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Original Research Article

Effect of sacubitril and valsartan combined with conventional therapy on patients with heart failure

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Abstract

Purpose: *To investigate the clinical effectiveness of the combination of sacubitril and valsartan with conventional therapy in the treatment of patients with heart failure.*
Methods: *This was a retrospective study comprising 100 heart failure patients randomized into study (n = 57) and control groups (n = 43). The study group received sacubitril/valsartan along with conventional drug therapy while control group received only conventional drugs, viz, irbesartan, metoprolol slow release, and furosemide tablets. Echocardiogram showing left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left anterior descending artery (LAD), N-terminal pro-b-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), glomerular filtration rate (eGFR), and homocysteine (HCY) of the two groups were compared before and after treatment. Multiple regression was used to analyze the correlation between re-hospitalization and sacubitril/valsartan intervention.*
Results: *The study group showed significantly lower LVEF, LVESD, LVEDD, LAD, NT-proBNP, and homocysteine levels after treatment compared to control group ($p < 0.05$). Re-hospitalization for abnormal cardiovascular events between the two groups was significantly different in the adjusted Cox proportional hazards regression model. Furthermore, multiple regression analysis showed that sacubitril/valsartan treatment was the independent variable ($p < 0.001$)*
Conclusion: *Sacubitril/valsartan improves heart function, with reduced incidence of adverse effects without affecting renal function. Further studies are required to validate these findings by expanding sample size, strictly controlling data quality and strengthening follow-up.*

Keywords: *Heart failure, Sacubitril/valsartan, Efficacy*

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INTRODUCTION

Heart failure (HF) is a complex group of clinical syndromes characterized by structural and/or functional abnormalities of the heart that lead to impaired pumping and/or filling function, resulting in dyspnea and decreased exercise tolerance. It is the common end stage of cardiac dysfunction secondary to various etiologies [1]. Over the past few decades, prevalence of heart failure has increased rapidly due to gradual increase in life expectancy and the dramatic increase in survival rate of patients with ischemic heart disease. As a result, it is a major clinical and public health challenge in most countries worldwide.

Prevalence of heart failure among adults over 35 years of age in China is about 1.3 % (about 8.9 million people) [2,3], while in some developed countries, it is between 1 – 3 %, and up to 10 % among elderly population over 70 years of age [4,5]. Mortality rate for patients with chronic heart failure per year is 5.9 %, which has decreased compared to past decades. However, it still remains the most common cause of death (62.1 %) among all cardiovascular diseases, and the proportion of hospitalizations is relatively higher in patients with more severe heart failure [6]. Therefore, ways to reduce mortality and hospitalization rates, and improve the prognosis of patients with heart failure have been the focus of research worldwide.

Sacubitril/valsartan (SAC/VAL) is the first drug in the angiotensin receptor neprilysin inhibitor (ARNI) class [7], and its first randomized placebo-controlled (RCT) study was the PARADIGM-HF study, which compared the prognosis of sacubitril/valsartan with enalapril in the treatment of heart failure with reduced ejection fraction. The result revealed that sacubitril/valsartan significantly reduced the risk of cardiovascular death by 20 %, the risk of hospitalization by 21 %, improved symptoms and activity limitation in heart failure compared to enalapril. While in terms of safety, sacubitril- valsartan was better tolerated, less likely to cause cough, hyperkalemia, renal injury or discontinuation due to adverse effects. It also did not increase the risk of severe angioedema, and the only adverse effect was increased risk of hypotension [8].

In a subsequent related analytical study [9], it was shown that the application of ARNI was more effective in reducing the risk and odds of malignancy of multiple clinical symptoms in patients with heart failure compared to angiotensin-converting enzyme inhibitor (ACEI) alone. Furthermore, ARNI reduces the risk and chances of worsening clinical symptoms, the number of emergency visits, and the need for intensive care and intravenous-positive inotropic drugs compared to ACEI alone [9]. Therefore, ARNI may be more effective than ACEI in halting the progression of HF, including sudden cardiac death [10]. It has been shown that sacubitril/valsartan has a greater advantage over ACEI and angiotensin receptor blockers (ARB) in reducing cardiovascular mortality as well as readmission rates in heart failure with reduced ejection fraction (HFrEF) [11-14]. In addition, animal studies have also confirmed the protective effect of sacubitril/valsartan in ventricular remodeling after acute myocardial infarction (AMI) [15,16]. However, it is not clear if this drug inhibits ventricular remodeling and cardiac function in patients with heart failure. Therefore, this study was aimed at investigating the clinical effectiveness of sacubitril/valsartan in the treatment of heart failure, thus providing useful information and improvement strategies for clinical cardiovascular physicians in implementing guideline recommendations.

METHODS

Participants

This study was a retrospective study of 100 participants diagnosed with heart failure between January 2019 and January 2022. The participants were randomized into study (n = 57) and control groups (n = 43). The study group received sacubitril/valsartan in addition to conventional drug therapy while control group received conventional drugs which included irbesartan tablets, metoprolol slow-release, and furosemide tablets. This study was approved by the Ethics Committee of People's Hospital of Feicheng City (approval no. 2023003), and complied with the guidelines of Declaration of Helsinki [17].

Inclusion criteria

Adult patients (aged ≥ 18 years) diagnosis with HF using the 2018 Chinese guidelines [18].

Exclusion criteria

History of renal parenchyma, severe lung disease, neuromuscular disease, mental or psychological diseases, and renal vascular disease. Also, patients who were allergic to sacubitril/valsartan were excluded.

Treatments

Control group received conventional anti heart failure drugs which included Oral administration of irbesartan tablet (Jiangsu Hengrui Pharmaceutical Co., Ltd., National medicine approval no. H20000513, 0.15 g), 0.15 g once daily; oral administration of metoprolol slow release (AstraZeneca AB, National medicine approval no. J20150045, 47.5 mg), 47.5 mg once daily; oral administration of furosemide tablets (Heilongjiang Baitai Pharmaceutical Co. Ltd, National medicine approval no. H23021069, 20 mg), 20 mg twice daily. Study group received on the basis of the control group, adopted sacubitril/valsartan tablets (Novartis Farma S.p.A., National medicine approval code HJ20170363, 100 mg) for oral treatment. The initial dose was 50 mg twice daily. The dose was increased once every 2 to 4 weeks until it reached 200 mg per time, and maintained at this dose.

Evaluation of parameters/indices

Baseline clinical data

Baseline clinical data such as gender, age, cause of heart failure, history of smoking, drinking, hypertension, diabetes, anemia, hyperkalemia, arrhythmia, heart rate, blood pressure, and New York Heart Association Functional classification were collected and compared.

Vital signs

Date of first encounter was used as the index date to obtain clinical information including laboratory data and vital signs (blood pressure, and heart rate).

Echocardiogram

Echocardiogram was performed to determine left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVEDS), and left ventricular Ejection fraction (LVEF).

Biochemical test

Level of N-terminal pro-b-type natriuretic peptide (NT-proBNP), glomerular filtration rate (eGFR), and homocysteine (HCY) were obtained through blood biochemical tests.

Statistical analysis

Data was analyzed using Statistical Package for Social Science (SPSS) 26.0 software (IBM, Armonk, NY, USA). The K-S (Kolmogorov-Smirnov) test was used to test the degree of normality. Normally distributed data were presented in mean ± standard deviation (SD), and an independent sample t-test was used for comparison. Non-normally distributed data were expressed as median (P25-P75), log-transformed and rank sum test was used for comparison. Categorical variables were presented in frequency and percentages, and chi-square test was used for comparison. Pearson correlation analysis was used for normally distributed data, and Spearman correlation analysis was used for non-normally distributed data. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline clinical data

There was no statistical difference in baseline clinical data (age, causes of heart failure sex, history of smoking, drinking, hypertension, diabetes, arrhythmia and other general conditions between both groups (Table 1).

Echocardiogram and NT-proBNP

Study group showed significantly higher LVEF after treatment compared to control group ($p < 0.05$). Furthermore, LVSED, LVEDD, LAD, and NT-proBNP significantly in study group after treatment compared to control group ($p < 0.05$, Table 2).

C-reactive protein (CRP), homocysteine (HCY), and eGFR

Level of CRP, HCY and eGFR reduced after treatment. Also, study group showed lower level of serum CRP, HCY and eGFR after treatment compared to control group (Table 3).

Outcomes of cox proportional hazards regression analysis

Incidence of major adverse cardiovascular effect was significantly lower in study group compared to control group ($p < 0.05$). As a result, difference in rehospitalization for cardiovascular effect between the two groups was significant in the adjusted Cox proportional hazards regression model (adjusted HR: 0.336; 95 % CI: 0.106–0.940; $p = 0.034$, Table 4).

Relationship between rehospitalization and independent variables

Influencing factors of rehospitalization were analyzed by regression analysis, and the results revealed that sacubitril/valsartan treatment and LVEF showed a significant correlation with rehospitalization (Table 5).

Multiple regression analysis

The multiple regression analysis showed that LVEF ($p = 0.053$) and sacubitril/valsartan treatment ($p < 0.001$) were the independent variables and the difference was significant ($p < 0.05$, Table 6).

DISCUSSION

Emergence and application of ARNI drugs such as sacubitril/valsartan, has been a new milestone in the treatment of heart failure in recent years. Prior to this development, the PARADIGM-HF study confirmed that ARNI brings more benefits to patients compared to ACEI [8].

Table 1: Baseline clinical data (N, %; mean ± SD)

Variable	Study (n = 57)	Control (n = 43)	χ^2t/Z	*P*-value
Age (years)	61.32±12.94	64.31±11.82	2.254	0.052
Male	43(75.44 %)	31(72.09 %)	0.192	0.661
Female	14(24.56%)	12(27.91%)		
Smoking history	26(45.61 %)	20(46.51 %)	1.036	0.309
Drinking history	7(12.28 %)	5(11.63 %)	0.866	0.352
Hypertension	22(38.60 %)	18(41.86 %)	0.571	0.450
Diabetes	14(24.56 %)	23(53.49 %)	0.19	0.663
Anemia	1(1.75 %)	0(0)	0.204	0.651
Hyperkalemia	1(1.75 %)	1(2.33 %)	0.459	0.498
SBP (mmHg)	22.25±18.08	122.90±18.29	0.378	0.705
DBP (mmHg)	82.21±47.88	79.17±12.75	-0.816	0.415
Heart rate(times)	86.55±16.44	86.65±17.81	0.066	0.947
Etiology of heart failure			2.986	0.055
Dilated cardiomyopathy	28(49.12 %)	12(27.91 %)		
CHDIC	22(38.60 %)	25(58.13 %)		
HHD	2(3.51 %)	2(4.65 %)		
OSC	3(5.26 %)	2(4.65 %)		
Heart valve disease	2(3.51 %)	1(2.33 %)		
Other	0(0)	1(2.33 %)		
Arrhythmias			3.298	0.404
Without arrhythmia	45(78.95 %)	35(81.4 %)		
Atrial fibrillation	8(14.04 %)	5(11.61 %)		
VPB	1(1.75 %)	1(2.33 %)		
Ventricular tachycardia	2(3.51 %)	1(2.33 %)		
Atrial flutter	1(1.75 %)	0(0)		
Other	0(0)	1(2.33 %)		
NYHA grading			-2.812	0.065
Ⅰ	1(1.75 %)	2(4.65 %)		
Ⅱ	6(10.53 %)	8(18.60 %)		
Ⅲ	32(56.14 %)	21(48.84 %)		
Ⅳ	18(31.58 %)	12(27.91 %)		

Note: SBP: Systolic blood pressure, DBP: Diastolic blood pressure, VPB: Ventricular premature beats, OSC: Other secondary cardiomyopathy, HHD: Hypertensive heart disease, CHDIC: Coronary heart disease ischemic cardiomyopathy

Table 2: Echocardiogram and NT-proBNP (mean ± SD)

Parameter		Study (n = 57)	Control (n = 43)
LVEF (%)	Before treatment	45.81±1.66	46.12±0.81
	After treatment	55.0±1.62*#	48.29±1.11*
LVESD (mm)	Before treatment	46.05±1.76	46.88±1.04
	After treatment	35.69±1.08*#	42.9±1.74*
LVEDD (mm)	Before treatment	60.24±0.92	59.14±1.12
	After treatment	48.64±0.89*#	53.64±0.89*
LAD (mm)	Before treatment	42.83±0.78	41.17±0.89
	After treatment	36.24±0.6*#	34.69±0.91*
NT-proBNP (pg/mL)	Before treatment	5464.21±483.95	4847.57±306.96
	After treatment	541.17±66.22*#	765.52±100.31*

Note: *$P < 0.05$ vs before treatment, #$p < 0.05$ vs control group after treatment

Table 3: Level of CRP and HCY, and eGFR (mean ± SD)

Parameter		Study (n = 57)	Control (n = 43)
CRP (mg/L)	Before treatment	18.31±3.97	15.57±5.87
	After treatment	12.77±2.7*	10.36±3.86*
HCY (μMno1/L)	Before treatment	23.38±1.17	21.07±1.52
	After treatment	14.9±1.25*	16.33±1.81*
eGFR (ml/min x 173^2)	Before treatment	76.02 ± 2.04	75.45 ± 2.10
	After treatment	73.76±1.81	77.17±2.34

Note: *$P < 0.05$ vs before treatment

Table 4: Outcomes of cox proportional hazards regression analysis (N, %)

Parameter	Study (n=57)	Control (n=43)	Adjusted HR (95 %CI)	*P*-value
Total major adverse cardiovascular effect	21(36.8)	32(74.4)	0.640 (0.421–0.969)	0.037
All-cause mortality	11(19.3)	20(46.5)	1.527 (0.887–2.569)	0.123
Systemic embolism	13(22.8)	15(34.9)	1.059 (0.609–1.845)	0.825
Rehospitalization for cardiovascular events	2(3.5)	7(16.3)	0.336 (0.106–0.940)	0.034
Bleeding events	3(5.3)	4(9.3)	1.134 (0.376–3.443)	0.835

Table 5: Relationship between rehospitalization and independent variables

Item	Rho	*P*-value
Age (years)	-0.072	0.455
Male	-0.073	0.471
Smoking history	0.074	0.521
Drinking history	-0.053	0.753
Hypertension	-0.557	0.067
Diabetes	-0.438	0.097
Anemia	-0.468	0.856
Hyperkalemia	-0.531	0.376
LVEF	0.276	0.033
LVESD	0.184	0.064
LVEDD	0.068	0.698
LAD	-0.072	0.398
NT-proBNP	-0.439	0.848
CRP	-0.864	0.665
HCY	0.064	0.984
Sacubitril/valsartan treatment	0.329	<0.001
eGFR	-0.576	0.881

These benefits are reflected in the fact that compared to enalapril, sacubitril/valsartan reduces the relative risk of cardiovascular death in patients with HFrEF by 20 %, risk of hospitalization for heart failure by 21 %, risk of hospitalization for cardiovascular death by 20 %, risk of all cause death by 16 %, and risk of sudden cardiac death by 20 % [8]. The main adverse reactions to ARNI drugs are symptomatic hypotension without the need to stop medication, renal function deterioration (serum creatinine elevation ≥ 2.5 mg/dL), hypokalemia, and milder adverse reactions such as cough.

PIONEER-HF study on sacubitril/valsartan included HFrEF patients with hemodynamic stability after hospitalization for acute decompensated heart failure (ADHF) [19]. The results showed that sacubitril/valsartan significantly reduced NT-proBNP levels in patients with heart failure compared to enalapril, and mortality rate alongside heart failure readmission. The incidence of serious composite endpoint effect such as implantation of left ventricular assist devices reached 46 % [19]. Therefore, ARNI is a good replacement for ACEI/ARB drugs and other drugs for heart failure such as β receptor blockers.

Treatment with sacubitril/valsartan significantly improves the prognosis in heart failure, and its mechanism involves various aspects such as ventricular remodeling. Compagner *et al* [20] included 125 patients with HFrEF, and evaluated ventricular remodeling after treatment with sacubitril/valsartan using echocardiography. The results showed that after 3-6 months of treatment, LVEF improved significantly, while left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) both decreased significantly compared to baseline.

In a prospective cohort study, Gu *et al* [21] found that after 3 months of treatment with sacubitril/valsartan in HFrEF patients, left ventricular systolic function improved significantly, with an average LVEF increasing from 28 % to 33 %, and patients also achieved significant improvement in their perceived symptoms. Jiang *et al* [22] found that after 6 months of treatment with sacubitril/valsartan, HFrEF patients achieved significant improvements in multiple parameters of echocardiography (LVEF increasing from an average of about 32 to 48 %, left ventricular end-diastolic diameter (LVEDD) decreasing from a mean of about 5.7 cm to about 5.3 cm, and left ventricular end-systolic diameter (LVESD) decreasing from an average of about 4.8 cm to about 4.2 cm).

Table 6: Multiple regression analysis

Dependent variable	Independent variables	B	SE	β	*P*-value
Rehospitalization	LVEF	0.343	0.033	0.543	0.053
	Sacubitril/valsartan treatment	1.468	0.534	0.374	<0.001

Note: B: Unstandardized regression coefficient; SE: standard error; β: multiple correlation coefficient adjusted for the degrees of freedom

Limitations of this study

This study was a single-center retrospective analysis with a small sample size. Additionally, there is information bias in the data collection process, as well as some had missing cases. Also, the short time-frame, non-collection of treatment compliance status and short follow-up may limit the general applicability of the results.

CONCLUSION

Sacubitril/valsartan improves heart function, lowers CRP, HCY and eGFR with minimal adverse effects without affecting renal function. Validation of these findings by expanding sample size, strictly controlling data quality, strengthening case follow-up and designing prospective cohort studies is required.

DECLARATIONS

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Ethical approval

The Ethics Committee of People's Hospital of Feicheng City, China approved this study (2023003).

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 pertaining to claims relating to the content of this article will be borne by the authors. Zhenyu Wu and Wen Cui contributed equally to this work.

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