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Review Article

Effect of ibutilide and propafanone on conversion of new onset atrial fibrillation to sinus rhythm in Chinese people: a meta-analysis

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Abstract: A number of clinical and experimental studies had investigated that ibutilide and propafenone were two of the most effective anti-arrhythmic agents for conversion of new onset atrial fibrillation (the duration time of atrial fibrillation are all within 90 days) to sinus rhythm. However, the differences between ibutilide and propafenone about curative effect or adverse reaction are equivocal. We therefore performed a meta-analysis to evaluate the reversion curative effect of ibutilide and propafenone in Chinese people. We systematically searched PubMed, EMBASE, the Cochrane Database, CNKI and WANGFANG Data for all published studies to examine the effect of ibutilide and propafenone on new onset atrial fibrillation from January 2005 to January 2015 (the administration way of drug are intravenous injection). Only randomized clinical trials were included. A random effects model was used when there was substantial heterogeneity and a fixed effects model when there was negligible heterogeneity. According to the Cochrane system evaluation method, we filter for inclusion criteria, extract information and evaluate quality from randomized controlled trials (RCTs). We used Revman 5.0 meta-analysis software in the end. Fourteen published studies including 1455 patients were identified for inclusion in the analysis. The results showed that there was no significant difference between two groups about the converting effect (OR=2.96, 95% CI 2.37, 3.69, P>0.05). In addition, the conversion time of ibutilide was obviously shorter than propafenone (OR=-22.7, 95% CI -25.26, -20.28; P<0.001). At last, there was no significant difference between two groups about the incidence of adverse reactions. (OR=0.75, 95% CI 0.46, 1.22, P=0.61). This meta-analysis suggests that there was no significant difference about the conversion effect between ibutilide and propafenone in Chinese people with new onset AF, as well as the incidence of adverse reactions. However the conversion time of ibutilide was obviously shorter than propafenone. Thus, further prospective studies are warranted.

Keywords: Ibutilide, propafenone, atrial fibrillation, meta-analysis

Introduction

Atrial fibrillation (AF) is a disturbance of the normally rhythmical beating of the cardiac atria, characterised by rapid (e.g., 400-600 beats/minute), irregular electrical and mechanical activation of the atrial muscle. It is the most common sustained arrhythmia observed in clinical practice with prevalence increasing with age [1]. In the general population, the incidence of atrial fibrillation is ranging from 0.4% to 1.0% [2]. These higher rates increase disease burden and treatment cost, with a 66% increase in hospital admissions over the past two decades, and it is increasingly recognized as a global public health problem. AF is an important risk factor for ischemic stroke and presents severe clinical manifestation [3]. Patients with AF have about 5-fold increase of stroke risk, which is prevalently dependent on thrombosis occurring in the left atrium or left atrium appendage. The thrombus, which be induced by AF, is often larger than one resulting from atherosclerosis. The previous results showed that AF could impact the neurological function and be associated with increased mortality after thrombolysis in the acute stroke patients [4]. AF is the common clinical complications of cardiovascular diseases, such as coronary heart disease, rheumatic heart disease, hypertension, cardiomyopathy and so on. Restoration of sinus rhythm in patients with AF

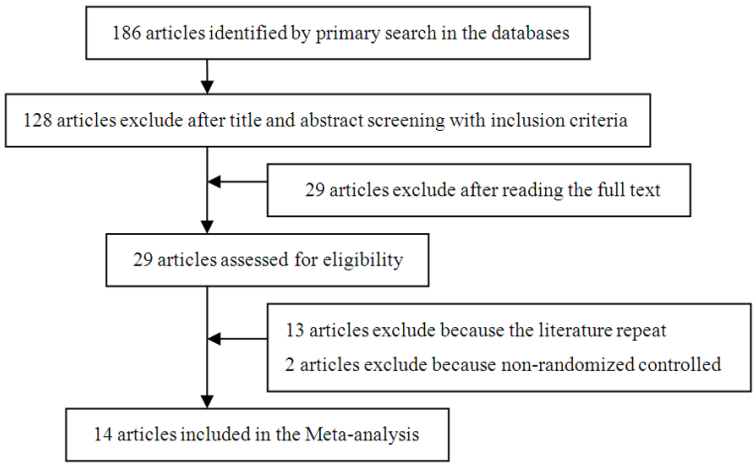

Figure 1. The Summary of the study selection and exclusion process.

is a strategy to prevent the cardiovascular and thromboembolic complications of this arrhythmia.

Propafanone is a kind of class I type drug of anti-arrhythmic agent. It can prolong the refractory period of atrial myocardium and increase the perimeter of retracing cycle, which can be used as blocker of sodium channel. In the meantime, it also block excitement gap in retracing cycle and reduce the number of retracing cycle to treat atrial fibrillation. The basis of electrophysiology is that it plays an important role in inhibiting the sodium channel to prevent internal flow of fast sodium current and slow down the speed of depolarization resulting in slow conduction velocity and extended mildly interphase of action potential and effective refractory period due to the basis of electrophysiology. Finally, we know that the effect of propafanone is in atrial and conduction fiber of myocardium.

Ibutilide, a kind of class III type drug of anti-arrhythmic agents, had been approved for use in conversion of atrial fibrillation more than 10 years in the United States and European countries. The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) pointed out that Ibutilide was the first-line drug as converting atrial fibrillation, and be recommended (class I, grade A) in the atrial fibrillation guidelines 2006 [5]. And the American College of Cardiology Foundation/American Heart Association/American Heart Rhythm Association give the same advice [6]. And the drugs are used to treat fibrillation are ibutilide and propafenone, however clinical studies of the two drugs and the results about their curative effect are not the same.

We therefore performed a systematic review and meta-analysis to evaluate the effect of ibutilide and propafanone on conversion of new onset atrial fibrillation to sinus rhythm, with the aim to assess the efficacy and safety of two drugs.

Methods

Publication search

We searched PubMed, EMBASE, the Cochrane Database, CNKI and WANGFANG for all published studies to examine the effect of ibutilide and propafenone on new onset atrial fibrillation from January 2005 to January 2015. We conducted text searches with the search terms “ibudilite” and “propafenone” and “atrial fibrillation”. We also manually searched references from selected clinical trials, recent meta-analysis and review articles.

Inclusion and exclusion criteria

Eligible articles had to meet the following criteria: (1) comparison of ibutilide or propafenone treatment; (2) randomized controlled human trials; (3) the efficiency and rate of adverse reactions in each group as an outcome. We used reliability of the methods for patient selection and statistical analysis as quality variables to accurately assess the quality measures of interest. All titles, abstracts and full papers of potentially relevant studies were assessed for eligibility. When several reports from the same study were published, only the most recent or informative one was included in this meta-analysis. Exclusion criteria were: (1) reviews or meta-analyses; (2) study time or research methods do not conform to this study. (3) non-randomized controlled human trials.

Data extraction and quality assessment

We extracted the following information from each study: (1) study population sample size

Table 1. Baseline characteristics of the studies included in the meta-analysis (T/C)

Author	Year	Number	Average age (years)	The duration of AF (days)	Average Conversion time (min)	Adverse events
Xing	2013	70/68	48.1/50.3		16.6/46.8	①②/③④
Zhang	2005	75/76	62.2/60.5	<90		①/③④
Wu	2012	17/17	58.2/60.5	<<2		
He	2013	173/172	59.9/61.2	<<4	53/123	
Liu	2014	80/80	59/59	1 hours~39 days		/④
Zhen	2012	33/33	59.8/59.8	3 hours~90 days	32.12/60.73	①②/③④
Ran	2010	21/21	62.2/60.5	<90		①/③④
Sun	2012	24/24	55/58	<90		⑤⑥/③
Yi	2009	21/20	18~70	<90		①②⑥/④⑦
Sun	2011	17/20	68.5/65.1	<<4	17.7/19.2	⑤⑥/⑧
Li	2011	70/53	47/48	<90	33.4/62.4	①②/③④
Ji	2012	19/19	65.2/66.1	2~6	11.65/26.21	⑨/⑧
Zhang N	2005	41/41		2 hours~90 days		⑩/③④
Zhang HC	2005	75/76		<90		⑩/③④

T: ibutilide; C: propafenone; Adverse events: ① ventricular premature contraction; ② sinus bradycardia; ③ sinus static; ④ hypotension; ⑤ frequent premature contration; ⑥ ventricular tachycardic shortly; ⑦ gastrointestinal reaction; ⑧ chest distress; ⑨ long QT syndrome; ⑩ sinus tachycardic.

Table 2. Methodological quality evaluation of the study included

Study	Random	Allocation concealment	Blinding	Loss to Follow-up/exit	Jadad score
Xing	**	**	**	*	7
Zhang	**	**	**		6
Wu	**	**	*	*	6
He	**	**	*	*	6
Liu	**	*	*	*	5
Zhen	**	**	**	*	7
Ran	**	**	*		5
Sun	**	*	*		4
Yi	**	*	*		4
Sun	**	**	**	*	7
Li	**	**	*		5
Ji	**	**	*	*	6
Zhang N	**	**	*	*	6
Zhang HC	**	**	*	*	6

*The methodological qualities of the included studies were assessed using the improved Jadad scale.

and characteristics; (2) dose and duration of treatment; (3) duration of atrial fibrillation (4) outcome measures. One reviewer abstracted the data, and then the other checked the documentation. They finally reached an agreement on the data by consensus. We used the Jadad score to assess the methodological quality of the included studies.

Statistical analysis

We performed the statistical calculations with RevMan version 5.0 (The Cochrane Collaboration, Oxford, UK). We allocated the results of each study as dichotomous frequency data to evaluate the effect of ibutilide and propafenone on new-onset AF or rate of adverse reactions. We calculated the odds ratio (OR) and 95% confidence interval (CI) for efficiency and adverse reactions in each trial separately. We used the chi-squared test to assess heterogeneity. The degree of heterogeneity across the results of different studies was quantitatively assessed by the I^2 statistic. The fixed-effect model or random effect model were used according to the significant heterogeneity results. If the chi-squared test *P*-value was >0.05 and I^2 was <50%, we analyzed the data using a fixed-effect model (the Mantel-Haenszel method), otherwise we used a random-effect model. If the heterogeneity was significant, we attempted to explain the differences based on the patient clinical characteristics of the included studies by using subgroup analyses. The results were summarized

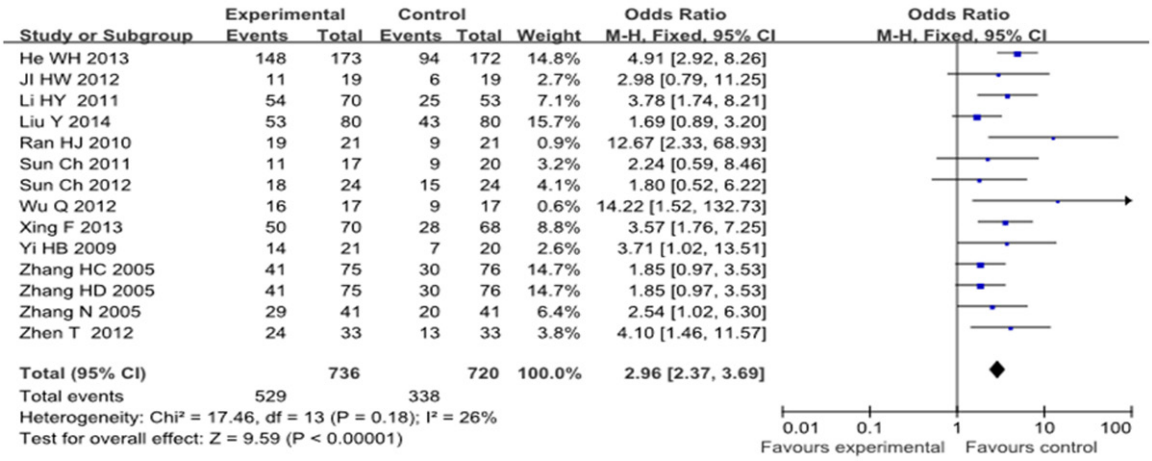

Figure 2. The contrast of converting effect of ibutilide and propafenone (fixed-effect model).

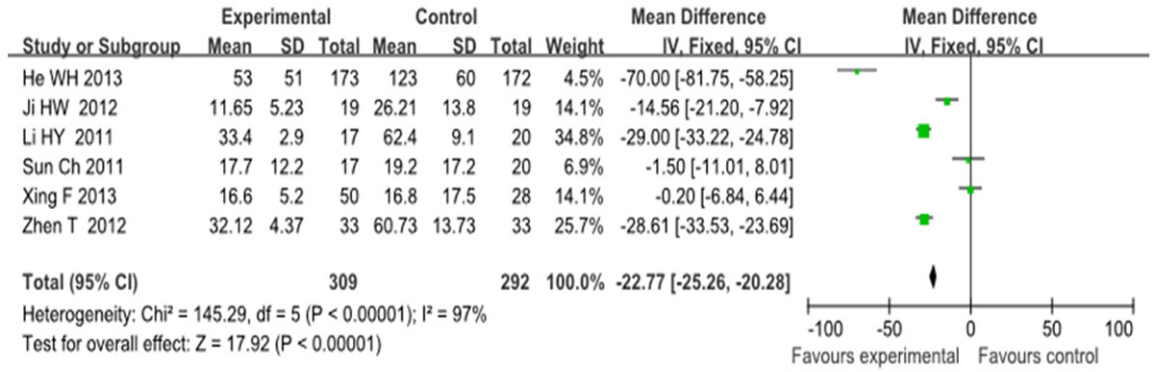

Figure 3. The contrast of converting time of ibutilide and propafenone.

in the form of relative risk (RR) and 95% confidence interval (CI). *P* values were considered statistically significant for P<0.05. The funnel plots were used to assess the publication bias of included studies.

Results

Characteristics of included studies

Fourteen published studies including 1455 patients with new onset were identified for inclusion in the analysis [7-20]. The process of study selection was summarized in **Figure 1**. These studies compared the use of ibutilide vs. propafenone on new onset AF in various populations. The studies received Jadad scores of 4 (n=2) [14, 15], 5 (n=2) [13, 17], 6 (n=6) [8-10, 18-20], 7 (n=3) [7, 12, 14] points. The characteristics of the studies included in the meta-analysis were shown in **Table 1**. And the studies of methodological quality evaluation were shown in **Table 2**.

Results of the meta-analysis

1) The meta-analysis of all included studies indicated the comparison between ibutilide and propafenone for the effect of new onset AF (OR 2.96, 95% CI 2.37-3.69, P<0.05), but there was substantial heterogeneity (P<0.00001, I^2=24%). The results were shown in **Figure 2**.

2) The meta-analysis was performed to evaluate the contrast of converting time of ibutilide and propafenone on treatment of new onset AF. The results showed that the time of ibutilide was shorter than propafenone (OR -22.77, 95% CI -25.26--20.28, P<0.0001). However, the heterogeneity remained substantial (P<0.0001, I^2=97%). The results were shown in **Figure 3**.

3) The results of meta-analysis showed that there is no significant difference between two groups about the incidence of adverse reactions. (OR 0.75, 95% CI 0.46-1.22, P=0.61). The results were shown in **Figure 4**.

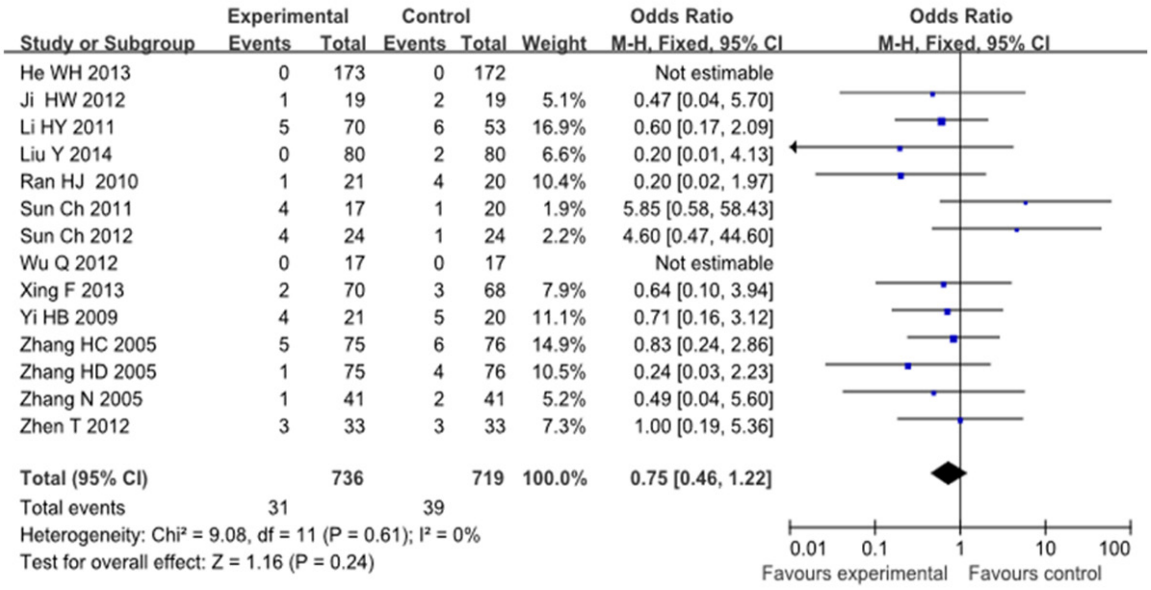

Figure 4. The incidence of adverse reactions of ibutilide and propafenone.

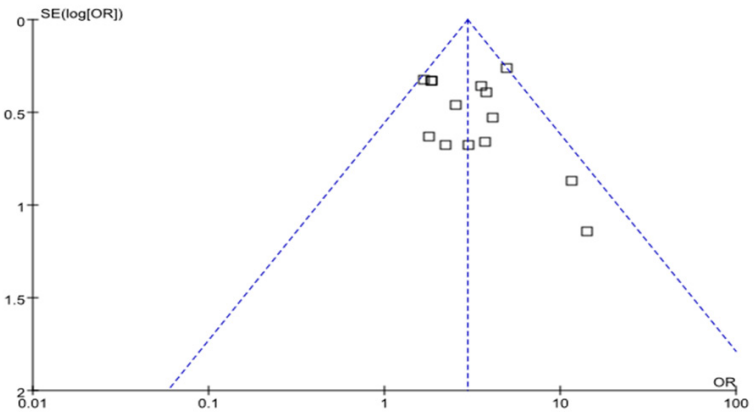

Figure 5. The bias of the effect ibutilide and propafenone.

4) The evaluation of bias: the funnel of this study was symmetrical and we could say that the bias was small. The results were shown in **Figure 5**.

Discussion

The structure of Ibutilide is similar with sotalol as a class III anti-arrhythmic agent, which increases the action potential duration (APD) by blocking the rapid component of the delayed rectifier potassium current and enhancing the slow inward sodium current. It is the effective basic principle is that ibutilide not only can prolong APD, but also block quickly the active potassium channel of cardiac cell with highly selection. In addition, Ibutilide can activate slow inward sodium current, which be used as classic blockers of the rapid delayed rectifier K^+ current. However, the regulation effect of ERP in atrial tissue is 10 time more than ventricular tissue [21-24]. Ibutilide can make ERP prolong 90%~110%, extend the wavelength of turnback wave and make turnback wave that it is not easy to form through slow conduction. It is the unique effect of ibutilide [25-37].

However, many commonly used antiarrhythmic drugs prolong ventricular repolarization leading to an enhanced risk of the development of adverse events. The noticeable adverse events of ibutilide are the polymorphous ventricular tachycardic (PVT), including the torsades de points (TDP) and the occurrence of TDP is 4.3%. In addition the vast majority of appearance is within 40 minutes, so it is very necessary to use early ECG monitoring [38, 39]. The electrophysiological mechanism of that ibutilide lead to TDP has not been fully expounded. However, the present study shows that it is owed to two main factors. One factor is the calcium overload, which lead to block of potassium current

and increased late sodium current. In addition, the heterogeneity of ion channel distribution in each layer myocardial cell makes the prolonged degree of APD and increase the complex discrete degree. In the end, the current become the turn-back wave and maintain the TDP [40-46]. External study showed that the percentage of probability of ibutilide-induced TDP is 9 [47]. APP10, the gap junction agonist, can inhibit the phosphorylation of CX40 to prevent the occurrence of TDP [48].

Because the quick distribution and metabolism of ibutilide, therefore it has a short plasma halftime. The extension of QT interphase is related to dosage, blood drug concentration and the using speed of drug. Along with the extension of dose and using speed of drug, the QT interphase also was extended [49, 50]. The general adverse reactions include premature ventricular beats, non-sustainable ventricular tachycardia, TDP and so on. And the adverse reaction usually happens within 4 hours after use of drug [51-57]. Some studies had pointed out that the converting rate of ibutilide is 41.5 in the persistent AF, but the comprehensive converting rate of ibutilide and propafenone is 71.4 [58].

This meta-analysis contains fourteen studies, and every study had a clear diagnostic criteria. We made the baseline consistency analysis about the age, course of diseases and so on before treatment. So it made the meta-analysis have the comparability between the patients of the two groups. The fourteen studies results were merged, we could find that the total value OR contain one, so there was no significant difference about successful rate of converting new onset AF between ibutilide and propafenone. We made the comparison between inbutilide and propafenone in this study. In the case of existing data, we reach the comprehensive conclusion, and provide reference for clinical medication. The subject baseline assessment was not comprehensive in the study and may affect the result of the system. Although this study funnel was almost symmetric, still not exclude the possibility of bias. Because the meta-analysis may not include some study that have been completed, but not been published. The trials were limited according to the numbers in some subgroups, so the results were less persuasive. We must collect more research to analyze, so as to make the conclusion more credible.

Conclusions

This meta-analysis suggests that there was no significant difference about the curative effect between ibutilide and propafenone in Chinese people with new onset AF, as well as the incidence of adverse reactions. However, the converting time of inbutilide was obviously shorter than propafenone. Thus, more large-scale prospective RCTs are required to investigate whether the ibutilide is better than propafenone for the converting effect of new onset AF in different populations.

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Disclosure of conflict of interest

None.

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