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Original Article

Effect of metoprolol combined with sacubitril valsartan in the treatment of elderly patients with severe heart failure

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Abstract: Objective: To investigate the effects of metoprolol combined with sacubitril valsartan in the treatment of elderly patients with severe heart failure. Methods: One hundred and twenty elderly patients with severe heart failure were stochastically fall as observation group and control group, with 60 cases in each group. On the basis of stable standard treatment, the control group received irbesartan and hydrochlorothiazide tablets and the observation group received metoprolol Sacubitril Valsartan Sodium tablets treatment. Related indexes, including cardiac function classification, left ventricular ejection fraction, B-type natriuretic peptide, clinical efficacy and quality of life were compared between the two groups. Results: After treatment, the observation group had much better cardiac function classification, left ventricular ejection fraction and clinical efficacy than the control group ($P<0.05$). Besides, the N-terminal pronatriuretic peptide of the two groups both decreased through the treatment, but the observation group had a more obvious decline than the control group ($P<0.05$); in addition, life quality of patients in the observation group was also obviously better than that of the control group ($P<0.001$). Conclusion: Compared with patients who accepted irbesartan and hydrochlorothiazide treatment in the control group, elderly patients with severe heart failure in the observation group who received metoprolol combined with sacubitril valsartan treatment had effectively improved cardiac function, more significant clinical curative effect, and largely improved quality of life.

Keywords: Elderly patients with severe heart failure, metoprolol combined with sacubitril valsartan, curative effect, heart failure indicators, quality of life

Introduction

As one of the most familiar cardiovascular diseases, heart failure is also the late stage of various types of heart diseases (including cardiomyopathy, coronary heart disease, cardiac valvular diseases), and is mainly manifested in the change of cardiac ejection function and the reconstruction of cardiac structure [1-3]. The rising incidence rate of chronic diseases such as hypertension, diabetes and obesity is also an inducement of the increasing morbidity of heart failure, with the elderly population as the main morbidity crowd [4, 5]. Moreover, the growing aging in China further aggravates the morbidity of heart failure in elderly patients, which not only greatly threatens the health of patients, but also brings great pressure on public health [6, 7].

Cardiac dysfunction is the clinical definition of severe heart failure, accompanied by organ hypoperfusion or congestion. Due to the common basal diseases and severe decline of immune and body functions, heart failure is generally more serious in the elderly than the young individuals. Severe heart failure is commonly found in the elderly with main clinical manifestations such as hemodynamic instability, rapid onset and rapid progress of the disease. Thus, serious adverse consequences will be brought to patients without positive and effective measures [5]. As the preferred department to receive elderly patients with severe heart failure, emergency internal medicine means a lot to the diagnosis and treatment of heart failure [8]. The conventional medical treatment methods such as cardiotonic, diuretic, vasodilator and so on can only alleviate the

clinical symptoms of patients to a certain extent, but are still unable to achieve good therapeutic effect. Metoprolol combined with sacubitril valsartan have been widely used because of their excellent effects on improving cardiac systolic function. However, the present evaluation of their therapeutic effect is mostly limited to a single index (heart failure index or cardiac ejection function) [9, 10]. Based on this, this study analyzed the application effects of metoprolol combined with sacubitril valsartan in elderly patients with severe heart failure, and comprehensively evaluated the clinical effect of this treatment on heart failure (including the subjective and objective indicators of cardiac function evaluation and patient's quality of life), so as to provide theoretical basis for improving patient's quality of life.

Materials and methods

General materials

A total of 120 elderly severe heart failure patients admitted to Sanmen People's Hospital from May 2018 to May 2019 were selected for a prospective study. Following the random number scale, the patients were fall as the observation group and control group, with 60 cases in each group.

Inclusion criteria: 1. Patients were diagnosed following Guidelines for the diagnosis and treatment of severe heart failure, the diagnostic criteria of the American Heart Association [11]. Main criteria include: (1) Hypoperfusion induced by pulmonary/organ hyperemia, edema and hypoperfusion in the resting state; (2) dyspnea and fatigue occurred during static or mild activity, NY grade (grade of New York Heart Association classification) was III-IV; (3) imaging evidence of severe heart failure: One of the following symptoms occurs, such as Ejection fraction (EF) <30%, restrictive mitral flow pattern, pulmonary hypertension and other manifestations. 2. Patients aged 60-80; 3. the cardiac function was classified as grade III-IV. Exclusion criteria: 1. Patients who are allergic or contraindicated to the drugs used in this study; 2. patients with previous history of nervous system diseases; 3. patients with malignant tumor and cachexia; two groups of patients were informed of the study and have signed the consent form. The study was approved by the Ethics Committee of Sanmen People's Hospital.

Methods

The treatment of control group: The control group received routine treatment measures according to the guidelines of acute left heart failure, mainly including: general treatment such as body position (half lying position or end sitting position), oxygen inhalation (peripheral oxygen saturation <90%, conventional oxygen inhalation is not required if there is no hypoxemia), input and output management (ensure negative balance of 1,000-2,000 mL/d) and opioid drugs such as morphine, diuretics, vasodilators, positive muscle strength and other drugs. At the same time, irbesartan hydrochlorothiazide tablets (Dose: 1 tablet per time; once a day by oral, produced by Sanofi Pharmaceutical Co., Ltd., Hangzhou) and metoprolol tablets (12.5-25 mg per time, 2 times/day by oral administration. Adjust the dose after one week but the maximum dose should not exceed 50mg, produced by Zhuhai Congyuan Pharmaceutical Co., Ltd., Guangdong) are taken for partner treatment for one month.

The treatment of the observation group: The patients in the observation group were also stabilized by basic treatment firstly, and then were treated with metoprolol combined with sacubitril valsartan once the condition was stable, mainly including: basic cardiotonic and diuretic therapy combined with sacubitril valsartan (Beijing Novartis Pharmaceutical Co., Ltd., Beijing). The initial dose of Sacubitril Valsartan Sodium tablets was 50 mg/per time, once a day. If the blood pressure was stable, increase additional 50mg every 3 weeks until the target dose was 150-200 mg/time, twice a day (dose: 50 mg, 1 tablet; oral) and metoprolol tablets (12.5-25 mg/time, 2 times/day through oral administration. Adjust the dose after one week but the maximum dose should not exceed 50 mg). After one month of treatment, the indexes of the two groups were monitored.

Outcome measures

Main outcome measures: The clinical effective rate of patients is divided into the following three levels: markedly effective (The symptoms were completely controlled and cardiac function NY grade was improved by at least two grades); effective (The clinical symptoms were relieved obviously, and the NY classification of cardiac function was improved by more than

one grade); invalid (The clinical symptoms were not relieved, and the NY classification of cardiac function did not improve or even worsen). Effective rate = (markedly effective + effective)/total number of people * 100%.

New York Heart Association (NYHA) classification of cardiac function: Grade I: Patients have no excessive fatigue, palpitation and asthma phenomenon in general physical activity; Grade II: The patient's physical activity was mildly limited. No conscious symptom appears at rest. Discomfort such as excessive fatigue, palpitation and asthma could be induced in general physical activity; Grade III: Patient's physical activity is largely limited. No symptom appears at resting state, but physical activity which even less than the general grade can induce excessive fatigue, palpitation and asthma; Grade IV: Patients can not engage in any physical activity. Heart failure symptoms appear in resting state, and are aggravated after physical activity.

Secondary outcome measures: The left ventricular ejection fraction (LVEF) was assessed by the same cardiologist before and after treatment with Doppler ultrasound (The LVEF was compared between the two groups before and after treatment); serum N-terminal pronatriuretic peptide (NT-proBNP) level: 6-8 mL of fasting venous blood was extracted from the two groups before and after treatment. After centrifugation (3,000 rpm) for 10 min, serum (plasma) samples were obtained, and NT-proBNP (using the kit; Shanghai Yubo Company) was detected by fluorescence immunoassay (BioMerieux Vidas, France). SF-36 scoring: The survey consists of the following eight dimensions: general health status, physiological function, social function, emotional function, physical pain, physiological function, mental health and energy [12]. The higher the score is, the better the quality of life is. The higher the score of mental health and energy is, the worse the mental status is.

Statistical analysis

All data were analyzed by SPSS 22.0 software. The measurement data were expressed as mean ± standard deviation ($\bar{x} \pm sd$). Comparison between groups was conducted by independent sample t test, and the intra group comparison was conducted by paired sample t test. The number of cases/percentage (n/%) was used to represent the enumeration data. Chi square test was used to compare the rates between groups, and the paired chi square test was used for the intra group differences before and after treatment. Common chi square test was used among groups, with $\alpha=0.05$ as the test standard. $P<0.05$ means statistically significant difference.

Results

Comparison of baseline data

No significant difference was shown in gender, age, body mass index, previous treatment history, combined diseases (hypertension, hyperlipidemia and diabetes) and course of disease between the two groups ($P>0.05$). Patients in the two groups were comparable. As shown in **Table 1**.

Comparison of the effective rate of clinical treatment

Results showed that the observation group had much higher clinical effective rate than the control group ($P<0.05$), preliminarily proving that metoprolol combined with sacubitril valsartan can improve the clinical therapeutic effect of heart failure. As shown in **Table 2**.

Comparison of cardiac function NY classification, serum NT-proBNP level and LVEF

Results showed that, cardiac function NY grade and left ventricular ejection fraction of both groups were significantly improved after treatment (all $P<0.001$), and serum NT-proBNP level was sharply decreased through the treatment ($P<0.001$). Besides, after the treatment with metoprolol combined with sacubitril valsartan, significant difference was found in these above indexes between the observation group and the control group (all $P<0.05$). As shown in **Table 3**, **Figures 1** and **2**.

Comparison of quality of life scores valued by SF-36 scale after treatment

Results showed that the observation group had higher SF-36 quality of life scores, and lower scores of mental health and energy dimension than the control group (all $P<0.001$), preliminary identifying that quality of life and mental status of patients were both improved to a cer-

Table 1. Comparison of baseline data (n, $\bar{x} \pm sd$)

Groups	Observation group (n=60)	Control group (n=60)	t/χ^2	P
Gender (male/female)	34/26	37/23	0.138	0.710
Age (year)	66.8±5.1	66.1±4.8	0.774	0.440
Hypertension	31	37	0.848	0.357
Hyperlipidemia	21	19	0.038	0.846
Body mass index (kg/m^2)	22.47±2.03	23.08±1.98	1.685	0.095
History of heart failure (Yes/No)	40/20	42/18	0.039	0.084
Diabetes	23	20	0.145	0.703
Course of disease (year)	6.67±2.30	7.32±2.75	1.529	0.129
Medical treatment (cardiotonics/diuretics/vasodilators/others such as myocardial nutrition)	57/58/33/28	55/59/29/25	0.134/1.000/0.300/0.135	0.714/1.000/0.584/0.713

Table 2. Comparison of the effective rate of clinical treatment between the two groups (n/%)

Groups	Clinical efficacy			Effective rate
	Markedly effective	Effective	Invalid	
Control group (n=60)	20 (33.33)	16 (26.67)	24 (40.00)	36/60 (60.00)
Observation group (n=60)	38 (63.33)	10 (16.67)	12 (20.00)	48/60 (80.00)
χ^2		10.971		4.802
P		0.004		0.028

Table 3. Comparison of cardiac function classification between the two groups before and after treatment (n)

Groups	Before treatment				After treatment				χ^2	P
	Grade I	Grade II	Grade III	Grade IV	Grade I	Grade II	Grade III	Grade IV		
Control group (n=60)	0	0	29	31	11	19	17	13	40.494	0.000
Observation group (n=60)	0	0	33	27	15	28	9	8		
χ^2			0.300				5.036			
P			0.584				0.026			

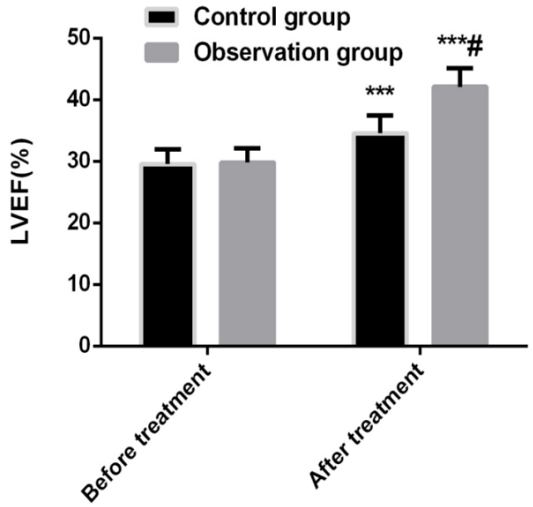

Figure 1. Comparison of LVEF before and after treatment. ***P<0.001, comparison within the same group before treatment; #P<0.05, comparison between the two groups after treatment. LVEF: left ventricular ejection fraction.

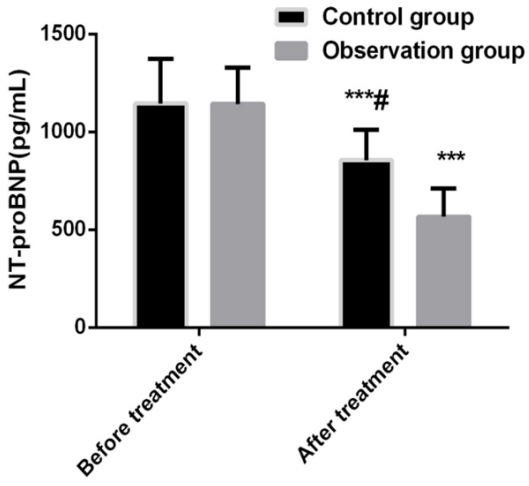

Figure 2. Comparison of NT-proBNP before and after treatment. ***P<0.001, comparion within the same group before treatment; #P<0.05, comparison between the two groups after treatment. NT-proBNP: B-type natriuretic peptide.

tain extent after the treatment of metoprolol combined with sacubitril valsartan. As shown in **Table 4**.

Discussion

Heart failure, also known as cardiac insufficiency, is a common cardiovascular disease in emergency department. At the same time, severe heart failure is the final stage of various heart diseases. At present, the elderly has become the main incidence of severe heart failure due to the particularity of their own body. The main pathophysiological changes of heart failure are coronary heart disease, pulmonary heart disease, long-term hypertension and valvular disease induced decreased myocardial contractility, which bring great harm to systemic circulation [13, 14]. Clinical symptoms of heart failure mainly include respiratory dysfunction, followed by gastrointestinal symptoms (nausea, vomiting, abdominal distension).

At present, main treatment principles of severe heart failure are myocardial oxygen consumption reduction, myocardial metabolism improvement, strengthen of the recovery of myocardial function and stabilizing of myocardial electrical

Table 4. Comparison of SF-36 quality of life scores between the two groups after treatment ($\bar{x} \pm sd$)

Groups	Control group (n=60)	Observation group (n=60)	t	P
General health	66.21±3.92	75.52±2.44	15.731	<0.001
Physiological function	64.89±5.81	77.44±3.48	14.402	<0.001
Social function	74. 54±4.92	83.08±3.77	10.723	<0.001
Emotional function	64.87±5.58	79.56±4.79	15.739	<0.001
Physical pain	65.33±3.28	78. 77±4.10	19.957	<0.001
Physiological function	70.11±3. 78	77.83±4.06	10.946	<0.001
Mental health	77.83±7.96	71.33±6.59	4.922	<0.001
Energy	69.53±7.14	60.68±8.04	6.445	<0.001

activity, thus ultimately improve the cardiac function [15]. Although showed certain clinical effects, these above treatments are still not able to achieve breakthrough treatment expectations. However, studies have shown that on the basis of the guidelines, metoprolol combined with sacubitril valsartan in the treatment of elderly patients with severe heart failure is more effective than the conventional treatment alone. Related potential mechanisms include: As a new neuroendocrine inhibitor, sacubitril valsartan has dual effects of highly selective inhibition of angiotensin receptor and enkephalinase. These two pathways can resist the pathophysiological changes of vasoconstriction, water sodium retention and ventricular remodeling induced by excessive activation of neuroendocrine, thus playing the role of diuretic sodium excretion, vasodilatation, inhibition of sympathetic nerve, oxidative stress and inflammatory response, anti-fibrosis, prevention and reversal of ventricular remodeling. At the same time, metoprolol obtains good clinical effects mainly relying on reversing ventricular remodeling and reducing heart rate [16]. Results of our study showed that cardiac function classification of the two groups was both improved through the treatment, especially in the observation group, which showed that treatment of metoprolol combined with sacubitril valsartan achieved better clinical effect in the treatment of heart failure than the conventional guidelines. Our results are also consistent with previous studies [17].

LVEF is not only the main parameter of cardiac systolic function, but also a reliable index to evaluate the therapeutic effect. Results of our study showed that observation group had much higher LVEF comparing to the control group. The possible mechanism is listed as follows: In the process of reversing myocardial remodeling, metoprolol cooperated with sacubitril valsartan to increase the concentration of regulators such as atrial natriuretic peptide and brain natriuretic peptide. Through natriuretic and diuretic, dilating arteriovenous and reducing cardiac preload and afterload, metoprolol improved the LVEF, which also confirmed the results of previous research [18]. In addition, increased patient's LVEF further elevated cardiac output and improved systemic blood supply, thus finally improving clinical symptoms. The results of our present study also showed that observation group had much better effective rate than the control group, which also confirmed the previous scholars' conclusion that metoprolol combined with sacubitril valsartan can improve the clinical treatment efficiency [19].

Serum NT-proBNP level is the most commonly used biochemical index in laboratory. Besides, it is also the only objective index to evaluate cardiac function at present because change of NT-proBNP level can directly reflect the heart function of patients [20]. In the results of this study, decreased level of NT-proBN in both groups reflected the effectiveness of the treatment firstly, while more obvious decrease in the observation group further confirmed the conclusion that metoprolol combined with sacubitril valsartan can improve the clinical treatment effect of severe heart failure [21].

SF-36 quality of life score is the most reliable index to evaluate the quality of daily life of patients after treatment. Through active and effective cardiac function treatment, the cardiac function and the cardiac function classification of patients were significantly improved, thus the quality of life would also be further improved [22]. Therefore, our study also showed that, the observation group had significantly higher score in quality of life than the control group after treatment, which was consistent with the conclusion of foreign research [23].

This study has deficiencies such as the small number of individuals and the single center study. Therefore, a large sample randomized

controlled study with multiple centers is needed to further confirm the clinical effect of this method. In addition, more clinical targeted exploration of metoprolol combined with sacubitril valsartan is also the focus of our next research. In conclusion, this study confirmed that metoprolol combined with sacubitril valsartan can significantly improve quality of life of patients through improving the cardiac function and NYHA classification and reducing the heart failure index NT-proBNP, which can be used as the preferred treatment for elderly patients with severe heart failure.

Disclosure of conflict of interest

None.

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