-group clinical study | Randomized; parallel-group clinical study | Randomized; parallel-group clinical study | Randomized; parallel-group clinical study | Randomized; parallel-group clinical study | Randomized; parallel-group clinical study |
| Study location | China | South Korea | China | China | China | China | China | China | China | China | China |
| Year | 2019 | 2011 | 1997 | 2003 | 2012 | 2007 | 2007 | 2014 | 2012 | 2009 | 2007 |
Further the confounding factors, such as age and sex were included in the regression analysis; the age regression (Fig. 9) showed that age was not associated with treatment effect, Coef. = −0.19, Std. Err. = 0.91, P = 0.841 (95% CI −2.70, 2.32). The sex ratio regression (Fig. 10) showed no significant association between sex
Fig. 2 Forest plot for all studies

Fig. 3 Meta-regression between different acupuncture points
Fig. 4 Forest plot included a similar method in needle pricking.

Fig. 5 Meta-regression for both Paroxysmal AF and Persistent AF.
and treatment effect, Coef. = −0.23, Std. Err. = 0.26, P = 0.42 (95% CI −0.91, 0.44).

Bias test
Visual observation of the funnel plot (Fig. 11) and the possible bias egger’s test (Fig. 12) showed P = 0.239 (95% CI −0.99, 3.42). Harbord’s modified test (Fig. 13) showed P = 0.748 (95% CI −2.51, 3.37), suggesting no significant publication bias.

Discussion
The results of this study demonstrated that acupuncture could restore sinus rhythm and improve the ventricular rate and rhythm control in patients with AF. The results of this study were consistent with previous studies and reaffirmed the effectiveness of acupuncture in the treatment of AF.

The pathophysiology of AF revolves around the promotion of ectopic discharge and folding mechanisms in four main areas: ion channel dysfunction, abnormal Ca^{2+} handling, structural remodeling, and impaired autonomic regulation [24]. It was found [25] that acupuncture could reduce the expression of L-type Ca^{2+} channels and Cl-channels and stop excessive Ca^{2+} inward flow. Acupuncture at the Neiguan point could reduce Cx40 expression in atrial tissue [26], reduce the degree of damage to atrial myofibers and mitochondria, reduce damage to atrial myocyte structures [27, 28], and delay the process of atrial structural remodeling. Acupuncture could also regulate autonomic balance, with vagal excitability increasing under acupuncture stimulation and vagal excitation decreasing, and sympathetic excitation increasing after stimulation disappears [29–31].

Nine studies compared the effects of acupuncture and drugs on atrial fibrillation, and found that the acupuncture group was significantly better than the drug group in converting atrial fibrillation to sinus rhythm. However, none of the above studies conducted follow-up to explore the recurrence rate of tremor and the maintenance time of acupuncture effect on cured patients. It
was very necessary to effectively control the recurrence of atrial fibrillation for patients who had converted sinus rhythm. Two studies compared the effects of acupuncture on the recurrence of atrial fibrillation in patients after electrical cardioversion or radiofrequency ablation. It was found that the recurrence rate of atrial fibrillation in the acupuncture group was significantly lower than that in the control group, suggesting that acupuncture could effectively reduce the recurrence rate of atrial fibrillation for patients who have converted to sinus rhythm. The subjects in these two studies were all converted to sinus rhythm after electrical cardioversion or radiofrequency ablation. There was currently no such study on the recurrence rate of atrial fibrillation in patients who converted to sinus rhythm with drugs or only using acupuncture. Therefore, the maintenance effect of acupuncture in the treatment of atrial fibrillation cannot be evaluated.

This was probably related to the fact that the Yingxiang acupuncture point regulated the excitability of the sensory nerves, parasympathetic nerves, and sympathetic nerves in the nasal mucosa, as well as the release of the corresponding neuropeptides and the reduction of inflammatory factors [32, 33]; however, since only one paper used the Yingxiang acupuncture point, it was not significant enough to suggest that the specificity of the Yingxiang acupuncture point was higher than that of other acupuncture points. The other trials included in this study (except for the Yingxiang acupoint and the acupuncture point) used the Neiguan acupoint. This was probably related to the acupoint specificity of the Neiguan point, which was found to affect the firing frequency of the amygdala and regulate autonomic balance [34], as well as to reduce the expression of c-fos cells in the nucleus tractus solitarius, thereby counteracting the activation of neurons in the nucleus tractus solitarius by afferent information brought on by arrhythmias and reducing heart rate [35]. Acupuncture at the Neiguan point also reduced the levels of the inflammatory factors, such as CRP, IL-8, and TNF-α and improved the index of heart rate variability [36], which were closely associated with the development and persistence of AF [13, 37].

In this study, we found that needle retention time < 20 min was the most effective for AF, 20–30 min was the second most effective, and > 30 min had the lowest benefit. According to Lin [38], similar to the metabolic process of drugs in the body, the duration of acupuncture could be divided into the optimal induction period, half-life, and residual effect period. For AF, the optimal induction period could be reached rapidly after acupuncture with maximum acupuncture effect, but too long a time might produce acupuncture tolerance and acupoint fatigue resulting in poor results. Therefore, the best efficacy was achieved at acupuncture times of < 20 min, while effects at > 30 min were rather poor. However, the sample sizes of the included studies are generally small,
and there are not enough studies on acupuncture for AF to draw definitive conclusions.

Patients with AF are usually treated with anticoagulants, such as warfarin or newer anticoagulants (NOACs), and some doctors and patients wonder whether needling might increase the risk of bleeding. A meta-analysis [39] of 428 patients showed that needling after anticoagulants and antiplatelet agents did not increase the incidence of bleeding-related adverse events. A meta-analysis [40] including 316 patients showed that acupuncture was safe for patients with AF taking NOAC and did not increase the risk of bleeding. Another meta-analysis [41] that included 384 patients also showed that acupuncture was safe in anticoagulated patients, provided that the location and depth of acupuncture were assured. These studies showed that acupuncture was safe in the treatment of patients with AF who were taking anticoagulants without an increased risk of bleeding and associated adverse events when the acupuncturist was trained in a standardized manner.

In the early stage of the application of acupuncture to atrial fibrillation, the effect of acupuncture alone in converting to sinus rhythm in patients with atrial fibrillation was better than antiarrhythmic drugs. With the development of modern medicine and the improvement of clinical guidelines, the anti-arrhythmic advantages of acupuncture were no longer, but the extracardiac side effects of anti-arrhythmic drugs were greater. Acupuncture combined with anti-arrhythmic drugs reduced the incidence of adverse events and enhanced the treatment effect. Catheter ablation therapy was superior to antiarrhythmic drugs in maintaining sinus rhythm and
improving quality of life [42, 43], but its postoperative rate of recurrence was high, and new-onset atrial tachycardia with antiarrhythmic drugs might occur during the 3 month postoperative gap. Catheter ablation was efficacious in the treatment of atrial fibrillation, but it might be ineffective in preventing recurrence of atrial fibrillation at 6 months, even if oral antiarrhythmic drugs were adhered to after the procedure [44]. Since surgery...
Fig. 11 Funnel plot for evaluating bias

Fig. 12 Egger’s test
was expensive and patients had a heavy medical burden, and acupuncture could reduce their postoperative atrial fibrillation recurrence rate, the difference in efficacy of different acupuncture treatment amounts to prevent recurrence rate after radiofrequency ablation in patients with atrial fibrillation may be a future research direction. It is also expected that future studies will explore the mechanism of action of acupuncture after catheter ablation from multiple perspectives and establish evidence-based evidence of acupuncture in the treatment of atrial fibrillation.

Limitations
This study had several limitations. (1) The methodology of some of the included papers was not comprehensive, and some of the biases could not be ruled out. (2) The heterogeneity of persistent AF was large, the number of papers was small, and the results of the random-effects model were not reliable. (3) The acupuncture points were not clearly described. As a result, the study results could be biased to some extent. Thus, further experimental studies are needed to support the efficacy of acupuncture in AF.

Conclusions
These studies found that the combination of acupuncture was significantly more effective in the treatment of AF compared to conventional pharmacological resuscitation, with the greatest benefit being achieved with acupuncture times of < 20 min. However, larger, more rigorous RCTs are needed to validate this in the future.

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Not applicable.

Author contributions
YL, JS and BW are the co-first authors who contributed equally to the statistical analysis and drafted the manuscript. YL helped design the study and draft the manuscript. XW, LH and ZH helped design the study and collect data. BW conceived of the study and drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All the data generated or analyzed during the study are available and included in this published article.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent for publication was obtained from all participants.

Competing interests
The authors declare that they have no conflicts of interest.

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