EFFECT OF IVABRADINE COMBINED WITH METOPROLOL ON SERUM GAL-3, CTNI LEVELS, AND CARDIAC STRUCTURE AND FUNCTION IN PATIENTS WITH CHRONIC HEART FAILURE

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ABSTRACT

Objective: *To explore the effect of ivabradine combined with metoprolol on serum Gal-3 and cTnI levels and cardiac structure and function in patients with chronic heart failure (CHF).*

Methods: *142 CHF patients at our hospital from February 2020 to March 2021 were randomly divided into an observation group (n = 71) and a control group (n = 71). The control group was treated with metoprolol sustained-release tablets, and the observation group was treated with ivabradine on the basis of the control group. The effective rate, the incidence of adverse reactions, the levels of Gal-3, cTnI, and B-type brain natriuretic peptide (BNP), and the improvement of NYHA cardiac function were compared between the two groups before and after treatment.*

Results: *Compared with the total effective rate of 76.06% (54/71) in the control group, the total effective rate of 91.55% (65/71) in the observation group represented a significant increase (P<0.05). Compared with levels prior to treatment, the levels of Gal-3, cTnI, and BNP in the two groups were significantly decreased following treatment (P<0.05); compared with the control group, the levels of Gal-3, cTnI, and BNP in the observation group were significantly decreased (P<0.05). Compared with conditions prior to treatment, LVESD and LVEDd in the two groups were significantly decreased, while LVEF was significantly increased (P<0.05); compared with the control group following treatment, LVESD and LVEDd in the observation group were significantly decreased, while LVEF was significantly increased (P<0.05). Compared with grades prior to treatment, the cardiac function grades of the two groups were significantly improved after treatment (P<0.05); following treatment, the improvement of cardiac function classification in the observation group was more significant (P<0.05). There was no significant difference in the incidence of adverse reactions between the observation group and the control group: 8.45% (6/71) vs 7.04% (5/71) (P>0.05).*

Conclusion: *The effect of ivabradine combined with metoprolol in the treatment of CHF patients is ideal—the combination can significantly improve their cardiac function and reduce the levels of Gal-3, cTnI, and BNP in serum, with high safety and reliability.*

Keywords: *Ivabradine, metoprolol, CHF, Gal-3, cTnI.*

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Introduction

Chronic heart failure (CHF) is the end period of the evolution of many cardiovascular diseases. Its morbidity and fatality rates are at high and rising levels worldwide, which seriously affects the normal patient quality of life[1-2]. Beyond the present drug-based clinical intervention in patients with chronic heart failure, the inclusion of beta blockers can effectively improve clinical manifestations for patients, reduce myocardial remodeling progress, and improve the patient survival rate. Metoprolol is a selective beta 1 receptor blocker which works by blocking the sympathetic nervous excitement; at the same time, it can be involved in controlling beta receptors in the renin-angiotensin system. The effects are ideal[3-4]. However, it has some limitations in clinical application, which may lead to intolerance or contraindications in patients[5]. Therefore, it is particularly important to explore new drugs that can

improve the condition and prognosis of patients with chronic heart failure.

As the first funny current (IF)-specific inhibitor using a sinoatrial node pacing current, ivabradine can effectively reduce patients' sinus rhythm without significant adverse reactions to myocardial contractility or the respiratory tract[6-7]. Galectin-3 (Gal-3) is an indicator closely associated with cardiac remodeling and myocardial fibrosis, and has important value in the assessment of CHF[8]. It has been reported that an increased level of cardiac troponin I (cTnI) is correlated with the severity and clinical prognosis of patients with CHF(9). However, there are few reports on the effects of ivabradine combined with metoprolol treatment on serum Gal 3 and cTn I levels or on cardiac structure and function in CHF patients. Therefore, this study aims to analyze those effects.

Materials and methods

General information

A total of 142 CHF patients admitted to the Department of Cardiology of our hospital between February 2020 and March 2021 were included in this study.

The inclusion criteria were as follows:

• All patients met the diagnostic criteria for CHF as outlined by the Journal of Internal Medicine;

• The course of the disease had advanced for more than six months;

• All participants were over 18 years old; (4) informed consent was obtained from patients or their family members;

• The application was submitted to the Ethics Committee of our hospital and was approved.

Exclusion criteria were as follows:

• Patients with drug allergies related to this study;

• Patients with disease deterioration within the last month;

• Patients who had recently undergone valvular heart surgery;

• Patients deemed at risk of non-response to follow-ups and/or poor compliance;

• Patients with malignant tumors, autoimmune diseases, or nervous system diseases.

The 142 CHF patients selected were divided into an observation group (n=71) and a control group (n=71) according to a random number table method. In the observation group, there were 41 men and 30 women, with an average age of (57.49±3.23) years and an average course of disease of (7.54±1.39) years. In the control group, there were 39 men and 32 women, with an average age of (57.58±3.17) years and an average course of disease of (7.47±1.45) years. A statistical software test determined no significant difference in general data between the two groups (P>0.05).

Methods

The control group was treated with metoprolol sustained-release tablets (specification: 1.25mg/tablet); the initial dose was set at 6.25mg twice a day. Dosage was then adjusted according to the patient's tolerance, with a maximum dose of 50mg/time, twice a day. The observation group was additively treated with ivabradine (specification: 5mg/tablet); the initial dose was set at 5mg/time, twice a day, and the dosage was adjusted to 7.5mg according to the patient's treatment condition after continuous treatment for three weeks. If bradycardia occurred, the drug dose could be reduced to 2.5mg/time, twice a day. If the heart rate dropped below 50 beats/min, medication was discontinued. Both groups were treated continuously for three months.

Observation indexes

• Clinical efficacy in the two groups was evaluated. Significant effects were found: sweating, palpitation, and other clinical manifestations disappeared, and the improvement in the New York Heart Association (NYHA) cardiac function grade was ≥2. Efficacy: sweating, palpitation, and other clinical manifestations were significantly improved, and NYHA cardiac function grade I was improved. Ineffective: clinical manifestations and cardiac function grades were not significantly improved. Total effective rate (%) = (significant effect + effective)/total number of cases observed × 100%.

• Fasting venous blood (4mL) was collected in the morning from the two groups both before and after three months of treatment, and the supernatant was extracted after centrifugation to detect the levels of Gal-3 and B-type brain natriuretic peptide (BNP) using ELISA. The serum cTnI content of the two groups was detected using immunochromatography.

• Before and after three months of treatment, the left ventricular end systolic diameter (LVESD) was detected by color Doppler ultrasound (produced by Jiangsu Jiahua Electronic Equipment Co., Ltd.) in the two groups. Left ventricular end diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) were also detected.

• Before and after three months of treatment, NYHA cardiac function grading was observed in the two groups.

• During treatment, the incidence of adverse drug reactions in the two groups was closely monitored.

Statistical analyses

The total effective rate and NYHA cardiac function grade of the two groups were expressed as (n (%)), and a χ^2 test was used for comparison between the two groups. Serum Gal-3, cTnI, BNP contents, and other measurement data from the two groups were expressed as ($\bar{x}\pm s$). Comparison between the two groups was performed by t test. All study data were analyzed using SPSS23.0, and P<0.05 was considered statistically significant.

Results

Comparison of treatment effects between the two groups

Compared with the total effective rate of 76.06% (54/71) in the control group, the total effective rate of 91.55% (65/71) in the observation group represented a significant increase (P<0.05). Data are presented in Table 1.

Group	Significant effect	Effective	Ineffective	Total effective rate
Observation group	43 (60.56)	22 (30.99)	6 (8.45)	65 (91.55)
Control group	35 (49.30)	19 (26.76)	17 (23.94)	54 (76.06)
χ2				6.278
P				*0.012*

Table 1: Comparison of effective rate between the two groups (n (%)).

Comparison of serum Gal-3, cTnI, and BNP contents between the two groups

Compared with levels prior to treatment, the levels of Gal-3, cTnI, and BNP in both groups were significantly decreased after treatment (P<0.05). Furthermore, compared with the control group after treatment, the levels of Gal-3, cTnI. and BNP in the observation group were significantly decreased (P<0.05). Data are shown in Table 2.

Comparison of cardiac function-related indexes between the two groups

Compared with conditions prior to treatment, LVESD and LVEDD in both groups were significantly decreased, while LVEF was significantly increased (P<0.05). Furthermore, compared with the control group after treatment, LVESD and LVEDD in the observation group were significantly decreased, and LVEF was significantly increased (P<0.05). Data are presented in Table 3.

Group	Time	Gal-3 (μg/mL)	cTnI (ng/mL)	BNP (pg/mL)
Observation group	Before treatment	27.45±4.64	0.73±0.07	768.93±77.46
	After treatment	11.35±2.76[ab]	0.23±0.03[ab]	260.43±34.64[ab]
Control group	Before treatment	27.98±5.72	0.69±0.09	760.79±76.37
	After treatment	15.64±3.02[a]	0.39±0.06[a]	317.72±35.39[a]

Table 2: Comparison of Gal-3, cTnI, and BNP levels between the two groups ($\bar{x}\pm s$).

Note: Compared with prior to treatment, [a]P<0.05; compared with the control group after treatment, [b]P<0.05.

Group	Time	LVESD (mm)	LVEDD (mm)	LVEF (%)
Observation group	Before treatment	51.52±3.98	64.29±4.55	32.20±3.53
	After treatment	43.64±3.81[ab]	45.62±3.74[ab]	52.34±4.73[ab]
Control group	Before treatment	51.43±4.02	64.18±4.49	32.22±4.48
	After treatment	52.95±4.16[a]	54.79±4.34[a]	45.74±3.71[a]

Table 3: Comparison of cardiac function-related indexes between the two groups ($\bar{x}\pm s$).

Note: Compared with prior to treatment, [a]P<0.05; compared with the control group after treatment, [b]P<0.05.

Comparison of cardiac function grading between the two groups

Compared with grades prior to treatment, cardiac function grades in both groups were significantly improved after treatment (P<0.05), although the improvement of cardiac function grading in the observation group was more significant (P<0.05). Data are shown in Table 4.

Group	Time	I grade	II grade	III grade	IV grade
Observation group	Before treatment	0 (0.00)	38 (53.52)	28 (39.44)	5 (7.04)
	After treatment	27 (65.85)[ab]	36 (50.70)[ab]	8 (11.27)[ab]	0 (0.00)[ab]
Control group	Before treatment	0 (0.00)	37 (52.11)	28 (39.44)	6 (8.45)
	After treatment	5 (7.04)[a]	33 (46.48)[a]	30 (46.48)[a]	3 (4.23)[a]

Table 4: Comparison of cardiac function grading between the two groups (n (%)).

Note: Compared with prior to treatment, [a]P<0.05; compared with the control group after treatment, [b]P<0.05.

Comparison of the incidence of adverse reactions between the two groups

Forty-four patients had side effects from the duloxetine (Table 5).

Group	Dizziness/ headache	Flash phenomenon	Body chills	Bradycardia	Fatigue	Incidence
Observation	2 (2.82)	1 (1.41)	2 (2.82)	1 (1.41)	0 (0.00)	6 (8.45)
Control	3 (4.22)	0 (0.00)	0 (0.00)	0 (0.00)	2 (2.82)	5 (7.04)
$\chi 2$						0.098
P						0.755

Table 5: Comparison of incidence of adverse reactions between the two groups (n (%)).

Discussion

CHF manifests as chronic progressive and persistent progress. Once the disease begins, it will induce many rational changes related to heart disease and continuous deterioration of heart function.

Cardiomyopathic remodeling is one of the important links in the pathogenesis of CHF, which includes two primary pathologic links:

• Apoptosis, death, and cardiomyocyte decline[10];

• Abnormal activation of the neuroendocrine system, leading to a series of pathophysiological changes.

The mechanism of action is mainly realized through activation of the renin-angiotensin-aldosterone system and abnormal sympathetic nerve excitation[11].Therefore, the prevention and treatment of CHF can be achieved by cutting off the cardiomyopathic rational reconstruction of the two disease pathways.

Metoprolol can play a protective role for the heart and improve myocardial remodeling, which has positive significance for the treatment of CHF patients[12]. Ivabradine can participate in the control of fatty acid and glucose metabolism in patients, relieving the damage of myocardial cells caused by myocardial ischemia and hypoxia, and can play a protective role for myocardial cells. In addition, ivabradine can participate in the regulation of cardiomyocyte acidosis induced by ischemia and hypoxia, and can block myocardial remodeling and changes in cardiac structure and function[13]. The results of this study showed that the total effective rate of the observation group was 91.55% (65/71), which was significantly higher than that of the control group (76.06%, 54/71). This suggests that the effect of ivabradine combined with metoprolol is better than that of metoprolol alone.

Gal-3 can be expressed in many tissues and organs of the body, leading to the formation of serum Gal-3 without specific conditions. Therefore, serum Gal-3 has been used as an important indicator to evaluate the condition of CHF patients both in China and abroad[14]. CtnI is an important marker to evaluate the degree of myocardial injury in patients with CHF, and the increase of its content in serum suggests that patients may have some degree of myocardial injury or necrosis[15]. BNP can diuretic sodium, dilate blood vessels, and block the release of aldosterone, and it can participate in the control of cardiac function. In recent years, and with the deepening of research on BNP, it has been used to evaluate the severity of CHF, clinical treatment effect, and prognosis[16]. The results of this study showed that, compared with the control group following treatment, the levels of Gal-3, cTnI, and BNP in the observation group were significantly reduced.

These results suggest that ivabradine combined with metoprolol can significantly reduce serum levels of Gal-3, cTnI, and BNP in CHF patients, which may be due to the fact that ivabradine can block the function of angiotensin II and decrease the level of Gal-3, thereby increasing the release of bradykinin and further promoting the release of serum soluble ST2 from vascular endothelium. The imbalance of serum soluble ST2 and Gal-3 content was reversed, which was beneficial for restoring the function of serum fibrinolysis system. The decrease of BNP may be due to the relative balance between the production and scavenging of oxygen free radicals in the body, which is conducive to the improvement of the centrifuge destruction caused by inflammation and lipid peroxidation reaction, and thus plays a protective role for the myocardium. In addition, the decrease of BNP content may be due to the fact that ivabradine can block the release of pro-brain natriuretic peptide from cardiomyocytes, which can significantly alleviate myocardial ischemia and block myocardial remodeling.

Compared with the control group following treatment, LVESD and LVEDD in the observation group were significantly decreased, LVEF was significantly increased, and the improvement of cardiac function grading was more significant. These results suggest that ivabradine combined with metoprolol can effectively improve cardiac function and play a protective role in patients with CHF, which may be due to the fact that ivabradine can block myocardial remodeling without affecting hemodynamics. In addition, the drug can also participate in the control of the body's neuroendocrine function, improving the damage

caused by inflammatory mediators to cardiac cells, and can ultimately achieve the purpose of improving cardiac function. In this study, we analyzed the incidence of adverse reactions in patients of the two groups, and found that there was no statistical significance in the incidence of adverse reactions between the observation group and the control group. This suggests that ivabradine combined with metoprolol in the treatment of CHF patients is safe and worthy of clinical application.

In conclusion, ivabradine combined with metoprolol can significantly improve cardiac function and reduce serum levels of Gal-3, cTnI, and BNP with high safety and reliability in patients with CHF.

References

1) Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003; 362(9386): 759-66.
2) Ponikowski P, Anker SD, Amadi A, Chua TP, Cerquetani E, et al. Heart rhythms, ventricular arrhythmias, and death in chronic heart failure. J Card Fail 1996; 2(3): 177-83.
3) Hernandez-Montfort Jaime ,Thayer Katherine , Zweck Elric ,Schaeffer August ,Mahr Claudius ,et al. CRT-600.54 Hemometabolic status impacts transitions in chronic heart failure-related shock: Insights from the CSWG registry. JACC Cardiovascular Interventions 2020; 13(4): S61-S61.
4) Liu Q, Huang X, Tian M, Dong X, Kang J, et al. Effectiveness and safety of Xinyin tablet in treatment of chronic heart failure: A protocol of systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2020; 99(51): e23759.
5) Lam PH, Packer M, Fonarow GC, Faselis C, Allman RM, et al. Early Effects of Starting Doses of Enalapril in Patients with Chronic Heart Failure in the SOLVD Treatment Trial. Am J Med 2020; 133(2): e25-e31.
6) Marciszek M, Paterek A, Oknińska M, Mackiewicz U, Mączewski M. Ivabradine is as effective as metoprolol in the prevention of ventricular arrhythmias in acute non-reperfused myocardial infarction in the rat. Sci Rep 2020; 10(1): 15027.
7) Koroma TR, Samura SK, Cheng Y, Tang M. Effect of Ivabradine on Left Ventricular Diastolic Function, Exercise Tolerance and Quality of Life in Patients With Heart Failure: A Systemic Review and Meta-Analysis of Randomized Controlled Trials. Cardiol Res 2020; 11(1): 40-49.
8) Lubrano V, Balzan S. Role of oxidative stress-related biomarkers in heart failure: galectin 3, α1-antitrypsin and LOX-1: new therapeutic perspective? Mol Cell Biochem 2020; 464(1-2): 143-152.
9) Katoh N, Wise BC, Kuo JF. Phosphorylation of cardiac troponin inhibitory subunit (troponin I) and tropomyosin-binding subunit (troponin T) by cardiac phospholipid-sensitive Ca2+-dependent protein kinase. Biochem J 1983; 209(1): 189-95.
10) Ni Y, Deng J, Liu X, Li Q, Zhang J, et al. Echinacoside reverses myocardial remodeling and improves heart function via regulating SIRT1/FOXO3a/MnSOD axis in HF rats induced by isoproterenol. J Cell Mol Med 2021; 25(1): 203-216.
11) Liu F, Liu Y, Zhuang Z, Ma J, Xu X, et al. Beclin1 Haploinsufficiency accentuates second-hand smoke exposure-induced myocardial Remodeling and contractile dysfunction through a STING-mediated mechanism. J Mol Cell Cardiol 2020; 148: 78-88.
12) Vinereanu D, Spinar J, Pathak A, Kozlowski D. Role of Metoprolol Succinate in the Treatment of Heart Failure and Atrial Fibrillation: A Systematic Review. Am J Ther 2020; 27(2): e183-e193.
13) Jin JL, Deng ZT, Lyu RG, Liu XH, Wei JR. [Expression changes of Notch and nuclear factor-κB signaling pathways in the rat heart with myocardial infarction]. Zhonghua Xin Xue Guan Bing Za Zhi 2017; 45(6): 507-512.
14) Pasquini LA. Novel Galectin-3 interactions involved in oligodendroglial differentiation make inroads into therapeutic strategies for demyelinating diseases. Neural Regen Res 2021; 16(2): 289-290.
15) Harjen HJ, Bjelland AA, Harris J, Grøn TK, Anfinsen KP, et al. Ambulatory electrocardiography and serum cardiac troponin I measurement in 21 dogs envenomated by the European adder (Vipera berus). J Vet Intern Med 2020; 34(4): 1369-1378.
16) Wan SH, Torres-Courchoud I, McKie PM, Slusser JP, Redfield MM, et al. Cardiac Versus Renal Response to Volume Expansion in Preclinical Systolic Dysfunction With PDEV Inhibition and BNP. JACC Basic Transl Sci 2019; 4(8): 962-972.

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