

Original Research Article

Concurrent administration of amiodarone and atenolol in the treatment of coronary artery disease complicated with arrhythmia, and its effect on serum levels of CD40L, TNF- α and IL-6

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Abstract

Purpose: To investigate the efficacy of the combination of amiodarone and atenolol in the treatment of patients with coronary artery disease (CAD) complicated with arrhythmia, and its effect on serum levels of CD-40L, TNF- α and IL-6.

Methods: One hundred and twenty CAD patients with arrhythmia on admission in The First People's Hospital of Shuangliu District Chengdu, China were assigned to groups A and B, each having 60 patients. Amiodarone was administered to all the patients, while atenolol was additionally given to patients in group A. Levels of heart function indicators, inflammatory factors, blood pressure, heart rate, adverse reaction rate (ARR) and overall efficacy were evaluated for the two groups.

Results: There were significantly improved levels of heart function indicators, and lower levels of CD40L, TNF- α and IL-6 in group A, when compared with group B ($p < 0.001$). Moreover, treatment effectiveness was higher in group A than in group B ($p < 0.05$). However, there was no significant difference ($p > 0.05$) in ARR between groups A and B.

Conclusion: The combined use of amiodarone and atenolol improves heart function indicators in patients with CAD and arrhythmia, reduces the levels of inflammatory factors, normalizes blood pressure and heart rate, and lowers ARR. However, further clinical trials on this combined therapy are required prior to its use in clinical practice.

Keywords: Amiodarone, Atenolol, Coronary artery disease (CAD), Arrhythmia

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INTRODUCTION

Coronary artery disease (CAD) is a clinical condition which is caused by blockage of arterial blood vessels, and it is usually accompanied by myocardial hypoxia and ischemia. After high-

intensity activities or dramatic mood swings, CAD patients exhibit significant precordial angina. Without prompt intervention, the patients may suffer several serious complications, including arrhythmia [1-3]. Studies have revealed that 70 % of CAD patients present with symptoms of

arrhythmia, as well as high probability of heart failure and high risk of death. Therefore, it is important to deepen research on treatment modalities for CAD complicated with arrhythmia. Currently, the use of medication is the most frequently-applied strategy for treating CAD complicated with arrhythmias. Although amiodarone enhances myocardial function in patients, it is associated with toxic effects which result in unsatisfactory outcomes [4-7]. Recently, with better understanding of arrhythmia-complicated CAD, studies have shown that atenolol alleviated stress reaction and stabilized cardiac electrophysiology in patients [8-10]. Therefore, the present study was carried out to investigate the effectiveness of combined use of amiodarone and atenolol in the treatment of CAD complicated with arrhythmia. A total of 120 CAD patients with arrhythmia in our hospital were selected for the study.

METHODS

General patient information

The subjects were one hundred and twenty patients with CAD complicated with arrhythmia who were admitted to our hospital for two years. They were equally assigned to groups A and B, between which general information were comparable. This research received approval from the ethical body of First People's Hospital of Shuangliu District (approval no. 20181142), and was carried out in line with the guidelines of the amended Helsinki Declaration [11]. Signed informed consent was received from the subjects or close relatives.

Inclusion criteria

The included patients were subjects diagnosed with arrhythmia-complicated CHD who satisfied the 2015 version of *Guidelines for Diagnosis and Treatment of Coronary Heart Disease* [12]; and those who did not have serious complications [13].

Exclusion criteria

Subjects who had mental challenges, those with communication problems, patients who had organic ailments in addition to CHD [14], subjects allergic to drugs involved in this study, and pregnant patients were excluded [15].

Drug administration

The patients took 150 mg of amiodarone hydrochloride tablets (SANOFI Pharmaceutical Co. Ltd., Hangzhou; NMPA Approval No. H19993254). three times per day for 14 days. Based on patients' conditions, the dose was adjusted to 150 - 250 mg/day, or 100 mg in some cases, as maintenance therapy. Atenolol therapy was administered for group A for 90 days in total. Patients took 6 mg of atenolol (Beijing Yimin Pharmaceutical Co.) two times daily. During the medication, changes in vital signs in both groups were monitored continuously, and the dose was adjusted according to status of recovery.

Evaluation of indices

Heart function indicators

Before and after treatment, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) were measured and compared between the two groups of patients.

Inflammatory factors

Following overnight fast, serum samples obtained from pre- and post-treatment venous blood specimens were assayed for CD40L, TNF- α and IL-6 levels using ELISA kits.

Blood pressure

The blood pressure of each patient in both groups was measured before and after treatment.

Change in heart rate

Pre- and post-treatment values of heart rate were measured and compared between the two groups.

Table 1: Comparison of patients' general information

Group	Male /Female	Age (years)		Course of disease (years)		BMI (kg/m ²)		Heart function grade		
		Range	Mean age	Range	Mean course	Range	Mean BMI	II	III	IV
A	32/28	45-68	54.12±5.65	1-4	2.62±0.71	18-32	22.45±3.12	11	30	19
B	33/27	45-68	55.68±5.12	1-4	2.63±0.72	18-31	22.61±3.32	10	30	20
t/ χ^2	0.034		1.585		0.077		0.272	0.058	0.000	0.038
P	0.855		0.116		0.939		0.786	0.810	1.000	0.845

Incidence of adverse side effects

Patients with toxic side effects were enumerated. The adverse side effects comprised gastrointestinal reactions, allergic reactions, sinus rhythm and hypotension.

Overall treatment effectiveness

Treatment effectiveness was classified as markedly effective, effective or ineffective. If symptoms such as chest distress and arrhythmia disappeared totally, and the EGG result was normal, the treatment was regarded as markedly effective. If the symptoms were alleviated and the heart function was improved, the treatment was deemed effective. However, if none of the above criteria was met, the treatment was ineffective. Total effectiveness was calculated as shown in Eq 1.

$$TE = \{(ME + E)/T\}100 \dots\dots\dots (1)$$

where TE = total effectiveness, ME = number of markedly effective cases; E = number of effective cases, and T = total number of cases.

Statistical analysis

The SPSS version 20.0 software was used to process data, while GraphPad Prism 7 was used for plotting graphs. The χ^2 test and Student's *t*-test were used for comparison of counting and measurement data, respectively. Values of *p* < 0.05 indicated statistical significance of differences.

RESULTS

Levels of heart function indicators

Post-treatment heart function indicators were markedly improved in group A, relative to group B (*p* < 0.001).

Table 2: Levels of heart function indicators in both groups (mean ± SD)

Group	LVEF (%)		LVESD (mm)		LVEDD (mm)	
	Before	After	Before	After	Before	After
A	33.65±2.65	54.12±2.58	59.56±3.45	50.65±3.54	66.59±2.57	52.11±2.10
B	34.10±2.54	41.11±5.68	59.98±3.26	56.11±3.68	66.98±2.54	60.21±2.65
T	0.950	16.154	0.685	8.283	0.836	18.556
P-value	0.344	0.000	0.494	0.000	0.405	0.000

Table 3: Comparison of levels of inflammatory factors (mean ± SD)

Group	CD40L (ng/mL)		TNF-α (pg/mL)		IL-6 (pg/mL)	
	Before	After	Before	After	Before	After
A	4.34±1.21	1.88±0.87	28.65±1.65	10.68±3.54	18.98±3.54	3.41±1.10
B	4.41±1.20	2.85±0.98	28.98±1.26	20.15±5.65	19.10±3.24	9.50±2.11
t	0.318	5.734	1.231	11.002	0.194	19.825
P	0.751	0.000	0.221	0.000	0.847	0.000

Levels of pro-inflammatory factors

Post-treatment levels of CD40L, TNF-α and IL-6 were markedly reduced in group A, relative to group B (*p* < 0.001).

Blood pressure levels

Figure 1 shows that after treatment, there was markedly lower blood pressure in group A patients than in patients in group B.

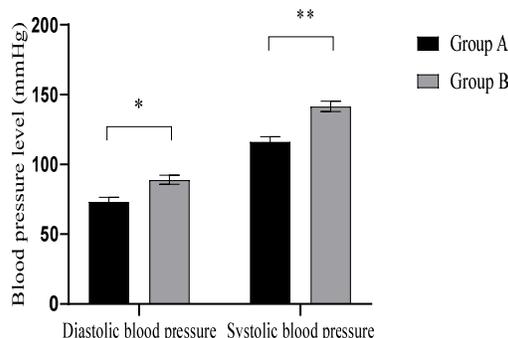


Figure 1: Comparison of blood pressure levels after treatment (mean ± SD, mmHg). **P* < 0.001, diastolic blood pressure of group A after treatment vs diastolic blood pressure of group B after treatment; ***p* < 0.001, systolic blood pressure of group A after treatment vs systolic blood pressure of group B after treatment

Changes in heart rate

After treatment, the heart rate was markedly lower in group A than in group B (*p* < 0.001, Figure 2).

Comparison of ARR

No statistically significant difference was observed in ARR when patients in groups A and B were compared. These data are presented in Table 4.

Overall treatment effectiveness

As shown in Table 5, treatment effectiveness was markedly better in group A than in group B.

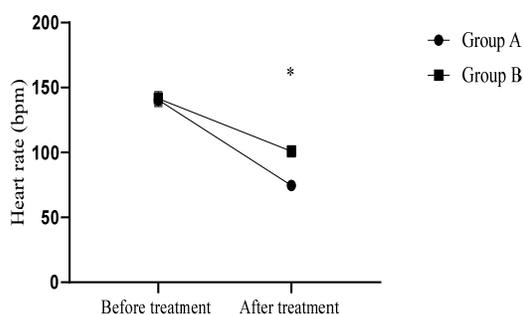


Figure 2: Comparison of heart rate changes (mean \pm SD, bpm). * $P < 0.001$, heart rate of group A after treatment vs heart rate of group B after treatment

DISCUSSION

In clinical practice, the symptoms of CAD in patients are usually alleviated through medication.

Amiodarone, a drug for treatment of CAD complicated with arrhythmia, not only enhances myocardial function in patients by blocking potassium channels, but also dilates coronary arteries, thereby optimizing metabolic levels of thyroxine. Clinical practice has shown that amiodarone is effective in mitigating angina symptoms in patients with CAD complicated with arrhythmias. Moreover, amiodarone slows down the rate of disease progression. However, the required dose of amiodarone is large, and long-term use leads to multiple toxic effects in patients. The ARR of group B was 8.3 %, which was lower than the general level, possibly due to the low dose of amiodarone used. Therefore, attention should be paid to the dose of

amiodarone used in clinics so as to avoid severe toxicity while enhancing therapeutic effect.

With increasing awareness of CAD complicated with arrhythmia, some researchers have found that atenolol can also be used in the treatment of the disease. Atenolol has high cardioselectivity, and it blocks potassium channels in cardiac muscle cells, resulting in elevated cardiac electrophysiology in patients. The addition of atenolol to the amiodarone regimen suppressed its toxicity to some extent and reduced the likelihood of patients experiencing myocardial toxicity. Thus, the ARR was slightly reduced in group A patients. In addition, atenolol delays the heart rate of patients, lowers the possibility of exposure to stress stimulation, and stabilizes cardiac electrophysiology [16]. Therefore, the blood pressure and heart rate after treatment were markedly reduced in group A, when compared to group B, thereby showing the high therapeutic value of atenolol.

Recent study results have shown that inflammatory factors are closely related to the occurrence of CAD because they open potassium channels, cause imbalance in myocardial potential, and eventually trigger arrhythmia. This study has demonstrated that post-treatment levels CD40L, TNF- α and IL-6 were markedly lower in group A than in group B. It has been reported that CD40L is an important indicator for assessing the prognosis of CAD patients: it could initiate arterial thrombus, cause myocardial hypoxia and ischemia, and ultimately lead to arrhythmia [17]. In addition to CD40L, TNF- α modulates blood lipid metabolism in patients by inducing vascular endothelial cells, which in turn reduces vasodilatation capacity and decreases cardiac function. Moreover, TNF- α affected the expression of immune factors in

Table 4: Comparison of ARR {n (%)}

Group	n	Gastrointestinal reaction	Allergic reaction	Sinus rhythm	Hypotension
A	60	1(1.7)	1(1.7)	1(1.7)	1(1.7)
B	60	1(1.7)	1(1.7)	2(3.3)	1(1.7)
χ^2		0.000	0.000	0.342	0.000
P-value		1.000	1.000	0.559	1.000

Table 5: Comparison of treatment effective rates {n (%)}

Group	n	Markedly effective	Effective	Ineffective	Total effective rate
A	60	30 (50.0)	26 (43.3)	4 (6.7)	56 (93.3)
B	60	20 (33.3)	25 (41.7)	15 (25.0)	45 (75.0)
χ^2		3.429	0.034	7.566	7.566
P		0.064	0.853	0.006	0.006

patients, and there was a correlation between TNF- α and IL-6. Therefore, TNF- α and IL-6 could be used as indexes of outcome of CAD complicated with arrhythmia. After treatment, the indicators were improved in both groups, but group A had better levels of inflammatory factors. This is because atenolol suppressed the expressions of these proteins and reduced the likelihood of thrombosis, thereby optimizing overall outcomes. This study also showed better post-treatment heart function indicators in group A patients than in patients in group B. This suggests that the combined treatment improved heart function indicators, and produced a better treatment effectiveness than when amiodarone was used alone. This is in agreement with a previous report [18].

CONCLUSION

Combined use of amiodarone and atenolol effectively improves heart function indicators, reduce levels of inflammatory factors, normalize the blood pressure and heart rate, and lower ARR in patients with CAD complicated with arrhythmia. However, further clinical trials on the combined therapy are required prior to its application in clinical practice.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Dejin Li and Anfang Chen conceived and designed the study, and drafted the manuscript. Chengyue Tang, Liqiong Xu, Xin Jin, Jianli Wu and Jiuju Ran collected, analyzed and interpreted the experimental data. Dejin Li, Chengyue Tang and Liqiong Xu revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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