Systematic Evaluation of Efficacy and Safety of Acupuncture Treatment for Patients with Atrial Fibrillation

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Abstract

BACKGROUND: Atrial fibrillation (AF) is one of the most common types of arrhythmia diagnosed in clinical practice. Due to its negative effects on people's physical and mental health, it is necessary to prevent and treat AF. Recently, scholars have found that acupuncture can be used to treat AF, but some scholars have questioned its therapeutic efficacy.

AIM: Therefore, this study was performed to assess the efficacy and safety of acupuncture treatment for AF patients.

METHODS: Previously published research articles were retrieved from six databases, and the data was analysed using RevMan5.3 software with a statistically significant difference defined as $P < 0.05$.

RESULTS: A total of 8 relevant kinds of literature were retrieved containing 633 AF patients (323 in the treatment group and 310 in the control group). Acupuncture treatment increased the total efficacy and the rate of AF cardioversion to sinus rhythm (RR: 1.38; 95% CI: 1.25 to 1.53 vs RR: 1.40; 95% CI: 1.16 to 1.69; each $P < 0.05$), and decreased the time of AF cardioversion to sinus rhythm, the heart rate and incidence of adverse effects (RR: -3.95; 95% CI: -4.98 to -2.91 vs RR: -14.54; 95% CI: -24.09 to -5.00 vs RR: 0.48; 95% CI: 0.21 to 1.11, each $P < 0.05$). There was difference between retention time more and less than 30 minutes ($I2 = 74.9\%$, $P = 0.05$). The funnel plot displayed a symmetrical and funnel-form shape, indicating low bias.

CONCLUSION: Acupuncture has a good therapeutic effect and safety profile on patients with AF, and its application in clinical practice should be considered.

Introduction

Atrial fibrillation (AF) is one of the most common types of arrhythmia diagnosed in clinical practice. Recent data shows that its incidence rate, prevalence rate, disability rate and mortality rate are increasing every year globally [1], depending on the country's geographical region, race, and gender [2]. The hemodynamics and thromboembolism caused by AF seriously affect people's physical and mental health, so it is necessary to search for treatments for AF patients.

The main treatment strategies for AF are rhythm control, rate control and anticoagulation [3], [4]. Rate control requires the use of antiarrhythmic drugs (AAD) to adjust the AF patient's heart rate to a reasonable state, while rhythm control is the attempt to restore and maintain sinus rhythm. Studies have shown that rate or rhythm control could reduce the risk of too fast AF rate and the harm caused by heart failure as well as a thrombus. It can also improve the quality of life of the patients [5], [6]. However, rhythm or rate control is not satisfactory in treating AF patients, such as AAD having obvious proarrhythmia, AF recurrence rate in electrical cardioversion, Cox-Maze and catheter ablation. All these influences the therapeutic effects of AF.

Acupuncture is a treatment method which has been used in Chinese traditional medicine for over 3000 years, and it is defined as the needling of specific points of the body. In many countries, acupuncture has become one of the most widely used complementary therapies in recent years. Some

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studies reported that acupuncture seems to be effective in preventing cardiac arrhythmias [7]. In traditional medicine, a study has shown that wrist-ankle acupuncture has an obvious effect on managing patients with paroxysmal supraventricular tachycardia [8]. However, some scholars also have cast some doubts over the safety of acupuncture in disease treatment [9].

In this study, we evaluated the efficacy and safety of acupuncture in treating AF patients [10], [11], [12], [13], [14], [15], [16], [17], so as to provide a basis for better treatment of AF.

Methods

Literature Search

Published reports were searched using the retrieval words "atrial fibrillation" OR "AF" and "acupuncture" OR needling and ("database "[PDAT] : "2018/01/31"[PDAT]) from PubMed, Cochrane Library, Web of Science, Scopus, China National Knowledge Internet, and Chinese Biomedical Literature Database. Crossover and parallel RCTs were selected if they focus on the acupuncture treatment for patients with AF, regardless of blinding. RCTs were selected if they included at least one group receiving acupuncture and one control group receiving another active treatment. There were no language restrictions in the search strategy.

Selection criteria

Inclusion criteria: 1) adult AF patients, paroxysmal AF was defined as self-terminating within seven days ; Persistent AF was defined as any AF episode either lasting longer than seven days or requiring drug or direct current cardioversion. 2) In addition to the intervention measures, acupuncture or electrical acupuncture were basically regarded as the same treatment. 3) with definite control groups and treatment groups; 4) with basic disease treatment, the record showed a mean ± standard deviation or effective rate; 5) with RCTs. Exclusion criteria: the article was excluded if 1) the same data was republished twice; 2) it had no control group; 3) it involved animal and basic experimental literature; 4) it was a thesis, conference or essay articles.

Data extraction and quality assessment

Data extraction and quality assessment were assessed by two reviewers independently and crosswise. Any differences were settled through discussion or consultation with a third party.

Evaluation of the content was as follows: 1) random method; 2) concealment of allocation method; 3) blind method; 4) integrity of the data; 5) selective reporting of the results; 6) other bias sources [18]. A grade: if meeting 4 of the above, the study showed that there was little possibility of the existence of bias; B grade: if there were one or more of the requirements which were only partially satisfied, it meant that there was a moderate bias in the study; C grade: if one or more of the requirements were not completely satisfied, it meant that there was a high degree of bias in the study.
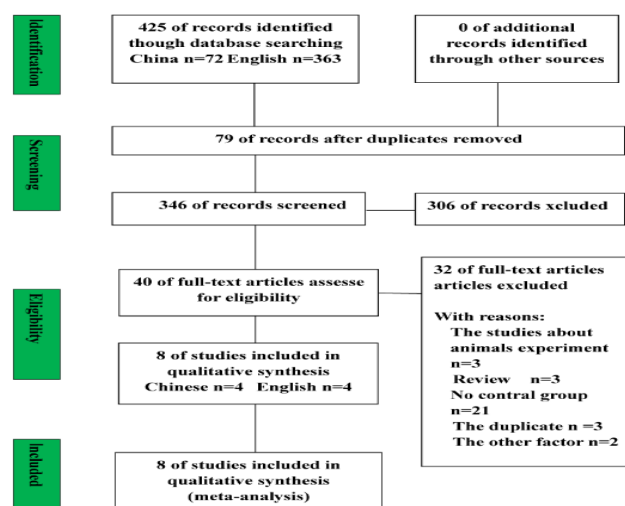

Figure 1: Flow of information through the different phases of a systematic review. The procedure led to the identification and inclusion of eligible studies in our analysis. Eventually, a total of 8 studies were selected for the analysis

Statistical analysis

The data analysis was done using RevMen5.3 software. Dichotomous data were expressed as relative risk (RR), and continuous outcomes were presented as mean differences (MD), while 95% confidence intervals (CI) were calculated for both. Random effect mode was used when the I squared (I^2) value exceeded 50% or P < 0.05; data was pooled using the fixed effect mode, when I^2 < 50% or P ≥ 0.05. Bias analysis was evaluated using the funnel plot. The differences were considered significant if P < 0.05.

Results

Original data description

A total of 425 relevant literature were retrieved, 79 duplicates and 306 irrelevant articles were excluded. 8 articles were finally included in this study after reading the abstract and full texts [10], [11], [12], [13], [14], [15], [16], [17].

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Table 1: Baseline characteristics of the trials included in the meta-analysis

Author	Year	Nationality	Group	Total case (m/f)	Age	AF Type	Drug	Treatment course (d)	Acupuncture points	Hold the needle time（min）	Quality grade
[10] Xu HK	2007	China	T	40 (25/15)	58.9 ± 10.5	Paroxysmal	A	-	PC6, CV17, CV6, CV12, ST36,SP10,ST40	60	C
			C	40 (27/13)	57.4 ± 9.4		a				
[11] Lomuscio A	2011	Italy	T	17 (10/7)	65 (62-67)	Persistent	A	70	PC6,HT7,BL15	15-20	C
			C	24 (17/7)	65 (63-67)		-				
[12] Han BD	2012	China	T	62 (35/27)	64.3	Paroxysmal	A+D	-	PC6,PC4,SP6,SP10	-	C
			C	52 (29/23)	65.7		D				
[13] Zhang XL	2013	China	T	30 (19/11)	59 ± 4	Paroxysmal	A+W	31	PC6,HT7,PC4	30	C
			C	30 (16/14)	55 ± 7		W				
[14] Xia YS	2014	China	T	50 (-)	62.8 ± 5.5	Paroxysmal	A+D	-	PC6,PC4,SP10,SP6	-	C
			C	40 (-)			D				
[15] Yan YH	2014	China	T	30 (18/12)	52.1 ± 6.7	Paroxysmal	A+D	-	PC6, HT7, BL14, CV17,BL15,BL17	30	C
			C	30 (16/14)	51,7 ± 5.8		D				
[16] Xu BZ	2015	China	T	54 (30/24)	63 ± 7	Paroxysmal	A+W	14	PC6,PC4,SP6,SP10	30	C
			C	54 (28/26)	64 ± 7		W				
[17] Park J	2015	Korea	T	40 (-)	-	Persistent	A	70	PC5,PC6,ST36,ST37,HT7	20	B
			C	40 (-)							

T: Treatment group; C: Control group; A: Acupuncture; a: amlodipine; D: Digitalis; W: Wenxinkeli; -: undescribed; m: male; f: female. PC4: Ximen; PC5: Jianshi; PC6: Neiguan; HT7: Shenmen; ST36: Zusanli; ST37: Shangjuxu; ST40: Fenglong; CV6: Qihai; CV12: Zhongwan; CV17: Tanzhong; SP6: Sanyinjiao; SP10: Xuehai; BL14: Juyinshu; BL15: Xinshu; BL17: Geshu.

There were 4 Chinese and 4 English articles, having a total of 633 AF patients (323 in the treatment group and 310 in the control group). All the 8 articles mentioned "random", but four articles mentioned digital random method [10], [13], [16], [17]. Except for one B grade, the others were C grade. The minimum age of the patients in the literature was 43 years old, and the maximum age was 79 years old, while the proportion of men to women was not mentioned [14], [17]. The literature was published between 2007 and 2015. There were 6 Paroxysmal AF cases [10], [12], [13], [14], [15], [16], and 2 cases of persistent AF [11], [17]. There were 3 articles that highlighted the time of AF cardioversion to sinus rhythm [10], [13], [16]. 3 articles mentioned the heart rate after treatment [10], [13], [16] and the adverse effects were discussed in 2 articles [10], [13]. All literature refer to "NeiGuan"(PC6) [10], [11], [12], [13], [14], [15], [16], [17]. The needling time was for more than 30min [10], [13], [15], [16] Figure 1, and Table1.

Outcome Measure

The total efficacy. The studies showed no heterogeneity (Chi^2 = 7.14, I^2 = 2%, P > 0.05); the combined effects using a fixed-effects model showed RR of 1.38 (95% CI: 1.25 to 1.53) and Z of 6.21 (P < 0.05).
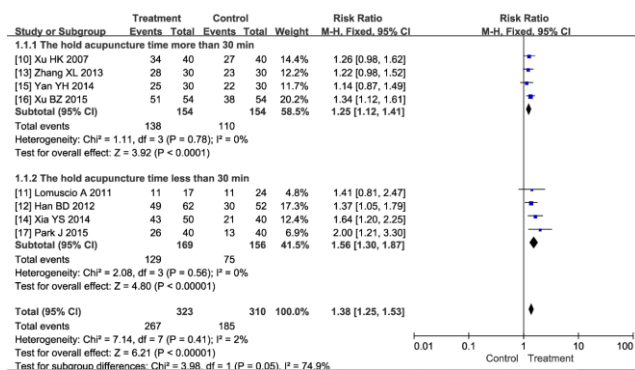

Figure 2: Forest plot of the total efficacy

Compared to the control group, the total efficacy of the treatment group was significantly enhanced. There was difference between retention time more and less than 30 minutes (Chi^2 = 3.98, I^2 = 74.9%, P = 0.05) (Figure 2).

The rate of AF cardioversion to sinus rhythm: The studies showed no heterogeneity (Chi^2 = 2.03, I^2 = 0%, P > 0.05); the combined effects using a fixed-effects model found an RR of 1.40 (95% CI: 1.16 to 1.69) and Z of 3.49 (P < 0.05). Compared to the control group, the rate of AF cardioversion to sinus rhythm of the treatment group was significantly enhanced (Figure 3).
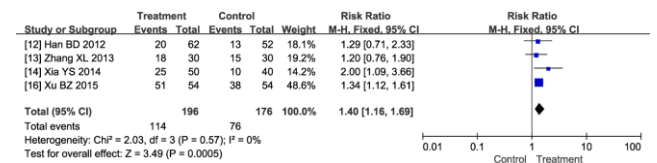

Figure 3: Forest plot of the rate of AF cardioversion to sinus rhythm

The time of AF cardioversion to sinus rhythm: The studies showed heterogeneity (Chi^2 = 4.61, I^2 = 57%); the combined effects using a random-effects model showed an MD of -3.95 (95% CI: -4.98 to -2.91) and Z of 7.46 (P < 0.05). Compared to the control group, the cardioversion time of treatment group was significantly decreased (Figure 4).
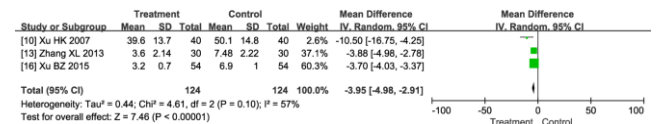

Figure 4: Forest plot of the time of AF cardioversion to sinus rhythm

Heart rate after acupuncture treatment: The studies showed heterogeneity (Chi^2 = 66.55, I^2 = 97%, P < 0.05); the combined effects using a random-effects model showed MD of -14.54 (95% CI: -24.09 to -5.00) and Z of 2.99 (P < 0.05). Compared to the control group, the heart rate of the treatment group

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was significantly reduced (Figure 5).

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV. Random, 95% CI
[10] Xu HK 2007	64.7	12.6	40	85.2	21.7	40	29.1%	-20.50 [-28.28, -12.72]
[13] Zhang XL 2013	81.23	4.24	30	87.44	3.66	30	35.5%	-6.21 [-8.21, -4.21]
[16] Xu BZ 2015	72	4	54	90	7	54	35.4%	-18.00 [-20.15, -15.85]
Total (95% CI)			124			124	100.0%	-14.54 [-24.09, -5.00]

Heterogeneity: Tau² = 65.79; Chi² = 66.55, df = 2 (P < 0.00001); I² = 97%
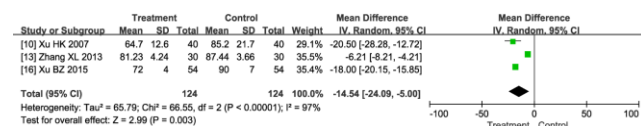Test for overall effect: Z = 2.99 (P = 0.003)

Figure 5: Forest plot of the heart rate after acupuncture treatment

Incidences of adverse effects: The studies showed no heterogeneity (Chi^2 = 0.9, I^2 = 0%, P > 0.05); the combined effects using a fixed-effects model showed RR of 0.48 (95% CI: 0.21 to 1.11) and Z of 1.72 (P < 0.05). Compared to the control group, the adverse effects incidence of the treatment group was significantly reduced (Figure 6).
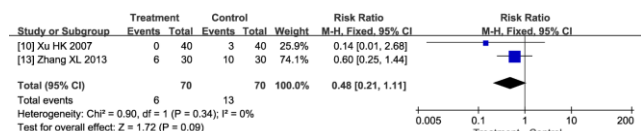

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
[10] Xu HK 2007	0	40	3	40	25.9%	0.14 [0.01, 2.68]
[13] Zhang XL 2013	6	30	10	30	74.1%	0.60 [0.25, 1.44]
Total (95% CI)		70		70	100.0%	0.48 [0.21, 1.11]
Total events	6		13			

Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)

Figure 6: Forest plot of the adverse effects

Assessment of risk of bias

The funnel plot displayed a symmetrical and funneled shape, indicating little bias (Figure 7).
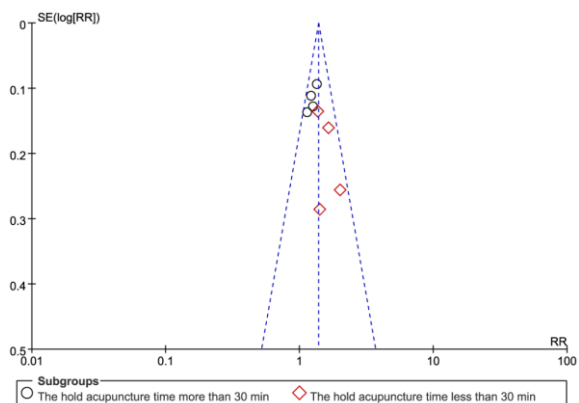

Figure 7: Funnel plot of the risk bias

Discussion

The treatment efficiency of 633 AF patients treated with acupuncture was analysed in 8 RCTs. It was confirmed that the total efficiency was improved after acupuncture treatment of AF. Further study found that the rate of restoration of sinus rhythm was enhanced, and the time for restore of AF sinus rhythm, heart rate and adverse effects incidence after treatment was reduced. There was a difference between retention time more and less than 30 minutes. Van Wormer et al. analysed 8 kinds of literature about needles treatment for arrhythmia (including SVT, AF, and ventricular extrasystole etc.),

the results showed that 87% patients were converted to sinus rhythm, and there was 100% decrease in the frequency of arrhythmia [19]. Dilber et al. showed that when a 57 years old patient with paroxysmal AF was treated with acupuncture after other methods failed to convert AF, it successfully converted AF to sinus rhythm. During 30 days follow up, there was no AF recurrence in the patients after sinus rhythm was established by acupuncture combined with peroral propafenone [20]. These experiments illustrated that acupuncture was effective in treating AF patients, but they were not completely randomised controlled trials (RCTs), and the cases of AF were few. Therefore, the conclusion had some limitations.

AF is a trial tachyarrhythmia characterised by rapid and disordered atrial electrical activity. A fast and irregular ventricular rate is the main cause of discomfort symptoms such as palpitation and chest distress. The rapid ventricular rate can make the ventricular diastole shorten, cardiac output reduce, blood pressure drop and coronary blood perfusion decrease, which induce or aggravate myocardial ischemia, and may lead to tachycardia cardiomyopathy. Rate control and rhythm control can relieve AF patients [5], [6]. This study showed that the rate of restoration of sinus rhythm was enhanced, and the time for restore of AF sinus rhythm and heart rate after treatment were reduced, which further indicated that acupuncture had an obvious therapeutic effect on patients with AF.

In this study, two literature referred to the adverse effects of acupuncture in treating AF patients. In the control group, adverse effects were shown through blood pressure decrease, vomiting, gastrointestinal reactions, bradycardia, and QT interval extension. There were bradycardia, gastrointestinal reactions, dizziness and dry mouth in the treatment group. The results showed that the adverse drug reactions occurrence rate of the treatment group was significantly reduced. Therefore, it was believed that acupuncture was safe to treat AF patients.

Acupuncture basic theory is based on the meridian and the tendon theory, the meridian theory states that the human body surface and internal organs are associated with twelve meridians, twelve tendons, twelve skins, fifteen collaterals and countless small collaterals, which unite the body, skull, musculoskeletal and trunk. Many acupoints and meridians have antiarrhythmic effect, such as the Meridian of Minister of Heart, the energy produced by acupuncture can be transferred to other areas of the heart through the related nerve fibers continuously, which can balance Yin and Yang [21], [22], [23], adjust ion channel [24], anti-inflammation [25] and modulate cardiac autonomic function [26]. The needle retention is a period of time when the needle is injected into the acupoints, acupuncture curative effect is closely related to the retention time. Because the time of needling is determined by the

pathogenesis, the course of illness, the patient, and the meridians, the retention time is different for each disease [27], [28], [29]. The effect of acupuncture treatment time on the effect of AF therapy was also compared and differences between different acupuncture times were noticed. This result suggests that the acupuncture treatment for AF patients should be administered for at least 30 minutes. Presently, there are few clinical and experimental studies on the relationship between acupuncture effect and needle retaining time among patients with AF. In view of Chinese traditional medicine, taking the randomness of the uncertain time of "qi arrival" as a reference, it is feasible to set the needle retention time at 30 minutes [30]. However, there is a need to prove whether longer acupuncture time translates to better effects.

The results of the experiment are often influenced by heterogeneity. There was heterogeneity in this study, and the reasons were as follows: 1) the origin of AF disease in the 8 articles were as follows: rheumatic heart disease [10], [11], [12], [14], coronary heart disease [10-12, 14], hypertensive heart disease [10], [12], [14], dilated cardiomyopathy [11]; 2) the original disease treatment drugs were different, for example, for coronary heart disease lipid-lowing drug and antiplatelet drugs were used. For dilated cardiomyopathy, myocardial nutrition drugs were administered, while for hypertension, pressure decrease drugs were taken, etc.; 3) For the diagnostic criteria of AF, two cases come from a 2005 book on the practice of internal medicine [10] and 2000 Emergency internal medicine science [12]. Two cases come from literature guidelines [15], [16], whiles others did not describe the source; 4) the treatment course and the position and time of acupuncture were different; 5) the quality of the literature was low, and all mentioned randomly in this study, but not all of them were described in detail. Only one case referred to double blindness; 6) the number of samples was small, and most of the literature came from China, which brought about unavoidable language and location bias. Therefore, it is necessary to follow the basic guidelines for reporting clinical trials conducted with clarity.

In conclusion, although fewer factors may affect the results of this meta-analysis, we believe that acupuncture can treat for AF, through improving conversion rate, slowing the heart rate, by reducing adverse drug reactions and the time of AF cardioversion to sinus rhythm. It is therefore worthy of clinical application.

Acknowledgement

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