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Original Research Article

Atorvastatin/trimetazidine combination therapy in patients with chronic cardiac failure

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Abstract

Purpose: *To explore the outcomes and safety of atorvastatin/trimetazidine combination therapy in patients with chronic cardiac failure.*
Methods: *A total of 144 patients with chronic cardiac failure were divided into test group (n = 72) and control group (n = 72). In addition to conventional anti-heart failure treatment, all patients in the two groups received atorvastatin, and those in the test group received, in addition, trimetazidine, for 28 days. The clinical outcomes and safety profiles of the two groups were determined and compared.*
Results: *Compared with pre-treatment stage, the left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), left ventricular early diastolic peak velocity (E), as well as E to left ventricular end diastolic peak velocity (A) ratio (E/A ratio) for both groups improved significantly after treatment, while A and serum brain natriuretic peptide (BNP) level decreased significantly (all $p < 0.05$). Moreover, compared with control group, the increases in LVEF, LVFS, E, and E/A ratio of the test group were greater (42.81 ± 3.04 vs 47.97 ± 4.22 %; 31.01 ± 3.19 vs 36.02 ± 3.31 %; 57.44 ± 5.18 vs 61.93 ± 5.42 cm/s; 1.02 ± 0.06 vs 1.19 ± 0.11, respectively), while the decreases in A and BNP level were greater (both $p < 0.05$) (57.34 ± 4.70 vs 52.37 ± 3.17 cm/s; 589.73 ± 41.19 vs 498.65 ± 30.89 pg/mL, respectively). Therapeutic outcomes were significantly better in the test group than in control group ($p < 0.05$). Blood pressure, heart rate and serum levels of alanine transaminase (ALT) and creatinine did not differ significantly between the two groups ($p > 0.05$), but serum potassium and aspartate amino transferase levels were lower in the test group than in the control group ($p < 0.05$).*
Conclusion: *Atorvastatin combined with trimetazidine effectively reduces BNP level and improves cardiac function in patients with cardiac failure. The safety profile of the combined therapy is good.*

Keywords: *Atorvastatin, Trimetazidine, Chronic cardiac failure, Combination therapy, Biochemical profile*

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INTRODUCTION

Chronic cardiac failure refers to cardiac systolic and/or diastolic functional insufficiency caused by various heart diseases; the cardiac output does not satisfy the metabolic demand. The condition manifests as blood stasis in the systemic and/or pulmonary circulation.

Chronic cardiac failure develops during the terminal stage of heart disease and is associated with high-level morbidity and mortality [1,2]. The incidence of chronic cardiac failure has increased annually, and the fatality rate over the last five years has attained 50 % [3]. Such patients are unable to output all returning blood, reducing the

stroke volume, causing pulmonary venous stasis and even acute pulmonary oedema. The combination of oxygen uptake, bed rest, diuresis, and heart strengthening with prescription of β-receptor inhibitors is the major therapeutic modality, but it is difficult to slow ventricular remodelling.

Currently, many drugs are used to treat chronic cardiac failure, but their effects vary. Atorvastatin is an advanced statin that not only reduces the blood lipid level, protects the vessel endothelium, and delays atherosclerosis progression, but it also inhibits ventricular remodelling [4]. Trimetazidine, commonly used to treat angina, improves myocardial energy metabolism and protects both myocardial cells and blood vessel endothelia [5].

The clinical effects of atorvastatin and trimetazidine and their safety profiles have been evaluated separately, but combined therapy has been rarely reported. We explored the outcomes of combined atorvastatin/trimetazidine therapy in patients who also received conventional anti-heart failure treatment; we sought to provide a practical and theoretical basis for clinical combination therapy.

EXPERIMENTAL

A total of 144 patients with chronic cardiac failure who underwent treatment in Taian City Central Hospital from February 2014 to June 2015 were selected. All met the chronic cardiac failure criteria of the New York Heart Association (NYHA). We excluded those who had undergone any other treatment during the prior 3 months and those diagnosed with acute myocardial infarction, a tumor, another organic lesion, hypotension, anaemia, or serum creatinine and potassium levels > 252.2 $\mu mol \cdot L^{-1}$ and > 5.5 $mmol \cdot L^{-1}$, respectively.

All patients were randomly allocated to a test or control group (72 patients/group). The study was approved by the Medical Ethics Committee of Taian City Central Hospital (approval no. TCCH20160301XH) and followed the relevant guidelines of the Declaration of Helsinki [6]. All patients signed informed consent forms.

Treatment method

All patients underwent conventional anti-heart failure treatment including oxygen supplementation, cardiac-strengthening exercises, diuresis, and prescription of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. All patients also took atorvastatin (Lipitor; Pfizer Inc., New York, USA; batch no.: J20120050) (10 mg daily for 28 days), and patients in the test group took additional trimetazidine (Vasorel; Servier Pharmaceutical Co., Ltd., Tianjin, China; batch no. H20055465) (20 mg three times daily for 28 days).

Observation indicators

Cardiac function-associated indicators and brain natriuretic peptide (BNP) levels were compared before and after treatment. Cardiac functions including the left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), left ventricular early diastolic peak velocity (E), left ventricular end diastolic peak velocity (A), and E/A ratio were examined via cardiac colour ultrasonography. Five millilitres of elbow venous blood were collected from each subject after fasting and 20 min of rest, both before treatment and 28 days after treatment commenced. The blood samples were centrifuged at 1,000 revolutions/min for 5 min to separate sera, which were stored at −20 ^{o}C. Serum BNP concentrations were determined using an enzyme-linked immunosorbent assay kit (Wuhan EIAab Science and Technology Co., Ltd., Wuhan, China), following the manufacturer's instructions. The positive threshold of BNP concentration was set as 100 ng/L.

The clinical outcomes and safety profiles of the two groups were compared using the NYHA criteria. Treatment was considered significantly effective if cardiac function improved by two or more grades; palpitations, anhelation, or dyspnoea disappeared or were significantly relieved; lung rales or crepitations disappeared or were reduced; heart rate normalized; and/or the electrocardiogram findings improved. Treatment was considered effective if cardiac function improved by one or more grades and/or if palpitations, shortness of breath, or dyspnoea were relieved or lung rales reduced. Treatment was considered ineffective if cardiac function did not improve by one grade, disease became aggravated, or the patient died. Overall effectiveness was computed as in Eq 1.

$$D\ (\%) = \{(a = b)/n\}100 \quad \text{..... (1)}$$

where D is the overall effectiveness, *a* the number of cases for whom treatment was significantly effective, b the number of cases for whom treatment was effective, and *n* the total number of patients.

To evaluate the safety of treatment, we monitored blood pressure, heart rate, and serum potassium, alanine transaminase (ALT), aspartate amino transferase (AST), and creatinine levels.

Statistical analysis

A database was established using SPSS ver. 21.0 software; all data were expressed as mean ± standard deviations (SD). The paired t-test was used to compare data obtained before and after treatment, and between-group comparisons were made using the two-sample t-test. Discrete and categorical data were expressed as percentages and compared using the chi-squared test. A *p*-value < 0.05 was considered to reflect statistical significance.

RESULTS

Demographic data

The demographic features of the two groups did not differ significantly (all $p > 0.05$, Table 1); therefore, the groups were comparable.

Cardiac functions

The cardiac function indicators prior to treatment did not differ significantly between the groups (all $p > 0.05$). Compared with before treatment, the LVEF, LVFS, E, and E/A ratio of both groups increased significantly, and A decreased significantly, after treatment (all $p < 0.05$). Compared with the control group, the improvements in the LVEF, LVFS, E, and E/A ratio of the test group were more obvious, as was the decrease in A (all $p < 0.05$, Table 2).

BNP level

Before treatment, the BNP levels of the test and control groups were 834.13 ± 22.46 and 832.87 ± 23.37 pg/mL, respectively; the difference was not significant (t = 0.032, $p = 0.973$). The BNP levels of the test and control groups decreased significantly after treatment (test group: 834.13 ± 22.46 vs 498.65 ± 30.89 pg/mL, t = 69.763, $p = 0.000$; control group: 832.87 ± 23.37 vs 589.73 ± 41.19 pg/mL), t = 38.875, $p = 0.000$, respectively). The decrease in the BNP level was greater in the test group (498.65 ± 30.89 pg/mL) than the control group (589.73 ± 41.19 pg/mL, t = 13.793, $p = 0.000$).

Effectiveness of the drug combination

The overall effectiveness in the test group was 87.5 % (63/72), thus greatly superior to that in the control group (65.3 %, 47/72; $X^2 = 14.941$, $p < 0.05$, Figure 1).

Table 1: Demographic data of the two groups (n = 72 in each group)

Group		Test group	Control group	X^2/t	*p*-value
Gender (male/female)		41/31	44/28	0.045	>0.05
Average age (years)		60.8±8.7	61.2±8.6	0.286	>0.05
Average disease course (years)		5.9±2.6	6.0±2.7	0.187	>0. 05
Underlying disease (n)	Hypertension	40	41	0.108	>0.05
	Coronary heart disease	15	14		
	Rheumatic heart disease	11	9		
	Dilated cardiomyopathy	6	8		
NYHA grade (n)	Grade II	43	42		
	Grade III	16	16	0.104	>0.05
	Grade IV	13	14		

Table 2: Cardiac function indicators in both groups before and after treatment (n = 72 in each group)

Indicator	Test group		Control group	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***
LVEF (%)	36.47±2.83	47. 97±4.22$^{*\#}$	36.50±2.82	42.81±3.04*
LVFS (%)	22.44±2.12	36.02±3.31$^{*\#}$	22.40±2.09	31.01±3.19*
E (cm/s)	50.78±4.57	61.93±5.42$^{*\#}$	50.81±4.60	57.44±5.18*
A (cm/s)	63.39±4.17	52.37±3.17$^{*\#}$	63.42±4.14	57.34±4.70*
E/A	0.81±0.09	1.19±0.11$^{*\#}$	0.79±0.07	1.02±0.06*

***Note*:** $^{*}P < 0.05$ compared with before treatment; $^{\#}p < 0.05$ compared with control group

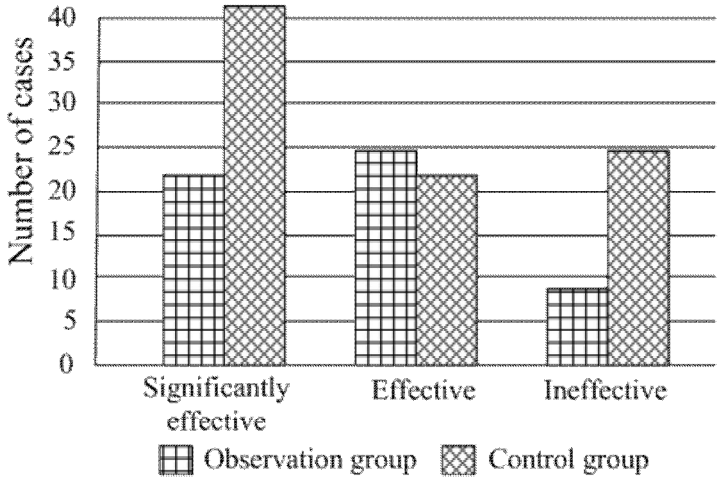

Figure 1: Cardiac function before and after treatment

Table 3: Medication safety in the two groups (n = 72 in each group)

Parameter		Test group	Control group	t	*P*-value
Blood pressure	*Systolic*	115.5±15.2	121.5±13.6	1.921	0.059
(mmHg)	*Diastolic*	77.3±13.7	79.8±13.7	0.872	0.382
Heart rate (beats/min)		76.4±7.1	76.2±6.7	0.142	0.894
Serum potassium (mmol/L)		4.26±0.48	4.86±0.44	6.783	0.000
AST(U/L)		22.92±7.05	26.46±8.24	2.219	0.034
ALT(U/L)		24.98±7.51	28.23±8.66	1.907	0.064
Creatinine (μmol/L)		82.23±24.51	93.05±28.75	1.954	0.054

Medication safety

The blood pressure, heart rate, and ALT and creatinine levels did not differ significantly between the two groups (all $p > 0.05$). The serum potassium and AST levels of the test group were significantly lower than those of the control group (both $p < 0.05$, Table 3). No adverse reaction was noted during treatment in either group.

DISCUSSION

Chronic cardiac failure, the terminal stage of many types of heart disease, is common and associated with complex clinical symptoms; the 5-year survival rate of patients with chronic cardiac failure is close to that of patients with malignant tumours. The condition severely compromises physical and psychological health [7].

Continual developments in cellular and molecular cardiology have allowed researchers to delve more deeply into the pathogenesis of chronic cardiac failure; many useful drugs have been developed [8,9]. The principal pathogenesis is activation of the renin-angiotensin and adrenergic system (RAAS). Such activation triggers a vicious cycle. Increased noradrenaline secretion caused by an increase in sympathetic excitability is also involved in the pathogenesis of chronic cardiac failure; the two factors interact such that continuous high-level sympathetic activation triggers excess renin secretion, exerting adverse effects on the heart [10-12]. In addition, RAAS activation enhances sympathetic excitability, aggravating the disease [13]. Therefore, the key goal of clinical treatment is to inhibit myocardial remodelling and excessive activation of the neuroendocrine system.

The control group received conventional treatment in combination with atorvastatin, and the test group received additional trimetazidine. Atorvastatin, an inhibitor of HMG-CoA reductase, reduces cholesterol and low-density lipoprotein (LDL) levels by inhibiting cholesterol synthesis [14] and promoting LDL catabolism, thus reducing plasma lipid levels. Atorvastatin also effectively reduces the level of C-reactive protein, which promotes atherosclerosis development. The drug reduces the death rate and delays atherosclerosis progression [15]. Atorvastatin also regulates the immune system, reduces inflammatory reactions, and protects blood vessel endothelia, in turn protecting the myocardium and inhibiting myocardial remodelling [16]. Trimetazidine selectively inhibits the mitochondrial long-chain 3-keto-acyl-

coenzyme athiolase but has no effect on haemodynamics in general or myocardial oxygen consumption in particular. Grube et al. [17] found that trimetazidine improved cardiac function and relieved myocardial ischaemia by partially blocking the β-oxidation of free fatty acids; the preferred myocardial energy substrate changed from fatty acids to glucose, which is associated with increased ATP production using less oxygen. Trimetazidine has shown great promise. Many clinical trials have found that the drug improves the LVEF, reduces the ventricular volume, and enhances quality of life [18,19]. Trimetazidine improved exercise tolerance, reduced the BNP level, and preserved cardiac function in patients with coronary heart disease [20].

This study found that cardiac function indicators and the BNP levels of the two groups improved significantly after treatment; this was especially true for the test group ($p < 0.05$). This indicated that combined atorvastatin and trimetazidine was useful for treating chronic cardiac failure associated with an elevated cardiac volume load, which in turn, increases ventricular pressure and ventricular wall tension and stimulates the synthesis of ventricular myocytes and BNP secretion. BNP triggers diuresis and natriuresis and inhibits the RAAS. Recent studies have suggested that monitoring the BNP level could aid in the early diagnosis of chronic cardiac failure and serve as an indicator of the curative effects of treatment and prognosis. Patients with more serious disease had higher BNP levels [21].

In the present study, the decrease in the BNP level in the test group was more striking than that in the control group, indicating that the atorvastatin/trimetazidine combination was more effective than atorvastatin alone. The overall effectiveness rate in the test group was 87.5 %, much higher than that (65.3 %) in the control group ($p < 0.05$). Combination therapy was safe, as reflected by the absence of any effects on the serum potassium level, blood pressure, or renal or hepatic function.

Limitations of the study

The sample size was small; further studies involving much larger samples are required. The prognosis of patients treated with the atorvastatin/trimetazidine combination who were discharged after improved health status has not been adequately assessed in China. Had these cases been followed-up, more useful data would have been obtained.

CONCLUSION

The findings indicate that atorvastatin/ trimetazidine combination improves the health conditions of patients, reducing BNP level of patients with chronic cardiac failure, and no medication-associated adverse reactions were reported. Thus, the combination therapy has some clinical potentials.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors 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 them.

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