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Original Research Article

Effect of sacubitril–valsartan on chronic systolic heart failure and its effect on LVEF, 6-MWT, NT proBNP and NT proBNP/BNP levels

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Abstract

Purpose: *To assess the effect of sacubitril–valsartan on chronic heart failure (CHF).*
Methods: *A total of sixty CHF patients were divided randomly into two groups of thirty patients each (conventional and sacubitril-valsartan groups, respectively). Conventional anti-heart-failure treatment was used in the conventional group, while the sacubitril–valsartan group received sacubitril–valsartan (25 mg) taken orally, twice daily, followed by up-titration to 100 mg, twice daily. After 3 months of treatment, the six-minute walking test (6-MWT), left ventricular ejection fraction (LVEF) scores, left ventricular end-diastolic diameters, serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and NT-proBNP/brain natriuretic peptide (BNP) levels, treatment efficacy, and adverse cardiovascular events were evaluated.*
Results: *After three months of treatment, the level of serum NT-proBNP and NT-proBNP/BNP in the sacubitril–valsartan group was lower, while the levels of LVEF and 6-MWT were higher ($p < 0.05$), compared with the conventional group. Sacubitril-valsartan treatment had a better therapeutic effect than the conventional treatment, while readmission rate for heart failure was lower in the sacubitril-valsartan treatment group ($p < 0.05$). Both LVEF and 6-MWT values had significantly negative correlation with NT-proBNP/BNP ratio.*
Conclusions: *The efficacy of sacubitril-valsartan in the treatment of CHF is significant and improves the short-term prognosis of patients. These findings will require validation in large multicentre trials and over a longer duration of study.*

Keywords: *Chronic heart failure, Sacubitril–valsartan, NT-proBNP/BNP ratio, Cardiac function*

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INTRODUCTION

Chronic systolic heart failure (CHF) is due to myocardial infarction, hemodynamic overload, cardiomyopathy, and inflammation caused by myocardial damage, which will result in varying degrees of changes to the structure or function of the myocardium, causing ventricular pumping or filling dysfunctions [1]. The etiology of chronic systolic heart failure is complex, but it is generally considered to be related to heart disease, acute severe myocarditis, dilated

cardiomyopathy, clinical manifestations of dyspnea, fatigue, and fluid retention [2]. At present, for CHF patients, clinicians often use the combination of various drugs to treat patients. After many years of clinical drug improvement and combined use of multiple drugs, the five-year morbidity and mortality of CHF is still more than 50 %, so there is still a great need for improved therapeutic drugs for CHF [3]. Sacubitril–valsartan is a novel anti-heart-failure drug that inhibits angiotensin receptors and neprilysin, and it also has diuretic, vasodilator, anti-hypertensive, and reverse ventricular remodeling effects [4], which can further improve the prognosis of CHF compared with ACEI/ARB drugs. Left ventricular ejection fraction (LVEF) is one of the diagnostic indices to evaluate heart failure and is used to evaluate the ejection capacity of the left ventricle [5]. The 6-MWT indirectly reflects the severity of heart failure in patients by assessing their exercise tolerance [6]. Many studies have proved that NT-proBNP/BNP is an important indicator in the treatment guidelines for CHF patients [7]. Brain natriuretic peptide (BNP) is positively correlated with the degree of heart failure, which is widely used in the diagnosis and prognostic evaluation of the condition [8]. However, in China, there are few reports about the ratio of NT-proBNP/BNP used to evaluate cardiac function and prognosis of CHF patients. This study aimed to investigate the effect of sacubitril–valsartan on chronic systolic heart failure and its effect on levels of LVEF, 6-MWT, and other indicators ratio.

METHODS

Subjects

This study included 60 patients with CHF in the First Affiliated Hospital of Anhui Medical University, from November 2018 to September 2019. They were randomly divided into two equal groups of 30 patients each. One group received conventional treatment, while the other group received sacubitril–valsartan treatment. This study was approved by the Ethics Committee of Binhu Hospital, Hefei and executed in line with the guidelines of Declaration of Helsinki [9]. All patients and their families who participated in this study were informed about the study and signed a consent form agreeing to the conduct of the study.

Inclusion criteria

Patients diagnosed with CHF in line with 2018 China Heart Failure Diagnosis and Treatment Guidelines, patients with definite left ventricular systolic dysfunction, consistent with the New York Heart Association's functional class II–IV and echocardiographic confirmation of LVEF score < 50 % and patients > 40 years of age were included.

Exclusion criteria

Patients with blood pressure < 90/60 mmHg, blood potassium > 5.5 mmol/L, acute coronary syndrome, a history of primary or hereditary angioedema, severe hepatic and renal dysfunction, combined malignancies, hematologic diseases, acute infectious diseases, and psychiatric diseases, as well as pregnant patients were excluded from the study.

Treatments

Conventional treatment included routine anti-heart failure drugs (ARBs, ACEIs, β-receptor blockers, and aldosterone receptor antagonists), rest, and salt and water restriction. The second treatment group was treated with sacubitril–valsartan sodium (Beijing Novartis Pharmaceutical Co. Ltd) in addition to the above conventional treatment. The initial dose of sacubitril–valsartan was 25 mg, which was taken orally twice a day. As tolerance grew, this was increased gradually over one week to 100 mg, which was also taken orally twice a day. If the patient had previously taken an ACEI or ARB, the ACEI was discontinued for at least 36 h for drug washout before administering sacubitril–valsartan. Patients in the two groups were treated continuously for three months, and the doses were adjusted according to their physical indicators.

Evaluation of parameters/indices

General indices

The 6-MWT was performed 24 h after admission and repeated after three months.

Biochemical parameters

After three months, venous blood was recollected and Plasma BNP/NT-proBNP levels were measured and NT-proBNP was determined by electrochemical luminescence immunoassay, using the Roche Elecsys ®NT-proBNP (Roche Diagnostics GmbH). The B-type natriuretic peptide was determined by Biosite Triage® assay (Biosite, San Diego, CA).

Echocardiography

Echocardiography was completed within 24 h after admission, LVEF and LVEDD were

measured and echocardiography was repeated after three months.

Clinical efficacy

Getting basic control of heart failure or improving heart function by more than two grades was deemed significantly effective, an improvement in cardiac function by one grade but less than two grades after treatment was deemed effective and a deterioration in cardiac function was considered as deterioration. Treatment efficacy (E) was determined using Eq 1.

$$E = (N/60)100 \quad \ldots\ldots\ldots\ldots (1)$$

where N = Number of effective and significantly effective cases [5].

Adverse cardiovascular events

This was the number of readmissions and deaths due to heart failure within three months.

Statistical analysis

Data analysis was conducted using SPSS 26.0 (IBM) software. Measurement data were presented as mean ± standard deviation (SD) and a two-sample independent t-test was used for comparisons. Enumeration data were presented as numbers and percentages (n and %), while Chi-squared test (χ^2) was used for comparisons. Association of NT-proBNP/BNP with 6-MWT and LVEF values was analyzed by Pearson's correlation analysis. $P < 0.05$ was considered statistically significant.

RESULTS

General characteristics of study subjects

Conventional treatment group had 18 males and 12 females, and mean age was 75.20 ± 13.22 years. In the sacubitril–valsartan treatment group, 16 males and 14 females were enrolled, and the mean age was 74.85 ± 16.28 years. The conventional treatment group had 18 cases of coronary heart disease, seven cases of hypertensive heart disease, and five cases of other types of heart disease, while the sacubitril–valsartan treatment group had 15 cases of coronary heart disease, eight cases of hypertensive heart disease and seven cases of other types of heart disease. General information (age, gender, hypertension history, diabetes history, primary disease) of the two groups was not statistically different ($p > 0.05$) (Table 1).

Serum NT-proBNP and NT-proBNP/BNP ratio levels

Level of NT-proBNP and NT-proBNP/BNP ratio in both groups decreased after treatment when compared with admission ($p < 0.05$). NT-pro BNP level in the sacubitril–valsartan treatment group was 1,378 ± 217 pg/mL, which was much lower than the conventional group ($p < 0.05$). At the same time, after treatment, the NT-pro BNP/BNP ratio in the sacubitril – valsartan treatment group was 2.41 ± 0.13, significantly lower than conventional treatment group ($p < 0.05$) (Table 2).

Table 1: General characteristics of study subjects (mean ± SD)

Variable	Conventional treatment group	Sacubitril–valsartan treatment group	t/χ^2	*P*-value
Age (y)	75.20±13.22	74.85±16.28	1.038	0.0762
Gender			0.271	0.602
Male	18	16		
Female	12	14		
Type of heart disease			0.673	0.714
Coronary heart disease	18	15		
Hypertensive heart disease	7	8		
Other	5	7		
Family history of diabetes			0.635	0.426
Yes	10	13		
No	20	17		

Table 2: Comparison of serum NT-proBNP and NT-proBNP/BNP ratio (mean ± SD, n = 30)

Group	NT-pro BNP (pg/mL)		NT-pro BNP/BNP	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***
Control	6834±2108	2650±189*	8.12±0.45	5.25±0.28*
Sacubitril–valsartan	7234±3012	1378±217*$^{\Delta}$	7.670±0.18	2.41±0.13*$^{\Delta}$

*$P < 0.05$ versus before treatment; $^{\Delta}p < 0.05$ versus conventional treatment group

Table 3: Comparison of cardiac function indices (mean ± SD, n = 30)

Group	6MWT (m)		LVEF (%)		LVEDD (mm)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Control	150±16.3	342±18.2*	38.8±7.5	44.7±8.0*	58.27±6.03	57.14±4.51
Sacubitril-valsartan	148±18.1	554±21.4*$^{\triangle}$	37.1±8.2	48.9±9.2*$^{\triangle}$	59.19±9.12	57.82±3.21

*$P< 0.05$ versus before treatment; $^{\triangle}p < 0.05$ versus conventional treatment

Table 4: Comparison of clinical efficacy (n = 30)

Group	Remarkable effect	Effective	Invalid	Deteriorated	Total efficacy
Control	20	5	3	2	83.30%
Sacubitril-valsartan	23	5	2	0	93.30%
χ^2					4.762
P-value					< 0. 05

LVEDD, LVEF, and 6-MWT Levels

The percentage LVEF (38.8 ± 7.5 vs 44.7 ± 8.0; 37.1 ± 8.2 vs 48.9 ± 9.2) and 6-MWT (150 ± 16.3 vs 342 ± 18.2; 148 ± 18.1 vs 554 ± 21.4) values of both groups improved after treatment ($p < 0.05$). LVEF (44.7 ± 8.0 vs 48.9 ± 9.2) and 6-MWT (342 ± 18.2 vs 554 ± 21.4) values in the Sacubitril – valsartan group were much higher than the conventional group ($p < 0.05$). LVEDD values before and after treatment in both groups were unchanged (Table 3).

Clinical efficacy

Efficacy was much higher in the sacubitril–valsartan group than in the conventional group (83.3 vs 93.3 %, respectively), and the difference was statistically significant ($\chi^2 = 4.762$, $p < 0.05$; Table 4).

Re-admission rate

Patients who were re-admitted because of heart failure were significantly lower in the sacubitril–valsartan group (6.6 vs 16.7 %, $\chi^2 = 8.124$, $p < 0.05$) compared with the conventional treatment group. There were no deaths due to heart failure in both groups.

Correlation between NT-proBNP/BNP ratio and 6-MWT/LVEF

The values of LVEF and 6-MWT were significantly negatively correlated with the NT-proBNP/BNP ratio ($r = -0.212$, $p < 0.01$; $r = -0.250$, $p < 0.01$, respectively).

DISCUSSION

Chronic heart failure is a common disease that seriously endangers people's lives and health, and it brings a heavy economic burden on both society and individual families. Studies have shown that heart failure causes hemodynamic changes, aggravating the myocardium, exacerbating ventricular remodeling, and deteriorating cardiac function [10,11]. Drugs used to treat heart failure inhibit ventricular remodeling and hinder further deterioration of the condition. Sacubitril–valsartan, an angiotensin receptor enkephalinase inhibitor (ARNI), antagonizes the angiotensin II receptor, inhibits the activity of enkephalinases, reduces enkephalin degradation, and increases natriuretic peptide level. Additionally, it inhibits the excessive activation of neuroendocrine system, reduces the release of aldosterone and renin, and has a positive effect on reducing cardiac load, thereby improving ventricular remodeling and delaying deterioration of the patient's conditions [12].

Some studies have shown that sacubitril–valsartan steadily maintains NT-proBNP at a lower level, while reversing ventricular remodeling and improving the remodeling index after 12 months of continuous treatment compared with only six months of treatment. This confirms that sacubitril–valsartan cannot only rapidly improve the myocardial remodeling index of outpatients, but also continue to provide benefits through long-term medication [13]. Because it inhibits the activity of enkephalinases, sacubitril–valsartan hinders the degradation of natriuretic peptides and enhance their role in diuresis and natriuresis. It is therefore used with diuretics to reduce early volume overload in patients with heart failure. Since it also contains valsartan components, sacubitril–valsartan effectively inhibit the excessive activation of RAAS [11].

Serum biomarkers such as BNP and NT-proBNP, have important guiding significance for

assessing the risk of heart failure. ARNI reduces left ventricular pressure load and decreases BNP gene transcription, thereby reducing NT-proBNP [14]. The decrease in plasma NT-proBNP levels during the clinical application of ARNI indicates an improved cardiac function in CHF patients, while BNP is a substrate of neprilysin. In 1991, Lang [15] found that enkephalin inhibitors increased serum BNP levels. Thus, BNP is no longer an appropriate biomarker for CHF patients receiving ARNI.

The NT-proBNP/BNP ratio has recently received widespread attention. Theoretically, the ratio is 1, but NT-proBNP is significantly higher than BNP because the two have different metabolic pathways and half-lives, and the NT-proBNP/BNP ratio is maintained at a relatively constant level in normal population [16]. In 2017, a Japanese study found that NT-proBNP/BNP ratio was a more effective predictor of in-hospital prognosis than any other factor [17]. Further investigation revealed that treatment efficiency in the sacubitril–valsartan group was higher and NT-proBNP/BNP ratio negatively correlated with the 6-MWT and LVEF values. The lower the NT-proBNP/BNP ratio, the more significant the improvement in LVEF, 6-MWT, and cardiac function. Moreover, compared with conventional group, the number of patients who were readmitted because of heart failure was much lower in the sacubitril–valsartan group. These results indicate that NT-proBNP/BNP ratio may have clinical significance for cardiac function assessment and prognosis in elderly CHF patients treated with sacubitril–valsartan.

In 2018, Suzuki *et al* [18] reported a correlation between NT-proBNP/BNP ratio and the prognosis of cardiovascular disease. They found that patients with a high NT-proBNP/BNP ratio had a higher incidence of cardiovascular-related events than those with a low ratio.

Limitations of this study

There were no deaths due to heart failure in either group, which was most likely due to the small sample size and short study duration.

CONCLUSION

Sacubitril–valsartan is effective in improving cardiac function in patients with CHF. The lower the NT-proBNP/BNP ratio, the better the cardiac function. Furthermore, sacubitril–valsartan reduces re-admission rate, indicating a potentially better short-term prognosis. These findings will require validation in a larger patient population and follow-up for a longer duration.

DECLARATIONS

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Ethical approval

This study was approved by the Ethics Committee of Binhu Hospital, Hefei, China.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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 about claims relating to the content of this article will be borne by the authors. Duan Y and Yu MM conducted research design, Duan Y and Xu Y provided administrative support, Duan Y, Yu MM, and Xu Y provided research materials for patients, and conducted data collection and analysis. All authors participated in the writing of the manuscript and approved the publication of the article.

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