Role of recombinant human brain natriuretic peptide combined with sodium nitroprusside in improving quality of life and cardiac function in patients with acute heart failure

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Abstract. The present study aimed to investigate the role of recombinant human brain natriuretic peptide (RHBNP) combined with sodium nitroprusside (SN) in improving quality of life and cardiac function in patients with acute heart failure. A total of 96 patients with acute heart failure who were admitted to The First Affiliated Hospital of Yangtze University were included in the current study. A total of 48 patients were treated with RHBNP combined with SN (research group) and 48 patients were treated with SN alone (control group). To assess the efficacy and safety of the two treatments, the study groups were compared in terms of improvement in clinical symptoms and cardiac function indices, including pulmonary capillary wedge pressure and left ventricular ejection fraction, which was measured using a non-invasive cardiac hemodynamic detector; changes in fluid intake and 24 h urine volumes after drug use; cardiac function classification before treatment and three days after treatment; adverse drug reactions during treatment and mortality within 1 month of treatment. Following treatment, compared with the control group, the research group demonstrated significantly higher fluid intake and 24 h urine volume after drug use, improved cardiac function indices, cardiac function classification, biochemical indicators and total effective rate of treatment (all $P<0.05$); significantly lower total incidence of adverse reactions ($P<0.05$) and similar mortality within 1 month of treatment. With improvements in cardiac and other organ function, RHBNP combined with SN was found to be effective in the treatment of acute heart failure. RHBNP can effectively promote urination, reduce inflammatory responses and rapidly relieve clinical symptoms without significant adverse reactions, indicating its potential use in further clinical application.

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Introduction

Acute heart failure is a fatal condition characterized by heterogeneous clinical manifestations, and its high incidence and mortality rates reportedly increase economic burden for many countries worldwide (1,2). Due to the rapid onset of acute heart failure and the progressive deterioration of its signs and symptoms, patients with acute heart failure require immediate treatment or emergency hospital admission (3). Currently, a number of treatment options, including vasodilation, diuresis, heart strengthening and symptomatic treatment are available for acute heart failure; however, the efficacy of these treatments are not satisfactory (4). Therefore, the identification of more effective treatment methods for acute heart failure remains vital for clinical research.

In recent years, with accumulating and detailed studies on the pathological mechanism underlying heart failure, neuroendocrine factors have drawn much attention (5,6). Recombinant human brain natriuretic peptide (RHBNP), which is a B-type natriuretic peptide, secretes an endogenous polypeptide, which is usually distributed in heart tissues and can effectively improve hemodynamic function (7). In addition, as a local multifunctional drug with spatial structure and biological activity similar to those of endogenous brain natriuretic peptides, RHBNP can regulate diuresis, promote the diuresis and relaxation of bladder smooth muscles, improve heart and kidney functions after cardiopulmonary bypass and accelerate healing following myocardial injury (7,8). Sodium nitroprusside (SN) is considered as the drug of choice for cardiac surgery as its short half-life enables high efficiency and rapid titration during and after cardiac surgery (9). However, SN administration needs to be carefully monitored as it can dilate venous and arterial vessels and reduce blood pressure without limitation (10). RHBNP and SN can be used to treat patients with acute heart failure and cardiac insufficiency, but only few studies have reported the effects of

the combinational use of these drugs on the quality of life and cardiac function in patients with acute heart failure. Therefore, the present study investigated the effects of the combination treatment of RHBNP and SN on acute heart failure based on improvements in clinical symptoms, thus aiming to provide a clinical basis for RHBNP applications in patients with acute heart failure.

Materials and methods

General characteristics. A total of 96 patients with acute heart failure admitted to The First Affiliated Hospital of Yangtze University (Hubei, China) from February 2018 to May 2019 were included in the current study. Among them, 48 patients were treated with RHBNP combined with SN (research group) and 48 patients were treated with SN alone (control group). The research group comprised 21 males and 27 females, with a mean age of 65.43±5.87 years (range, 44-76 years) and mean heart failure duration of 17.2±1.6 years (range, 9-24 years). According to the New York Heart Association (NYHA) classification, 15 patients belonged to Class II, 20 patients to Class III and 13 patients to Class IV (11). The control group comprised 25 males and 23 females, with a mean age of 66.31±6.12 years (range, 43-78 years) and mean heart failure duration of 17.4±1.8 years (range, 19-22 years). Based on NYHA classification, 13 patients belonged to Class II, 25 patients to Class III and 10 patients to Class IV.

Inclusion and exclusion criteria. The inclusion criteria were as follows: Diagnosis of acute heart failure before treatment (12); either sex; complete general clinical data available; age ≥18 years; expected survival time of ≥1 year and no history of chemotherapy or radiotherapy until the initial diagnosis. The exclusion criteria were as follows: Presence of serious diseases such as infection, severe hepatic and kidney dysfunction, malignant tutor, autoimmune disease, myocarditis, severe valvular heart disease and mental disease; family history of psychosis; inability to cooperate during treatment; history of a major surgery within 15 days before the treatment; dropping out from the study or allergies to RHBNP and SN.

The present study was approved by the Ethics Committee of the First Affiliated Hospital of Yangtze University. All study subjects and their family members were informed of the experiment and signed informed consent forms were obtained.

Treatment methods. Both study groups were administered routine therapy involving vital sign monitoring, oxygen inhalation, diuresis, digitalis and angiotensin-converting enzyme inhibitor and β-blocker administration. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers were administered to patients according to current best practice. The use of diuretics was determined by the attending physician. Digitalis was prohibited in the initial 24 h of symptom onset. In addition to routine medication, the control group was administered SN injections (cat. no. H20058959; Youcare Pharmaceutical Group Co., Ltd.) at an initial rate of 5 μg/min and then at timely increments of 5 μg every 5 min based on the initial dose according to the patients' response; the course of treatment was 3-7 days. In addition to routine medication and SN injections as administered in the control group, the research group was administered 0.5 mg freeze-dried RHBNP at an initial pump speed of 5 ml/min, which was adjusted on a timely basis according to the patients' blood pressure; the course of treatment was a period of three days.

Observation indices. The following observation indices were determined: i) Fluid intake and 24 h urine volumes following drug use; ii) Pulmonary capillary wedge pressure (PCWP) and left ventricular ejection fraction (LVEF) before and three days after treatment detected using a non-invasive cardiac hemodynamic detector [Shanghai Meike Medical Instrument Co., Ltd.; Item number: Country feeds medical inspect machinery (quasi) word 2008 No. 2211255]; iii) Cardiac function before and three months after treatment based on NYHA classification (13), where a lower score indicated better treatment efficacy and iv) Levels of biochemical indicators before and 24 h after treatment. To measure levels of biochemical indicators, fasting venous blood samples (5 ml) were obtained from the research group 1 day before treatment and 24 h after drug use. The samples were centrifuged at 1,500 x g at 4˚C for 10 min. Serum high-sensitivity C-reactive protein (hs-CRP) (Wuhan Vector Science Technology Co. Ltd.; cat. no. ELA-E0821r) levels were determined using rate nephelometry. Plasma N-terminal pro-brain/B-type natriuretic peptide (NT-proBNP) (Shanghai Xiyuan Biotechnology Co. Ltd., cat. no. XY-RD191486200R) and cardiac troponin I (cTnI) (Guangzhou Wondfo Biotech Co. Ltd., cat. no. A217) levels were determined using chemiluminescence ELISA with magnetic bead isolation.

Efficacy assessment. Based on previously reported criteria (14), efficacy was assessed as a i) Marked effect, defined as complete resolution of clinical symptoms, improvement in cardiac function by at least two classes and recovery of vital signs to normal; ii) Effect, defined as alleviation of clinical symptoms, improvement in cardiac function by at least one class and recovery of vital signs to normal and iii) No effect, defined as the absence of improvement in vital signs, clinical symptoms, and cardiac function. The total effective rate was calculated using the following formula: (Number of patients with marked effect + number of patients with effect)/total number of patients x100%.

Follow-up. Following discharge, all patients were routinely followed up and heart failure was treated with rest, blood glucose control and basic medication such as angiotensin-converting enzyme inhibitors, diuretics, oral nitrates and aspirin. After a period of 1 month, all patients were followed up via telephone interviews and were inquired whether they developed recurrence of heart failure and if so, those patients were re-admitted for treatment.

Statistical analysis. SPSS 22.0 (IBM Corp.) was used to evaluate the data and GraphPad Prism 5.0 (GraphPad Software, Inc.) was used to generate figures. Intragroup enumeration data were expressed as number and percentage [n (%)]. Intergroup comparison was analysed using the χ^2 test and variables with

Table I. General clinical data of patients in research and control groups.

Classification	Research group (n=48)	Control group (n=48)	t/χ^2 value	P-value
Sex			0.668	0.414
Male	21 (43.75)	25 (52.08)		
Female	27 (56.25)	23 (47.92)		
Age (years)	65.43±5.87	66.31±6.12	0.719	0.474
Course (years)	17.2±1.6	17.4±1.8	0.575	0.566
Weight (kg/cm^2)	25.9±3.9	26.3±4.2	0.484	0.629
Residence place			1.503	0.220
Urban area	22 (45.83)	28 (58.33)		
Rural area	26 (54.17)	20 (41.67)		
Nationality			0.178	0.673
Han	29 (60.42)	31 (64.58)		
Minority	19 (39.58)	17 (35.42)		
Educational background			0.168	0.682
≥Senior high school	23 (47.92)	21 (43.75)		
<Senior high school	25 (52.08)	27 (56.25)		
Smoking history			0.464	0.496
Yes	33 (68.75)	36 (75.00)		
No	15 (31.25)	12 (25.00)		
Alcohol consumption history			0.168	0.682
Yes	25 (52.08)	27 (56.25)		
No	23 (47.92)	21 (43.75)		
Diabetes history			1.191	0.275
Yes	35 (72.92)	30 (62.50)		
No	13 (27.08)	18 (37.50)		
Hypertension history			0.405	0.525
Yes	29 (60.42)	32 (66.67)		
No	19 (39.58)	16 (33.33)		
Etiology of heart failure			0.749	0.945
After acute myocardial infarction	11 (22.92)	12 (25.00)		
Ischemic cardiomyopathy	9 (18.75)	7 (14.58)		
Valvular heart disease	8 (16.67)	10 (20.83)		
Dilated cardiomyopathy	13 (27.08)	11 (22.92)		
Perinatal cardiomyopathy	7 (14.58)	8 (16.67)		
NYHA classification			1.090	0.579
Class II	15 (31.25)	13 (27.08)		
Class III	20 (41.67)	25 (52.08)		
Class IV	13 (27.08)	10 (20.83)		

Values are presented as n (%).

a theoretical frequency of <5 in the χ^2 test were analysed using the continuity correction χ^2 test. Measured data were expressed as the mean ± standard deviation. Measured data between research and control groups were compared using Student's t-test. Measured data before and after treatment were compared within the groups using a paired Student's t-test. Kaplan-Meier method was used to plot the overall survival of patients with acute heart failure in one month. $P<0.05$ was used to indicate a statistically significant difference.

Results

General characteristics. No significant difference was observed between the two groups regarding baseline demographic data, including sex, age, heart failure duration, weight, residence place, nationality, educational background, history of smoking and alcohol consumption, diabetes, hypertension, disease type and NYHA classification. These findings are summarized in Table I.

Table II. Comparison of the fluid intake and 24 h urine volumes after drug use between research and control groups.

Group	Number of cases	Fluid intake volume (ml)	Urine volume (ml)
Research group	48	1,148.69±65.24[a]	1,721.47±246.24[a]
Control group	48	1,121.23±62.57	1,405.69±216.74
t-value		2.105	6.669
P-value		0.038	<0.001

[a]P<0.05 vs. 24 h urine volume of the control group after drug use.

Table III. Comparison of cardiac function indices before and after treatment between research and control groups.

		PCWP (mmHg)		LVEF (%)	
Group	Number of cases	Before treatment	After treatment	Before treatment	After treatment
Research group	48	17.2±2.8	9.2±1.9[a,b]	42.2±5.1	58.9±6.3[a,b]
Control group	48	17.3±2.4	11.7±2.3[a]	42.1±4.4	51.2±5.8[a]
t-value		0.188	5.806	0.103	6.230
P-value		0.851	<0.001	0.918	<0.001

[a]P<0.05 vs. before treatment; [b]P<0.05 vs. control group after treatment. PCWP, pulmonary capillary wedge pressure; LVEF, left ventricular ejection fraction.

Comparison between research and control groups in terms of fluid intake and 24 h urine volume after drug use. The fluid intake and 24 h urine volume following drug use were higher in the research group compared with the control group (P<0.05; Table II; Fig. 1).

Comparison between research and control groups in terms of cardiac function indices before and after treatment. No significant difference was observed between the two groups in terms of cardiac function indices before treatment. Following treatment, PCWP levels were lower and LVEF levels were higher in the research group compared with the control group (P<0.05; Table III; Fig. 2).

Comparison between research and control groups in terms of cardiac function classification after treatment. No significant difference was observed between the two groups in terms of cardiac function classification before treatment. Following treatment, compared with the control group, the research group had more patients belonging to NYHA Class I and Class II and less patients belonging to NYHA Class III and Class IV (both, P<0.05; Table IV).

Comparison between research and control groups in terms of biochemical indicator levels before and after treatment. No significant difference was observed between the two groups in terms of NT-proBNP, hs-CRP and cTnI levels before treatment. However, following treatment, these levels decreased in both groups compared with before treatment (P<0.05) and NT-proBNP, hs-CRP, and cTnI levels were lower in the research group compared with the control group (P<0.05; Table V; Fig. 3).

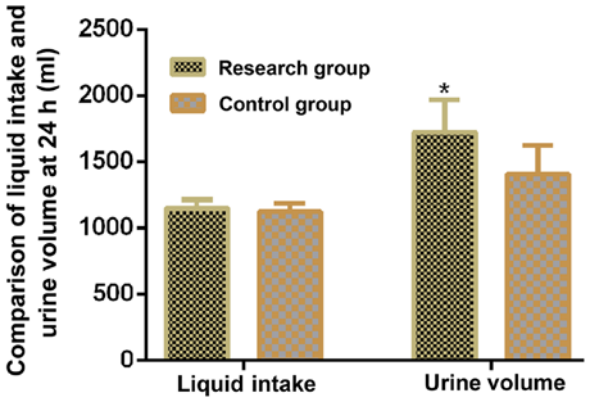

Figure 1. Fluid intake and urine volumes at 24 h after drug use were significantly higher in the research group compared with the control group. *P<0.05.

Comparison between research and control groups in terms of treatment efficacy. The research group showed a total effective rate of 97.92%, with marked effects in 30 patients (62.50%), effects in 17 patients (35.42%) and no effect in 1 patient (2.08%). The control group showed a total effective rate of 81.25%, with marked effects in 20 patients (41.67%), effects in 19 patients (39.58%) and no effects in 9 patients (18.75%). The total effective rate of treatment was higher in the research group compared with the control group (P<0.05; Table VI).

Table IV. Comparison of cardiac function classification before and after treatment between research and control groups.

		Class I		Class II		Class III		Class IV	
Group	n	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research group	48	0	25 (52.08)[a]	0	18 (37.50)[a]	29 (60.42)	4 (8.33)[a]	19 (39.58)	1 (2.08)[a]
Control group	48	0	15 (31.25)	0	9 (18.75)	31 (64.58)	18 (37.50)	17 (35.42)	6 (12.50)
t-value		-	4.286	-	4.174	0.178	11.561	0.178	3.852
P-value		-	0.038	-	0.041	0.673	0.001	0.673	0.049

Values are presented as n (%). [a]P<0.05 vs. control group after treatment.

Table V. Comparison of biochemical indicator levels before and after treatment between research and control groups.

		NT-proBNP (pg/ml)		hs-CRP (mg/l)		cTnI (ng/ml)	
Group	n	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research group	48	4,521±625	2,083±204[a,b]	18.51±3.93	11.65±1.82[a,b]	2.41±0.22	1.32±0.10[a,b]
Control group	48	4,606±549	2,348± 217[a]	17.8± 3.61	13.47±2.43[a]	2.39±0.24	1.56±0.12[a]
t-value		0.708	6.164	0.818	4.153	0.426	10.640
P-value		0.481	<0.001	0.416	<0.001	0.671	<0.001

[a]P<0.05 vs. before treatment; [b]P<0.05 vs. the control group after treatment. NT-proBNP, N-terminal pro-brain/B-type natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; cTnI, cardiac troponin I.

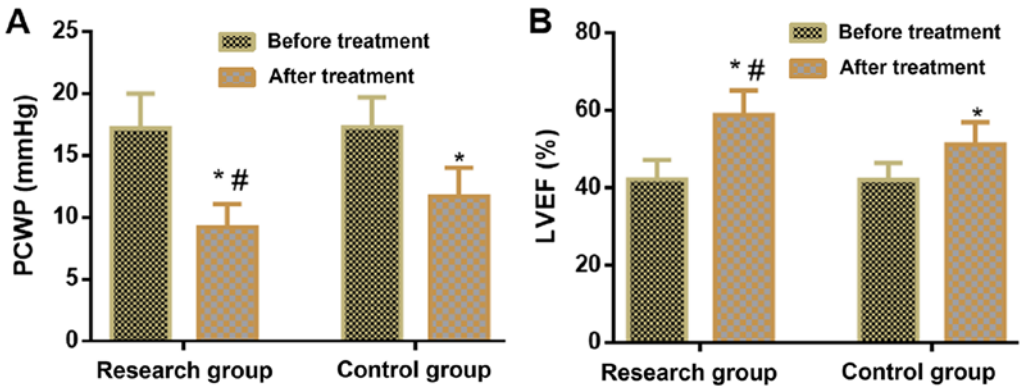

Figure 2. Comparison of cardiac function indices between research and control groups. Cardiac function indices before treatment were similar between the two groups. After treatment, (A) PCWP levels were significantly lower and (B) LVEF levels were significantly higher in the research group compared with the control group. *P<0.05 vs. before treatment; #P<0.05 vs. the control group after treatment. PCWP, pulmonary capillary wedge pressure; LVEF, left ventricular ejection fraction.

Comparison between research and control groups in terms of adverse reactions following treatment. Adverse reactions after treatment are listed in Table VII. The total incidence of adverse reactions in the research group was 10.42%, including headache in 2 patients (4.17%), hypotension in 1 patient (2.08%) and rashes in 2 patients (4.17%); bradycardia was not observed in any patient. The total incidence of adverse reactions in the control group was 27.08%, including headache in 4 patients (8.33%), hypotension in 5 patients (10.42%), rashes in 3 patients (6.25%) and bradycardia in 1 patient (2.08%), indicating that the total incidence of adverse reactions was lower in the research group compared with the control group (P<0.05; Table VII).

Comparison between research and control groups in terms of mortality within 1 month of treatment. No significant difference was observed between the two groups in terms of mortality within 1 month of treatment: Research group, 4 deaths (8.33%) and control group, 9 deaths (18.75%; Fig. 4).

Table VI. Comparison of adverse reactions after treatment between research and control groups.

Efficacy	Research group (n=48)	Control group (n=48)	χ^2 value	P-value
Marked effect	30 (62.50)	20 (41.67)	-	-
Effect	17 (35.42)	19 (39.58)	-	-
No effect	1 (2.08)	9 (18.75)	-	-
Total effective rate	47 (97.92)	39 (81.25)	7.144	0.001

Values are presented as n (%).

Table VII. Comparison of the incidence of adverse reactions after treatment between research and control groups.

Category	Research group (n=48)	Control group (n=48)	χ^2 value	P-value
Headache	2 (4.17)	4 (8.33)	0.711	0.399
Hypotension	1 (2.08)	5 (10.42)	2.844	0.092
Rash	2 (4.17)	3 (6.25)	0.211	0.646
Bradycardia	0 (0.00)	1 (2.08)	1.011	0.315
Total incidence of adverse reactions	5 (10.42)	13 (27.08)	4.376	0.036

Values are presented as n (%).

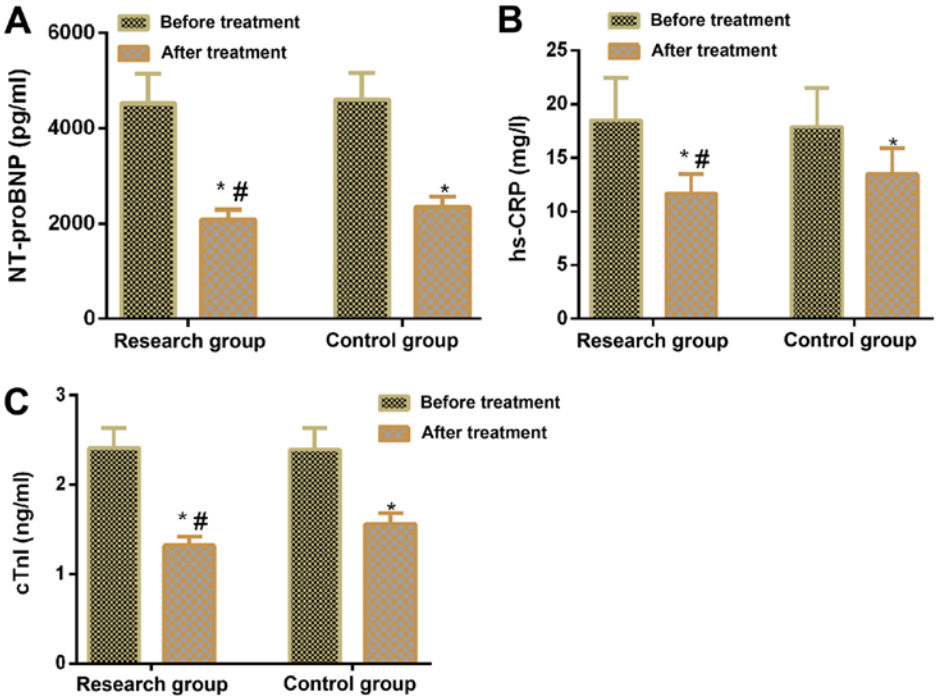

Figure 3. Comparison of biomedical indicator levels between research and control groups before and after treatment. No significant difference was indicated in (A) NT-proBNP, (B) hs-CRP and (C) cTnI levels before treatment between both groups. *P<0.05 vs. levels before treatment; #P<0.05 vs. the control group. NT-proBNP, N-terminal pro-brain/B-type natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; cTnI, cardiac troponin I.

Discussion

Heart failure is the leading cause of morbidity and mortality in developed countries, with increasing incidence (15). As one of the common causes of hospitalization, acute heart failure is a symptom, which indicates acute or subacute cardiac function deterioration owing to several possible underlying heart diseases and stimulating factors (16). Primary clinical symptoms of acute heart failure include hyperemia, cardiogenic shock or peripheral hypoperfusion, subsequently causing organ injury and failure (17,18). Therefore, clinicians are facing increasing pressure

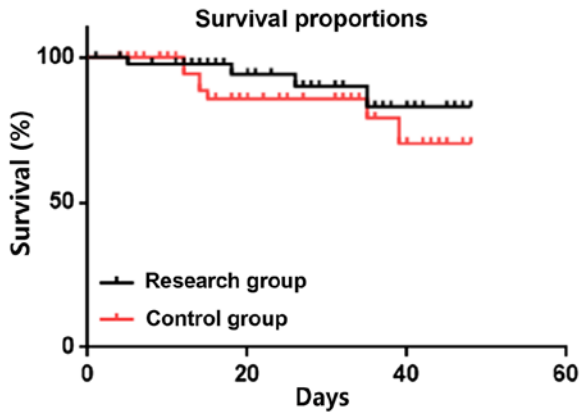

Figure 4. Mortality within 1 month of treatment did not significantly differ between the research and control groups.

regarding the treatment of acute heart failure, shortening hospital stays and preventing urgent treatment, re-hospitalization and short-term death after discharge (19). Therefore, a novel and safe treatment is required to alleviate acute heart failure.

RHBNP can promote hemangiectasis, diuresis and excretion, reduce cardiac load and preload, retrieve dynamic disturbance in patients with heart failure, inhibit neuroendocrine activation and improve ventricular remodelling (20). The perioperative administration of RHBNP can improve prognosis, shorten hospitalization time and decrease postoperative mortality in patients who have undergone cardiac surgery (21). SN is used to treat hypertensive emergency cases due to its ability to rapidly release nitric oxide and reduce blood pressure (22). As a vasodilator, it has the advantages of being cost-effective, useful, rapid and safe in pulmonary hypertension (23). Wei *et al* (24) demonstrated the advantages of RHBNP over SN in terms of short-term treatment efficacy for acute heart failure and reported that RHBNP can improve hemodynamics and cardiac function, decrease inflammatory cytokine levels and upregulate inflammatory cytokines. In another study, Guiha *et al* (25) reported that SN could effectively treat refractory heart failure by reducing the impedance to left ventricular ejection. Furthermore, Mullens *et al* (26) demonstrated that RHBNP combined with SN could effectively optimize inflammatory cytokine levels and improve cardiac function and hemodynamics. Inflammation is a well-known feature of heart failure (27), and studies have shown that the increase of serum hs-CRP, NT-proBNP and cTnI in patients can increase the risk of heart failure (28). The results of the present study indicated that compared with SN alone, the combination of RHBNP and SN can improve the urine volume of the patients, which is more effective for diuresis, such that it reduces pulmonary artery pressure, decreases cardiac preload and afterload, improves cardiac function classification, promotes the recovery of patients, inhibits the expression of inflammatory cytokines, exerts anti-inflammatory effects, accelerates healing after myocardial injury, rapidly improves dyspnea, and subsequently relieves clinical symptoms. In the present study, the combination treatment had a significantly lower incidence rate of adverse reactions and similar mortality rate within 1 month of treatment. Notably, the similar baseline clinical data between the study groups confirmed the rigor and reliability of the current study.

In the present study, the clinical indicators, adverse reactions and short-term follow-up of the two groups of patients after treatment were compared, which confirmed that RHBNP combined with SN was more effective than SN alone in the treatment of acute heart failure. The novelty of the present study was to observe changes in fluid intake volume at 24 h after treatment and to follow up the one-month survival rate. The changed records of fluid intake volume of patients at 24 h confirmed that the combination of the two methods could improve the urine volume and exhibited an improved diuretic effect. However, the present study did not evaluate quality of life of the patients. This needs to be assessed in future studies to further corroborate the results of the present study.

In conclusion, compared with SN alone, RHBNP combined with SN is more effective in the treatment of acute heart failure, such that it can effectively promote urination, reduce inflammatory response and rapidly improve clinical symptoms without significant adverse reactions. This may be due to the synergistic effects of RHBNP and SN, indicating its potential use in further clinical applications.

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Availability of data and materials

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

Authors' contributions

YP drafted the manuscript. HW reviewed the manuscript. YP and HW designed the study, collected the data and performed statistical analysis. YP and HW also read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the First Affiliated Hospital of Yangtze University. All research subjects and their family members were informed of the experiment and signed informed consent forms were obtained.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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