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Original Article

Effects of candesartan on relapse of atrial fibrillation after radiofrequency ablation and duration of atrial fibrillation attack

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Abstract: Objective: The goal of this study was to investigate and discuss the effects of candesartan on relapse of atrial fibrillation after radiofrequency ablation and duration of atrial fibrillation attack. Methods: A total of 96 patients with atrial fibrillation admitted that were treated in our hospital from February 2016 to January 2017 were selected and randomly divided into a control group (n = 48) and an observation group (n = 48). All patients were treated with radiofrequency ablation. After the operation, patients in the control group were given warfarin sodium tablets treatment, and those in the observation group were treated with candesartan in addition to aspirin therapy. The relapse rate, number of occurrence, and duration of attack of atrial fibrillation in the two groups were compared after treatment, and the atrial fibrillation burden was observed. The conditions of ventricular remodeling and levels of cardiac troponin I (cTnI), serum angiotensin II (Ang-II), and high-sensitivity C-reactive protein (hs-CRP) after treatment were compared. The autonomic nervous functions after treatment in the two groups were observed, to which indexes related included standard deviation of normal-to-normal (SDNN) of R-R interval, low frequency power (LF), high frequency power (HF) and ratio of LF to HF (LF/HF). The quality of life of the patients was compared after 12 months of follow-up. Results: After treatment, the relapse rate and number of attack of atrial fibrillation in the observation group were significantly lower and its duration was shorter than those in the control group ($P < 0.05$). Compared with those in the control group, the left ventricular ejection fraction (LVEF) was increased after treatment in the observation group, while the left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and ratio of peak E to peak A (E/A) were decreased remarkably ($P < 0.05$). The levels of Ang-II, hs-CRP, and cTnI of the two groups of patients were lowered notably after treatment, of which the levels of the indexes in observation group were significantly lower than those in the control group ($P < 0.05$). After treatment, the SDNN and LF/HF in the observation group were remarkably higher than those in the control group, while the LF and HF were obviously lower ($P < 0.05$). The quality-of-life score in the observation group was notably higher than that in the control group ($P < 0.05$). Conclusion: Candesartan can effectively lower the levels of serum Ang-II and inflammations in patients after the radiofrequency ablation for atrial fibrillation, decrease myocardial injury, and ameliorate ventricular remodeling and autonomic nervous function, thus reducing the recurrence of atrial fibrillation and its duration of attack and improving the patients' quality of life, which is of great clinical significance.

Keywords: Candesartan, atrial fibrillation, relapse, duration of attack

Introduction

Atrial fibrillation is one of the common arrhythmias in clinic, and its incidence rate is rising with the increases in aging population and incidence rate of cardiovascular diseases [1]. Atrial fibrillation is characterized by decreased cardiac function, disordered ventricular rhythm/rate, and formation of mural thrombus in the atrium [2]. When atrial fibrillation occurs, cardiac output from the ventricle is decreased, and cardiac hemodynamics are changed, so the symptoms such as decline in blood pressure, fluster, palpitation, chest tightness, and syncope are triggered, leading to heart failure, angina pectoris, stroke, and other complications, as well as death of the patients [3]. In clinical practice, therapeutic methods for atrial fibrillation include pharmacologic and non-pharmacologic treatments, of which radiofrequency ablation is an important type of therapeutic method with the highest success rate. In particular, radiofre-

Table 1. Comparison of general data of the two groups of patients

Item	Control group (n = 48)	Observation group (n = 48)	t/χ^2	*P*
Gender (male/female)	27/21	25/23	0.042	0.838
Age (years old)	60-80	60-75		
Average age (years old)	65.26 ± 8.42	64.97 ± 7.52	0.178	0.859
Body mass index (BMI) (kg/m^2)	23.23 ± 1.15	23.56 ± 1.16	1.400	0.165
Past medical history [n (%)]				
Hypertension	15 (31.25)	17 (35.42)	0.047	0.829
Hyperlipidemia	11 (22.92)	13 (27.08)	0.056	0.814
Diabetes mellitus	4 (8.33)	6 (12.50)	0.136	0.713

Table 2. Comparison of atrial fibrillation between the two groups of patients after treatment

Group	N	Relapse rate [n (%)]	Number of attack (time/month)	Duration (h/time)
Observation group	48	2 (4.17)	3.42 ± 1.12	0.13 ± 0.24
Control group	48	11 (22.92)	9.39 ± 1.35	0.87 ± 0.52
t/χ^2		5.694	23.580	8.952
P		0.017	< 0.001	< 0.001

quency ablation is the sole therapy when pharmacologic treatment is unsuccessful [4]. Relapse of atrial fibrillation is still inevitable after radiofrequency ablation. A large quantity of studies have indicated that age, postoperative ventricular remodeling, atrial fibrosis, inflammation, autonomic nervous function and duration of atrial fibrillation are major factors influencing relapse after radiofrequency ablation [5]. Therefore, it is very important to improve the success rate of radiofrequency ablation, lower the relapse rate after operation, and conduct medicine intervention in relapse-related factors for postoperative patients. Candesartan is a kind of angiotensin II (Ang-II) receptor blocker that is often applied to treat essential hypertension. However, it has other uses and is of positive significance for amelioration of atrial fibrillation. In this research, candesartan therapy was given to patients after radiofrequency ablation for atrial fibrillation, hoping to provide a basis for prevention and treatment of relapse of atrial fibrillation after radiofrequency ablation.

Clinical data

General data: A total of 96 patients with atrial fibrillation admitted and treated in our hospital from February 2016 to January 2017 were selected. Inclusion criteria: 1) patients meeting the diagnostic criteria for atrial fibrillation [6], 2) patients receiving treatment with radiofrequency ablation and 3) patients who signed the informed consent. Exclusion criteria were: 1) patients with psychiatric diseases, 2) patients allergic to the experimental drugs and 3) patients complicated with malignant tumor. All the patients were divided into control group (n = 48) and observation group (n = 48) by means of a random number table. General data of the two groups of patients had no statistically significant differences ($P > 0.05$), which were comparable (**Table 1**).

Methods

Treatments

After the radiofrequency ablation, patients in the control group took warfarin sodium tablets orally [manufacturer: Shanghai Xin Yi Pharmaceutical Co., Ltd, approval number: national medicine permission number (NMPN) H31-022123] (3 mg, once a day). On this basis, patients in the observation group were given oral candesartan (manufacturer: Guangzhou Baiyunshan Tianxin Pharmaceutical Co., Ltd., approval number: NMPN H20051217) (8 mg, once a day).

Electrocardiogram examination

After treatment, both groups of patients were in the supine position and kept free breathing in resting state. The 12-lead electrocardiograms (voltage: 10 mm/mV and paper-advance speed: 25 mm/s) were recorded, in which cardiac cycles with clear patterns and stable baselines were selected to record the total indexes for activity changes of 1 sympathetic nerve and parasympathetic nerve [standard deviation of normal-to-normal (SDNN) of R-R interval], activity indexes of sympathetic and parasympathetic nerves [low frequency power (LF)], activity indexes of vagus nerve [high frequency power

Table 3. Comparison of ventricular remodeling between the two groups of patients after treatment

Group	N	LVEF (%)	LVEDV (mL)	LVESV (mL)	E/A
Observation group	48	57.53 ± 3.48	87.52 ± 3.64	36.46 ± 3.05	1.56 ± 0.34
Control group	48	46.68 ± 3.53	95.16 ± 3.86	42.73 ± 3.15	2.67 ± 0.47
t		15.165	9.977	9.907	13.257
P		< 0.001	< 0.001	< 0.001	< 0.001

Table 4. Comparison of Ang-II level between the two groups of patients before and after treatment (ng/L)

Group	N	Before treatment	1 month after treatment	3 months after treatment	6 months after treatment
Observation group	48	114.28 ± 3.25	93.48 ± 3.18*	87.23 ± 3.63*	83.27 ± 3.16*
Control group	48	113.84 ± 3.48	105.43 ± 3.46*	98.75 ± 3.82*	92.42 ± 3.45*
t		0.627	11.474	12.253	17.614
P		0.532	< 0.001	< 0.001	< 0.001

Note: Compared with that before treatment, *$P < 0.05$.

Table 5. Comparison of hs-CRP level between the two groups of patients before and after treatment (mg/L)

Group	N	Before treatment	1 month after treatment	3 months after treatment	6 months after treatment
Observation group	48	14.82 ± 2.15	9.05 ± 1.41*	5.69 ± 0.74*	2.62 ± 0.35*
Control group	48	14.86 ± 2.18	11.84 ± 1.48*	9.54 ± 1.08*	6.58 ± 0.54*
t		0.206	9.628	20.175	39.847
P		0.838	< 0.001	< 0.001	< 0.001

Note: Compared with that before treatment, *$P < 0.05$.

(HF)] and indexes reflecting the equilibrium state between sympathetic and vagus nerves [ratio of LF to HF (LF/HF)]. Acuson SC2000 ultrasonic diagnostic equipment (Siemens, Germany) was used for three-dimensional ultrasonic examinations on the two groups of patients (probe frequency: 2.8 MHz, scanning depth: 15-16 cm and volume rate ≥ 12 volume frame/s). Dynamic three-dimensional images of 3 complete cardiac cycles were collected and stored at the end of expiration, so as to observe and record the left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF).

Measurement of relevant laboratory indexes

A total of 5 mL venous blood was drawn from every patient in the two groups (in the morning, fasted for more than 8 h) before treatment and at 1, 3, and 6 months after treatment, respectively. After centrifugation at 4°C and 3,000 r/min for 10 minutes (centrifugal radius: 15 cm), the supernatant was taken and stored in a refrigerator at -80°C. The enzyme-linked immunosorbent assay (ELISA) was performed to measure the concentrations of Ang-II, high-sensitivity C-reactive protein (hs-CRP) and cardiac troponin I (cTnI). Relevant kits were offered by Rapidbio (RB), USA, and the operations were conducted in strict accordance with the kit instructions. A microplate reader (ELx800, Bio Tek, USA) was utilized to measure the optical density (OD) at the wavelength of 450 nm, and the concentrations of Ang-II, hs-CRP and cTnI were calculated.

Evaluation indexes

The two groups of patients were examined using the 12-lead surface electrocardiogram after treatment, and relapse, number of attacks, and duration of atrial fibrillation within

Table 6. Comparison of cTnI level between the two groups of patients before and after treatment (ng/L)

Group	N	Before treatment	1 month after treatment	3 months after treatment	6 months after treatment
Observation group	48	1.85 ± 0.55	1.04 ± 0.28*	0.96 ± 0.27*	0.82 ± 0.26*
Control group	48	1.83 ± 0.58	1.46 ± 0.63*	1.27 ± 0.29*	1.06 ± 0.24*
t		0.173	4.221	5.421	4.699
P		0.863	< 0.001	< 0.001	< 0.001

Note: Compared with that before treatment, *$P < 0.05$.

Table 7. Comparison of autonomic nervous functions between the two groups of patients

Group	N	SDNN (ms)	LF (ms^2)	HF (ms^2)	LF/HF
Observation group	48	106.43 ± 3.24	516.82 ± 9.79	507.45 ± 95.32	1.03 ± 0.64
Control group	48	93.62 ± 3.58	598.67 ± 9.23	1596.35 ± 178.25	0.47 ± 0.23
t		18.381	42.146	37.322	5.705
P		< 0.001	< 0.001	< 0.001	< 0.001

1 year of the patients were observed and recorded. The judgment criteria for relapse: symptomatic atrial tachyarrhythmias occurred within 3 months after ablation, or there was asymptomatic arrhythmia with duration exceeding 10 minutes. The synchronous 12-lead dynamic electrocardiogram system was adopted for Holter monitoring and observation of SDNN, LF, HF, and LF/HF.

Real-time three-dimensional ultrasonic examinations were performed for the patients after treatment to record the indexes [LVEF, LVEDV, LVESV and ratio of peak E to peak A (E/A)]. Changes in the concentrations of Ang-II, hs-CRP, and cTnI in the serum of the patients were detected via ELISA before treatment and at 1, 3, and 6 months after treatment.

The patients' quality of life was evaluated from the aspects of physical strength (70 points), disease conditions (26 points), medical conditions (6 points), general life functions (17 points), psychological functions (26 points), and working status (9 points) at 6 months after treatment, of which the score was positively correlated with the quality of life.

Statistical processing

Statistical Product and Service Solutions (SPSS) 19.0 (SPSS Inc., Chicago, IL, USA) software was used to process the data. Measurement data are presented as mean ± standard deviation ($\bar{x} \pm s$), and *t*-test was performed. Enumeration data are presented as ratio, and X^2 test was conducted. $P < 0.05$ suggested that the difference was statistically significant.

Results

Comparisons of atrial fibrillation between the two groups of patients after treatment

After treatment, the relapse rate and number of attack of atrial fibrillation in the observation group were significantly lower and its duration was shorter than those in the control group ($P < 0.05$) (**Table 2**).

Comparisons of ventricular remodeling between the two groups of patients

Compared with those in the control group, the LVEF was increased obviously after treatment in the observation group, while the LVEDV, LVESV and E/A were decreased remarkably ($P < 0.05$) (**Table 3**).

Comparisons of Ang-II, hs-CRP and cTnI levels between the two groups of patients

There were no significant differences in the levels of Ang-II, hs-CRP and cTnI between the two groups of patients before treatment ($P > 0.05$). At 1, 3, and 6 months after treatment, the levels of Ang-II, hs-CRP, and cTnI of the two groups of patients were lowered notably, of which decreases in the observation group were more

Table 8. Comparison of quality of life between the two groups of patients after treatment

Group	Physical strength	Disease condition	Medical condition	General life function	Psychosocial function	Working status
Observation group	62.77 ± 3.25	21.72 ± 3.05	5.86 ± 0.75	15.48 ± 2.02	23.73 ± 3.15	7.23 ± 1.02
Control group	51.46 ± 3.23	15.26 ± 3.48	3.73 ± 0.64	10.65 ± 2.23	16.64 ± 3.08	4.65 ± 0.85
t	17.145	9.431	14.258	10.712	10.776	13.708
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

obvious than those in the control group ($P < 0.05$) (**Tables 4**-**6**).

Comparisons of autonomic nervous functions between the two groups of patients after treatment

After treatment, the SDNN and LF/HF in the observation group were higher than those in the control group, while the LF and HF were lower ($P < 0.05$) (**Table 7**).

Comparison of quality of life between the two groups of patients

The quality-of-life scores for various aspects in the observation group were notably higher than those in the control group after treatment ($P < 0.05$) (**Table 8**).

Discussion

As an age-related disease, atrial fibrillation is generally caused by intra-atrial reentry induced by sinus node dysfunction, bradycardia, and extended refractory period of atrial cells in the patients, which are triggered by sinus node cell fibrosis and pathological changes of atrial myocytes [7]. Treatment for atrial fibrillation includes pharmacologic and non-pharmacologic therapies. However, although traditional medicines can relieve bradycardia to some extent, thus making the cardiac rhythm to be identical and ameliorating atrial fibrillation, the effects are not ideal [8]. Radiofrequency ablation is an effective non-pharmacologic therapy. In spite of its significant short-term efficacy, the postoperative relapse rate is increased due to the impacts of various factors, such as inflammation, atrioventricular remodeling, and autonomic nervous function change. In particular, the success rate of radiofrequency ablation is decreased during the operation process because of the too long duration of atrial fibrillation, increased atrial diameter, and intra-atrial reentry. In addition, the energy of ablation is increased with the enlargement of the atrium during the operation, leading to aggravated cicatrix, and thus increasing the risk of postoperative recurrence. Therefore, it is very important to prevent and treat the recurrence of atrial fibrillation after operation [9, 10].

Candesartan is a type of Ang-II receptor antagonist that has positive effects on preventing and reversing atrial fibrillation [11]. The results of this research showed that after treatment, the relapse rate and number of attack of atrial fibrillation in observation group were significantly lower and its duration was shorter than those in control group. Compared with those in the control group, the LVEF was obviously increased in the observation group, while the LVEDV, LVESV and E/A were decreased ($P < 0.05$). Candesartan can thus reduce the atrial fibrillation burden and decrease its recurrence after radiofrequency ablation, playing a crucial role in preventing the recurrence. Candesartan can protect the cardiac ejection fraction, extend the ejection time, improve the myocardial compliance and flaccid capacity, and reduce LVEDV and LVESV by means of ameliorating the status of myocardial ischemia as well as ventricular systolic and diastolic functions, thereby improving structural remodeling and electrical remodeling, restoring normal transduction pathways in the atrium and reducing intra-atrial reentry. As a result, the success rate of radiofrequency ablation is increased and the postoperative relapse is decreased effectively [12].

Ang-II has a very high biological activity and strong vasoconstrictive effects [13]. Plenty of studies have indicated that the levels of inflammatory factors in patients with atrial fibrillation are higher than those in normal population, which may be related to myocardial cell apoptosis, atrial myocyte injury, and atrial interstitial fibrosis [14]. Hs-CRP, as a marker of inflammatory reaction, can promote the necrosis and fibrosis of atrial myocytes [15]. CTnI is not only

an inhibitory protein of troponin-tropomyosin regulating complex but also a marker of myocardial injury [16]. It was shown in the results of this research that at 1, 3, and 6 months after treatment, the levels of Ang-II, hs-CRP and cTnI of the two groups of patients were lowered notably, of which the decreases in the observation group were more obvious than those in the control group ($P < 0.05$). Ang-II can increase secretion of noradrenaline by stimulating the sympathetic nerves, thus accelerating atrial electrical remodeling and aggravating atrial fibrillation symptoms. Candesartan can reverse the atrial remodeling and alleviate preload and afterload of the heart by means of inhibiting and blocking Ang-II, thereby exerting the effect of reducing postoperative relapse of atrial fibrillation [17]. Candesartan can effectively improve the myocardial systolic function, reduce myocardial cell apoptosis, ameliorate myocardial ischemia and hypoxia status, exert myocardial protective effect, decrease cTnI leaking from the myocardial cells and lower the incidence rate of arrhythmia induced by myocardial cell injury [18]. After radiofrequency ablation, elevated hs-CRP level can trigger inflammation of the atrial muscle, while candesartan can block the mechanism of those inflammations by suppressing the massive secretion of hs-CRP, thus lowering the relapse rate of atrial fibrillation and shortening the duration of atrial fibrillation after operation [19].

Studies have proven that the autonomic nervous system plays a crucial role in initiating and maintaining atrial fibrillation, and that the incidence rate of atrial fibrillation is increased through the sympathetic nerve system and parasympathetic nerve system as well as the combined action of the two systems [20]. It was found in this study by examining the autonomic nervous conditions after radiofrequency ablation that the SDNN and LF/HF in the observation group were higher than those in the control group after treatment, while the LF and HF were lower ($P < 0.05$). It means that medicine intervention with candesartan can have an impact on the function of sympathetic and vagus nerves and effectively decrease LF and HF, thereby maintaining the balance of cardiac autonomic nervous functions, relieving atrial fibrillation burden, alleviating local electrical conduction block, and reducing the occurrence of conduction reentry in the atrium. Therefore, it is conducive to preventing the recurrence of atrial fibrillation.

In conclusion, candesartan therapy applied to patients with atrial fibrillation after radiofrequency ablation can decrease the postoperative recurrence, shorten the duration of attack of atrial fibrillation, and further improve the quality of life of the patients by improving the atrial remodeling, lowering inflammation level, reducing myocardial injury, and regulating functions of the autonomic nervous system, which has very important clinical significance. However, the bias of data was inevitable due to relatively small sample size and short follow-up time. Therefore, long-term observations need to be conducted with larger sample sizes.

Disclosure of conflict of interest

None.

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