BRITISH JOURNAL OF HOSPITAL MEDICINE

ARTICLE

The Effects of Recombinant Human Brain Natriuretic Peptide in Combination With Sacubitril Valsartan Sodium on Cardiac Function, Inflammatory Markers, and Oxidative Stress Indicators in Elderly Patients With Acute Left Heart Failure: A Retrospective Study

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Abstract

Aims/Background Acute left ventricular failure (ALVF), a common cardiovascular emergency characterized by rapid occurring and progressing, poses a severe threat to the patient's life. The purpose of this study is to investigate the impact of combining recombinant human brain natriuretic peptide (rhBNP) with sacubitril valsartan sodium on cardiac function, inflammatory markers, and oxidative stress indicators in elderly ALVF patients.

Methods This retrospective study included 167 elderly ALVF patients between June 2022 and June 2024. Based on the treatment regimen, the patients were divided into three groups: a control group (n = 49, who received traditional treatment), an observation group (n = 61, who received replacement treatment with sacubitril and valsartan sodium), and a combination group (n = 57, who administered with a combination of rhBNP and sacubitril and valsartan sodium). Clinical data of patients were accessed from the electronic medical record system in the Second Affiliated Hospital of Nanjing Medical University, and the pre- and post-treatment cardiac function, inflammatory marker levels, oxidative stress indicators, and incidence of adverse reactions were compared among the three groups of patients.

Results Following treatment, the left ventricular ejection fraction (LVEF) and superoxide dismutase (SOD) levels were significantly higher in the combination group compared to the observation and control groups. Furthermore, the combination group exhibited a substantial decrease in the left ventricular end-diastolic diameter (LVEDD), creatine kinase isoenzyme MB (CK-MB), alpha hydroxybutyrate dehydrogenase (α-HBDH), high-sensitivity C-reactive protein (hs-CRP), malondialdehyde (MDA) and tumor necrosis factor-alpha (TNF-α). Moreover, TNF-α, MDA and interleukin-6 (IL-6) levels were significantly lower in the observation group compared to the control group ($p < 0.05$). Additionally, no significant difference was observed in the incidence of adverse reactions between the two groups ($p > 0.05$).

Conclusion Combining rhBNP with sacubitril and valsartan sodium can effectively improve the cardiac function among elderly ALVF patients, significantly reducing the levels of inflammatory factors and alleviating oxidative stress reactions. This approach provides superior efficacy and safety for managing elderly ALVF patients.

Key words: heart failure; aged; recombinant human brain natriuretic peptide; sacubitril valsartan sodium; drug combinations

Submitted: 29 September 2024 Revised: 1 November 2024 Accepted: 12 November 2024

How to cite this article:
Gao Y, Cheng Z. The Effects of Recombinant Human Brain Natriuretic Peptide in Combination With Sacubitril Valsartan Sodium on Cardiac Function, Inflammatory Markers, and Oxidative Stress Indicators in Elderly Patients With Acute Left Heart Failure: A Retrospective Study. Br J Hosp Med. 2025. https://doi.org/10.12968/hmed.2024.0706

Introduction

Acute left ventricular failure (ALVF) is one of the most common cardiovascular diseases, representing a subset of acute heart failure (AHF). The typical symptoms of this condition are dyspnea, orthopnea, or systemic edema (Long et al, 2019). Research shows that AHF remains a highly prevalent disease among the older age groups, with a high risk of 1-year mortality (Emmons-Bell et al, 2022; Wintrich et al, 2022). Crucial steps in managing ALVF include reducing cardiac load, improving myocardial remodeling, and regulating the neuroendocrine system. However, the present clinical treatment regimen primarily focuses on symptomatic treatment, with little attention being paid to possible pathophysiological characteristics (Arrigo et al, 2020).

With advances in investigating the pathophysiological mechanism of AHF, natriuretic peptides—atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide as antagonistic regulatory hormones secreted by the body when there is failure of heart function—are considered crucial in the occurrence and progression of this disease (Abassi et al, 2022). Recombinant human brain natriuretic peptide (rhBNP) is a synthetic engineered peptide that has been widely used to treat AHF (Yang et al, 2020). rhBNP produces multifaceted mechanisms of action by stimulating sodium excretion, facilitating diuresis, causing vasodilation and inhibiting the renin-angiotensin aldosterone system (RAAS). Previous studies have revealed that rhBNP can significantly reduce N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in patients, and improve cardiac function and hemodynamics, thereby enhancing their quality of life (Ning et al, 2020; Wang et al, 2024). Furthermore, sacubitril valsartan sodium can effectively improve cardiac function and reverse myocardial remodeling by inhibiting enkephalinase and blocking angiotensin II receptors (Lyu et al, 2022). This drug has been proven to reduce mortality risk and urgent hospitalization of these patients with reduced ejection fraction (Le et al, 2024).

To date, there is a scarcity of research on the use of rhBNP in combination with sacubitril valsartan sodium in elderly patients with acute left heart failure. However, given the specific physiological functions and metabolism of drugs, exploring how this combination therapy impacts cardiac function, inflammatory markers, and oxidative stress indicators in elderly patients with acute left heart failure poses great clinical significance. Therefore, we conducted retrospective analysis to provide more optimized treatment strategies for elderly ALVF patients.

Methods

Inclusion and Exclusion Criteria of Study Subjects

Inclusion criteria were set as follows: ① Patients who meet the diagnostic criteria for acute left heart failure (McDonagh et al, 2021) and are categorized as New York Heart Association (NYHA) functional class III–IV (Caraballo et al, 2019). ② Patients with age ranged between 60 and 75 years. ③ Those without mental disorders and who are able to communicate normally and cooperate during treatment. ④ Those with complete medical records and baseline data.

Exclusion criteria included: ① Patients with allergies to the drugs used in the study. ② Those with severe liver and kidney dysfunction. ③ Those diagnosed with malignant tumors. ④ And patients with a history of cardiac surgery.

Study Participants and Their Grouping

This study included 174 elderly ALVF patients admitted to the Second Affiliated Hospital of Nanjing Medical University between June 2022 and June 2024. Following the preliminary screening, two patients with mental disorders, two with incomplete medical records and baseline data, one with renal failure, one with concurrent malignant tumors, and one with a history of cardiac surgery were excluded, 167 elderly ALVF patients were ultimately included as the study subjects for subsequent investigation.

Based on various treatment regimens, patients were divided into three groups. The patients receiving traditional treatment were designated as the control group (n = 49), those undergoing replacement therapy with sacubitril and valsartan sodium were classified as the observation group (n = 61), and patients receiving rhBNP in combination with sacubitril and valsartan sodium were categorized as the combination group (n = 57). A flow chart of the study design is shown in Fig. 1.

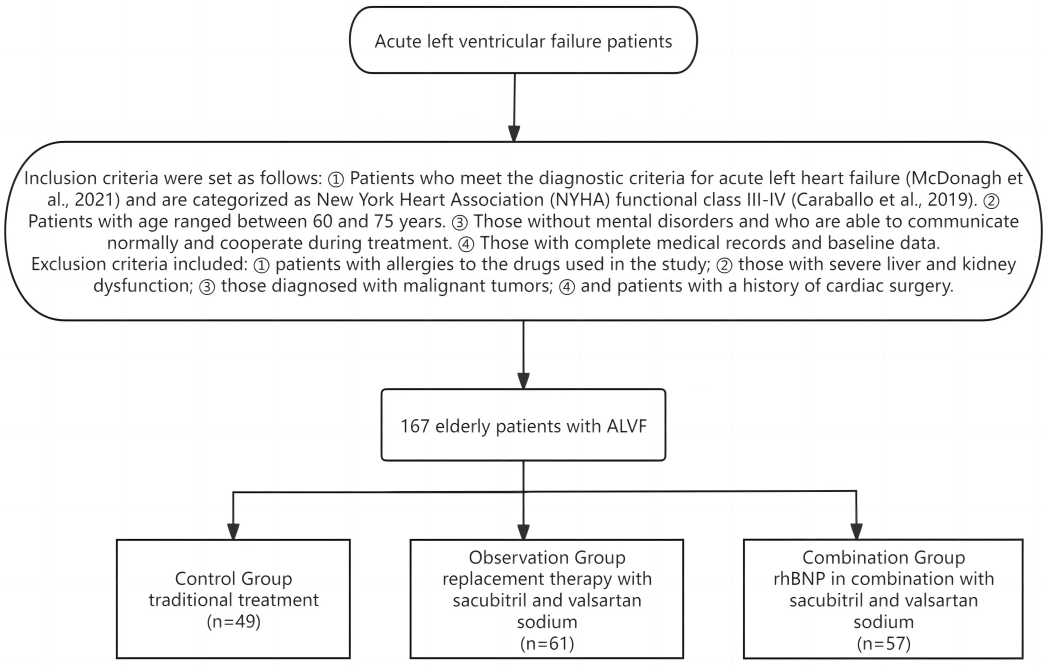

Fig. 1. A flow chart of the study design. ALVF, acute left ventricular failure; rhBNP, recombinant human brain natriuretic peptide.

Treatment Protocol

Patients in the control group received routine standard treatments such as diuretics and vasodilators, along with traditional treatments such as angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid antagonists. Addi-

tionally, comorbidities were carefully monitored with measures such as controlling blood pressure and blood sugar levels.

In the observation group, angiotensin-converting enzyme inhibitors were replaced with sacubitril valsartan sodium (batch number: BV219, Novartis Pharma Stein AG, Basel, Switzerland). The recommended initial dose of sacubitril valsartan sodium is 50 mg, given twice a day, and dosage was adjusted based on the patient's blood pressure, renal function, and other features. The dosage was doubled every 2 weeks as required, up to a maximum of 200 mg per dose.

The treatment regimen of the combination group included all interventions from the observation group, with the addition of rhBNP (batch number: 20220110, Chengdu Nordicorn Biopharmaceutical Co., Ltd., Chengdu, China). rhBNP was administered intravenously at a dose of 1.5–2.0 μg/kg at a rate of 0.0075 μg/(kg·min) for 24 hours over 3–5 days, adjusted to the specific condition of the patient. Note: Sacubitril-valsartan sodium was resumed on the day rhBNP was discontinued, following the same dosage as in the observation group.

Observation Indicators

Cardiac Function Indicators

We obtained cardiac ultrasound and myocardial enzyme spectrum examination results from the hospital's electronic medical record system for each patient, performed before treatment (on the first day of admission) and after treatment (one month after drug treatment). The data included left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), creatine kinase isoenzyme MB (CK-MB), and alpha hydroxybutyrate dehydrogenase (α-HBDH).

Inflammatory Markers

Inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) levels were retrieved from the electronic medical record system in the Second Affiliated Hospital of Nanjing Medical University, evaluated before treatment (on the first day of admission) and after treatment (one month of drug treatment). These inflammatory markers were assessed using enzyme-linked immunosorbent assays.

Oxidative Stress Indicators

The levels of malondialdehyde (MDA) and superoxide dismutase (SOD) determined before treatment (on the first day of admission) and after treatment (one month of drug treatment) were also obtained from the hospital's electronic medical record system.

Adverse Reaction Indicators

We collected records of adverse reactions, such as dizziness, nausea, and hypotension experienced by each patient within one month of treatment.

Statistical Analysis

This study used SPSS 27.0 (International Business Machines Corporation, Armonk, NY, USA) for statistical analysis. Categorical variables were expressed as

n (%) and analyzed using the chi-square test or Fisher's test. The Shapiro-Wilk test was used to assess the distribution of continuous variables, with the analysis method applied accordingly. Data following a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$). ANOVA was used to examine differences between multiple groups, with the Least Significant Difference-q (LSD-q) test used multiple comparisons; results were represented by F-values. Moreover, pairwise comparisons within each group were conducted using the N-K test. However, data that do not follow a normal distribution were represented as median M (P_{25}, P_{75}), and the Kruskal Wallis test was used to examine differences across multiple variables, with results expressed by H values. Additionally, Bonferroni method was used for pairwise comparisons within the group. A p-value of <0.05 indicated a statistically significant difference.

Results

Comparison of Baseline Data Among the Three Groups of Patients

As shown in Table 1, baseline characteristics, such as gender, age, weight, marital status, educational background, NYHA cardiac function classification, other complications (diabetes, hypertension, atrial fibrillation), blood circulation reconstruction, heart rate, and systolic blood pressure were not significantly different across the three groups ($p > 0.05$).

Comparison of Cardiac Function Indicators Before and After Treatment Across the Three Groups

Before treatment, there were no significant differences in cardiac function indicators among the three groups ($p > 0.05$). However, after treatment, the LVEF was significantly higher in the combination group than in both the observation and control groups, while the levels of LVEDD, CK-MB, and α-HBDH were significantly lower than the observation and control groups ($p < 0.05$). Furthermore, statistically significant differences were observed in LVEF, LVEDD, CK-MB, and α-HBDH ($p < 0.05$) between the observation and control groups (Table 2).

Comparison of Inflammatory Markers and Oxidative Stress Indicators Before and After Treatment Across the Three Groups

Before treatment, there were no significant differences in the levels of various inflammatory markers among the three groups ($p > 0.05$). After treatment, hs-CRP, TNF-α, IL-6 and MDA levels were significantly lower in the combination group compared to the control and observation groups, while the level of SOD was significantly higher than the control and observation groups ($p < 0.05$). After treatment, compared to the control group, the observation group had lower levels of hs-CRP, TNF-α, IL-6, and MDA and higher levels of SOD ($p < 0.05$) (Table 3).

Incidence of Adverse Reactions Among the Three Groups

As shown in Table 4, there were no significant differences in the incidence of adverse reactions among the three groups ($p > 0.05$), and no record of renal function deterioration or new-onset atrial fibrillation was observed.

Table 1. Comparison of baseline characteristics across the three groups of patients (M (P_{25}, P_{75}), ($\bar{x} \pm s$), n (%)).

Variables	Control group (n = 49)	Observation group (n = 61)	Combined group (n = 57)	χ^2/Fisher/H/F	*p*-value
Gender				0.549	0.760
Male	21 (42.86)	22 (36.07)	23 (40.35)		
Female	28 (57.14)	39 (63.93)	34 (59.65)		
Age (years)	69.00 (63.00, 73.00)	69.00 (64.00, 72.50)	68.00 (64.50, 72.00)	0.420	0.810
Weight (kg)	61.00 (64.50, 72.00)	62.40 (55.45, 67.90)	61.70 (55.55, 66.85)	0.844	0.656
Marital status				Fisher	0.751
Married	40 (81.63)	51 (83.61)	50 (87.72)		
Divorce/Widow	9 (18.37)	9 (14.75)	6 (10.53)		
Unmarried	0 (0.00)	1 (1.64)	1 (1.75)		
Education levels				0.728	0.694
Elementary school and below	31 (63.27)	41 (67.21)	34 (59.65)		
Junior high school and above	18 (36.73)	20 (32.79)	23 (40.35)		
NYHA classification				0.394	0.821
Grade III	24 (48.98)	33 (54.10)	28 (49.12)		
Grade IV	25 (51.02)	28 (45.90)	29 (50.88)		
Diabetes				0.747	0.688
Y	12 (24.49)	16 (26.23)	18 (31.58)		
N	37 (75.51)	45 (73.77)	39 (68.42)		
Hypertension				1.423	0.491
Y	28 (57.14)	30 (49.18)	34 (59.65)		
N	21 (42.86)	31 (50.82)	23 (40.35)		
Atrial fibrillation				0.321	0.852
Y	9 (18.37)	13 (21.31)	13 (22.81)		
N	40 (81.63)	48 (78.69)	44 (77.19)		
Revascularization				0.416	0.812
Y	13 (26.53)	15 (24.59)	17 (29.82)		
N	36 (73.47)	46 (75.41)	40 (70.18)		
Heart rate (beats/min)	123.31 ± 15.83	124.02 ± 18.82	126.98 ± 17.03	0.693	0.502
Systolic blood pressure (mmHg)	151.00 (126.00, 156.00)	139.00 (110.00, 164.50)	145.00 (124.50, 171.50)	1.537	0.464

NYHA, New York Heart Association.

Table 2. Comparison of cardiac function indicators before and after treatment among the three groups (M (P_{25}, P_{75}), ($\bar{x} \pm s$)).

Variables	Time	Control group (n = 49)	Observation group (n = 61)	Combined group (n = 57)	F/H	*p*-value
LVEF (%)	Before treatment	35.55 ± 4.56	35.84 ± 5.13	36.14 ± 5.54	0.175	0.839
	After treatment	37.00 (34.50, 42.00)	40.00 (38.00, 46.00)*	46.00 (43.00, 50.00)**##	45.330	<0.001
LVEDD (mm)	Before treatment	58.16 ± 7.14	57.64 ± 6.84	58.42 ± 6.50	0.202	0.818
	After treatment	43.02 ± 4.97	41.02 ± 5.11*	36.28 ± 4.76**##	26.490	<0.001
CK-MB (U/L)	Before treatment	26.00 (22.50, 30.00)	26.00 (22.00, 32.00)	28.00 (21.00, 30.50)	0.441	0.802
	After treatment	23.00 (20.50, 26.50)	20.00 (16.50, 23.00)*	15.00 (13.00, 17.00)**##	54.440	<0.001
α-HBDH (U/L)	Before treatment	163.00 (141.50, 182.50)	160.00 (147.00, 182.50)	161.00 (140.50, 170.50)	0.390	0.823
	After treatment	160.00 (138.50, 179.00)	133.00 (109.00, 159.00)**	102.00 (79.50, 138.00)**#	43.615	<0.001

Note: Compared to the control group, $^{*}p < 0.05$, $^{**}p < 0.001$; Compared to the observation group, $^{\#}p < 0.05$, $^{\#\#}p < 0.001$.
LVEF, left ventricle ejection fraction; LVEDD, left ventricular end-diastolic diameter; CK-MB, creatine kinase isoenzyme MB; α-HBDH, alpha hydroxybutyrate dehydrogenase.

Table 3. Comparison of inflammatory markers and oxidative stress indicators before and after treatment among the three groups (M (P_{25}, P_{75}), ($\bar{x} \pm s$)).

Variables	Time	Control group (n = 49)	Observation group (n = 61)	Combined group (n = 57)	F/H	*p*-value
hs-CRP (mg/mL)	Before treatment	12.11 ± 1.73	12.39 ± 2.12	12.69 ± 1.92	1.144	0.321
	After treatment	5.50 (5.20, 6.40)	4.30 (3.80, 4.50)**	2.50 (2.10, 2.90)**##	140.707	<0.001
TNF-α (ng/L)	Before treatment	8.50 (7.70, 9.20)	8.80 (7.30, 9.90)	8.60 (7.55, 10.30)	1.449	0.485
	After treatment	6.75 ± 1.01	4.88 ± 0.61**	3.42 ± 0.39**##	300.647	<0.001
IL-6 (ng/L)	Before treatment	13.61 ± 2.06	13.98 ± 2.68	13.16 ± 2.48	1.627	0.200
	After treatment	10.12 ± 1.24	7.92 ± 1.03**	5.21 ± 0.78**##	308.135	<0.001
MDA (mmol/L)	Before treatment	19.30 (17.90, 19.95)	19.40 (15.95, 22.00)	19.50 (17.55, 21.60)	0.269	0.874
	After treatment	15.32 ± 1.85	13.02 ± 2.06**	10.61 ± 1.35**##	92.597	<0.001
SOD (U/L)	Before treatment	86.55 ± 5.79	86.11 ± 6.27	87.14 ± 5.26	0.462	0.631
	After treatment	92.00 ± 6.52	95.11 ± 6.82*	99.33 ± 7.28**#	15.194	<0.001

Note: Compared to the control group, $^{*}p < 0.05$, $^{**}p < 0.001$; Compared to the observation group, $^{\#}p < 0.05$, $^{\#\#}p < 0.001$.
hs-CRP, high-sensitivity C-reactive protein; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; MDA, malondialdehyde; SOD, superoxide dismutase.

Table 4. Comparison of adverse reaction rates among the three groups (n (%)).

Variables	Control group (n = 49)	Observation group (n = 61)	Combined group (n = 57)	χ^2	*p*-value
Dizziness	6 (12.24)	4 (6.56)	6 (10.53)	1.104	0.576
Nausea	3 (6.12)	4 (6.56)	2 (3.51)	0.610	0.737
Hypotension	5 (10.20)	4 (6.56)	6 (10.53)	0.694	0.707

Discussion

AHF includes a wide range of disease states resulting from the interaction between acute triggering factors and the patient's underlying cardiac matrix and comorbidities (Chioncel et al, 2023). Therefore, it is necessary to find a treatment plan that can improve cardiac remodeling from the perspective of pathogenesis, under the premise of symptomatic medication. In this context, our retrospective study grouped patients based on their treatment regimen to explore the clinical efficacy of combining rhBNP treatment with sacubitril and valsartan sodium.

Restoration of Cardiac Function by Sacubitril-Valsartan Sodium

We found that the combination group showed the most significant improvement in cardiac ultrasound indicators (LVEF, LVEDD) and myocardial enzyme spectrum indicators (CK-MB, α-HBDH) after treatment, followed by the observation group and then the control group. This indicates that sacubitril valsartan sodium can effectively replace traditional angiotensin-converting enzyme inhibitors. Furthermore, when used in combination with rhBNP, more significant improvements in cardiac function can be achieved. Studies have demonstrated that the basic physiological and pathological mechanism of heart failure involves the persistent activation of the neuroendocrine system specifically the sympathetic nervous system, RAAS, and the arginine vasopressin system, causing tachycardia and subsequently increasing systemic vascular resistance (Aikins et al, 2021; Manolis et al, 2023; Polónia and Gonçalves, 2019). Based on these observations, we further analyzed the interaction mechanisms between rhBNP and sacubitril valsartan sodium.

Combined Effect of rhBNP With Sacubitril Sodium

The rhBNP, an artificially synthesized peptide, contains a spatial structure and biological activity similar to endogenous peptides, which can effectively improve cardiac function through various pathways. Firstly, through its vasodilatory effects, rhBNP can relax the smooth muscles in the arteries and veins, increase cardiac output, and reduce the pre- and post-cardiac load (Liu et al, 2021). Secondly, rhBNP also promotes sodium and water excretion, reducing the capacity load on the heart (Peng and Wei, 2020). Shakubitrile sodium, an angiotensin receptor enkephalin enzyme inhibitor, inhibits the enkephalin enzyme, increases levels of natriuretic peptide, and results in sodium diuresis, vasodilation, and inhibition of RAAS. Additionally, blocking angiotensin II receptors further reduces cardiac afterload, consequently improving cardiac remodeling (Docherty et al, 2020). More

importantly, there is a synergistic effect between the two drugs, and their combined use can achieve more significant outcomes. This is because natriuretic peptide signaling weakness will lead to a pharmacological equivalence between angiotensin receptor enkephalinase inhibitors and angiotensin receptor antagonists (Mann et al, 2022). On the contrary, when patients receive rhBNP treatment in combination with sacubitril and valsartan sodium, the signal transduction of natriuretic peptide is enhanced and more pronounced clinical efficacy is achieved.

Treatment Effects of rhBNP and Sacubitrate Sodium on Markers of Cardiac Inflammation

Inflammation and oxidative stress are crucial in the occurrence and progression of ALVF. TNF-α and hs-CRP are the most common pro-inflammatory markers, and IL-6 is an important inflammatory mediator that can be a potential drug target for heart failure (Markousis-Mavrogenis et al, 2019). Furthermore, CK-MB and α-HBDH, myocardial enzymes released during myocardial cell injury, are valuable indicators in evaluating myocardial injury and cardiac function. Our findings indicated that the levels of inflammatory markers and oxidative stress indicators in the combination group were significantly lower than in the control and observation groups. Furthermore, combining rhBNP with sacubitril valsartan sodium showed better anti-inflammatory and antioxidant effects among elderly ALVF patients. rhBNP has been reported to inhibit myocardial ischemia-reperfusion injury by enhancing the phosphorylation of the phosphatidylinositol 3-kinase/protein kinase b/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway and inhibiting cluster of differentiation 4 (CD4) T cell proliferation (Li et al, 2020). Furthermore, research has verified that both rhBNP and sacubitril valsartan sodium can inhibit RAAS, reduce the secretion of angiotensin and the expression of serum inflammatory factors such as TNF-α, reduce or prevent myocardial ischemia, thus improving heart function (Yang et al, 2023). Additionally, the safety of treatment among elderly ALVF patients is also crucial. In this study, no statistically significant differences were observed in the incidence of nausea, dizziness, and hypotension among the three groups. Furthermore, there was no record of renal function deterioration or new onset of atrial fibrillation among these patients. These observations indicated a good safety of combining rhBNP with sacubitril valsartan sodium among elderly ALVF patients, evidenced by no significant increase in the adverse reactions.

In summary, this study demonstrates that the combination of rhBNP and sacubitril valsartan sodium has a synergistic effect in treating elderly ALVF patients, which can significantly improve cardiac function, reduce inflammatory cytokine levels, alleviate oxidative stress, and possesses certain advantages and clinical significance. However, there are also some limitations to this study. It was a single-center, retrospective study; hence it had a small sample size, and the chance of a selectivity bias is more likely. Although this study produced some promising outcomes, considerable caution needs to be exercised before publicizing its clinical significance. Additionally, this study did not include long-term follow-up data, which limits its ability to demonstrate the long-term benefits and safety of rhBNP combined with sacubitril valsartan sodium. The therapeutic effects were examined

in an age-specific elderly patient population. Future prospective studies should aim to expand the sample size and develop rigorous research designs to investigate the interaction mechanisms between the two drugs at both cellular and molecular levels, as well as their specific effects on processes such as cardiac remodeling, cardiomyocyte apoptosis, and fibrosis.

Conclusion

In summary, we observed that combining rhBNP with sacubitril valsartan sodium has a significant therapeutic impact on elderly ALVF patients, positively impacting their cardiac function, inflammatory response, and oxidative stress.

Key Points

- Sacubitril and valsartan sodium demonstrates superior clinical effectiveness in elderly ALVF patients than traditional angiotensin-converting enzyme inhibitors.
- The combination of rhBNP and sacubitril valsartan sodium improves cardiac function.
- The combination of rhBNP and sacubitril valsartan sodium significantly alleviates inflammatory markers.
- The combination of rhBNP and sacubitril valsartan sodium has a positive effect on oxidative stress.

Availability of Data and Materials

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

Author Contributions

YG and ZC designed the study. Both authors conducted the study. YG and ZC collected and analyzed the data. YG and ZC participated in drafting the manuscript, and both authors contributed to critical revision of the manuscript for important intellectual content. Both authors gave final approval of the version to be published. Both authors participated fully in the work, took public responsibility for appropriate portions of the content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work were appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study was approved by the Second Affiliated Hospital of Nanjing Medical University (institution review board number, 2023-KY-106-02). This study was performed in accordance with the principles of the Declaration of Helsinki. Informed consent has been obtained from all participants involved in the study.

Acknowledgement

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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