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Original Article

Effect and prognosis analysis of lyophilized recombinant human brain natriuretic peptide combined with isosorbide dinitrate in the treatment of acute heart failure

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Abstract: Objective: The research in this paper was designed to investigate the effect of lyophilized recombinant human brain natriuretic peptide (rhBNP) and isosorbide dinitrate in the treatment of acute heart failure. Methods: A total of 93 patients with acute heart failure admitted to our hospital during June 2018-May 2019 were divided into Group 1 (n=48) and 2 (n=45) in accordance with the order of admission. Patients were later treated with 1 rhBNP in Group 1 and isosorbide dinitrate in Group 2 following the initial therapies for both groups. Outcome measures included overall response rate, adverse reactions, prognosis, cardiac function, humoral factors, and quality of life of the two groups of patients. Results: (1) Overall response rate was reported in Group 1 as 91.67%, and 75.56% in Group 2 (P<0.05); (2) In terms of the incidence of adverse reactions, Group 1 showed an incidence of 22.92%, slightly higher than 20.00% in Group 2 (P>0.05); (3) 3 months after treatment, the readmission of patients in Group 1 was 6.25%, which was lower than that in Group 2, 11.11% (X^2=0.698, P=0.403); (4) After 3 days of treatment, relatively high LVEF and SV were observed in Group 1, but the Group 2 reported superior levels of LVEDD and LVESD (P<0.05); (5) After 3 days of treatment, renin, angiotensin Iand angiotensin II as well as aldosterone in patients of Group 1 were inferior to those in patients of Group 2 (P<0.05); (6) 1, 2, & 3 months after the treatment, patients in Group 1 expressed superior quality of life as shown in related scores compared with those in the patients of Group 2 (P<0.05). Conclusion: rhBNP could be more effective in the treatment of patients with acute heart failure by inducing responses and instant neuro-humoral regulation plus lower readmission rate and therefore superior quality of life, as compared with isosorbide dinitrate.

Keywords: Acute heart failure, lyophilized recombinant human brain natriuretic peptide, isosorbide dinitrate, treatment, prognosis, mechanism

Introduction

Heart failure (HF) serves as the distinct manifestation in patients with cardiac diseases when the advanced stage approaches, and the foremost cause of death in these diseases [1]. Among HF patients, further declined cardiac function predicts poorer quality of life and the worse prognosis [2]. By clinical features, HF is categorized as acute heart failure (AHF), and chronic heart failure (CHF) [3].

Ventricular remodeling follows the onset of HF. Specifically there will be increased norepinephrine and endothelin, activated renin-angiotensin-aldosterone system, as well as the active sympathetic nerves [4]. Many studies in fact also found increased peptide called B-type natriuretic peptide (BNP) that is released by ventricular myocytes, especially as seen in the presence of AHF. BNP plays roles in, among others, natriuretic, diuretic, balancing and/or dilation of pulmonary artery and systemic arteriovenous [5]. Modern researches proved BNP to be effective in antagonizing the renin-angiotensin-aldosterone system. It organizes antagonism to sympathetic nerves, endothelin, and norepinephrine, and inhibits the actions taken by fibroblasts and smooth muscle cells to reverse myocardial remodeling. These are conductive to better prognosis of AHF [6, 7].

Recombinant human brain natriuretic peptide is a novel drug synthesized by recombinant

DNA, with biological activities close to those of endogenous brain natriuretic peptide. Lyophilized recombinant human brain natriuretic peptide (rhBNP) refers to China's independently developed rhBNP capable of reducing water-sodium retention and improving natriuresis and/or dieresis [8, 9]. There has been no large-scale clinical trial conducted on rhBNP. Besides, its specific application has yet to be confirmed. In view of this, 93 patients with AHF admitted to our hospital were enrolled in order to investigate the effects of rhBNP and isosorbide dinitrate in the treatment of such diseases.

Material and methods

Material

A total of 93 AHF patients admitted to our hospital during June 2018-May 2019 were divided into Group 1 (n=48) and 2 (n=45) in accordance with the order of admission. All of them were informed of the study in detail and signed the informed consent of their own free will in a conscious state. (1) Inclusion criteria: patient who meets the diagnostic criteria for HF [10] with acute onset; shows typical AHF manifestations; is rated Grade III-IV by the New York Heart Function Rating (NYHA) [11]; has systolic pressure/diastolic pressure ≥90/60 mm Hg; and beyond all these above has left ventricular ejection fraction ≤40%, is allowed to be included. (2) Exclusion criteria: patient who has CHF; or associated with hepatic and renal insufficiency; or accompanied with severe underlying disease that affects the treatment in this study; or recently continued taking drugs that affects the autonomic nerves; or related to hypovolemia, shall be excluded. This study was approved by Ethics Committee of Affiliated Hospital of Panzhihua University.

Methods

Before the specific administration as mentioned below, patients were managed with the same initial therapies including routine anti-heart failure drugs, such as diuretics, vasodilators, β-blockers, digitalis preparations, and aldosterone receptor blockers, accompanied with basic disease control as well.

Patients in Group 2 were in addition treated with isosorbide dinitrate (Specification: 5 mg × 100 tablets, Approval No.: SFDA H12020816, Manufacturer: Tianjin Pacific Pharmaceutical Technology Group) for 3 days, 5-10 mg each time, 2-3 times a day.

Patients in Group 1 were additionally treated with rhBNP (Specification: 0.5 mg: 500 U, Approval No.: SFDA S20050033, Manufacturer: Chengdu Nuodikang Biopharmaceutical Co., Ltd.) for 3 days, 0.075 μg/(kg·min) daily by intravenous injection.

Outcome measures

Effectiveness of therapy: Criteria for evaluation of curative effects on heart failure were made by reference to Guidelines for the Diagnosis and Treatment of Heart Failure [12]. Excellent: rales disappeared; dyspnea removed; heart rate recovered; normal urine volume; and increased NYHA level by 2. Improved: reduced rales; slight dyspnea; nearly normal heart rate; normal urine volume; and increased NYHA level by 1. Ineffective: missed the requirements as specified in improved above; or deteriorated conditions. Overall response rate = percentage of excellent cases + percentage of improved cases.

Adverse reactions: Incidence of gastrointestinal reactions, postural hypotension, dizziness and headache, decreased serum creatinine, and decreased serum potassium after the treatment were recorded.

Prognosis: A follow-up for 3 months was carried out after the treatment so as to determine the readmission of patients due to deteriorated illness within the 3 months.

Cardiac function: Left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), and stroke volume (SV) of the two groups of patients before and 3 days after treatment were measured by cardiac sonography.

Humoral factors: Of the two groups of patients before and 3 days after treatment, levels of renin, angiotensin I, angiotensin II, and aldosterone were determined by the homogeneous competitive radioimmunoassay with 8 ml of cubital vein blood collected in the morning where the patient was in lying position.

Table 1. General information of patients in both groups ($\bar{x}$ ± sd)/[n (%)]

Item		Group 1 (n=48)	Group 2 (n=45)	t/X^2	*P*
Sex	M	22 (45.83)	23 (51.11)	0.259	0.611
	F	26 (54.17)	22 (48.89)		
Age (yr)		63.56±11.82	65.92±12.37	0.941	0.349
BMI (kg/m^2)		22.31±2.19	22.53±2.24	0.479	0.633
NYHA grading	III	30 (62.50)	28 (62.22)	0.001	0.978
	IV	18 (37.50)	17 (37.78)		
Pathogeny	Coronary heart disease	27 (56.25)	31 (68.89)	0.639	0.281
	Dilated Cardiomyopathy	10 (20.83)	7 (15.56)		
	Hypertensive heart disease	8 (16.67)	6 (13.33)		
	Others	3 (6.25)	1 (2.22)		

Table 2. Overall response rate reported by the two groups [n (%)]

Group	Excellent	Improved	Ineffective	ORR
Group 1 (n=48)	17 (35.42)	27 (56.25)	4 (8.33)	44 (91.67)
Group 2 (n=45)	12 (26.67)	22 (48.89)	11 (24.44)	34 (75.56)
X^2				4.457
P				0.035

Quality of life: The used Minnesota Heart Failure Quality of Life Questionnaire (MLHFQ) [13] is composed of 21 questions of which 5 are related to emotion, 8 related to physical activities and the last 8 cover other aspects. To each question there are 6 answer options scored as 0-5 respectively. The total scale is 0-105, inversely proportional to the quality of life. Evaluation was performed separately before treatment, and 1, 2, and 3 months after treatment.

Statistics analysis

Statistical analysis was performed with SPSS 22.0. Measurement data was expressed as mean ± standard deviation ($\bar{x}$ ± sd); comparison among groups was subject to independent sample *t* test. Enumeration data was expressed as [n (%)]; comparison among groups was subject to X^2 test. P<0.05 indicated statistically significant differences.

Results

General information

There were no significant differences in gender distribution, average age, average body mass index (BMI), NYHA classification, and/or etiology between the two groups (P>0.05) (**Table 1**).

Overall response rate

The overall response rate in Group 1 was 91.67%, superior to that of 75.56% in Group 2, with significant difference (P<0.05) (**Table 2**).

Adverse reactions

The rate of adverse reactions occurred in Group 1 was 22.92%, which was slightly higher than that in Group 2 (20.00%) (P>0.05) (**Table 3**).

Prognosis

At 3 months after treatment, 3 (6.25%) patients treated with rhBNP in Group 1 were readmitted to the hospital. It was 5 (11.11%) in Group 2 where isosorbide dinitrate was used. The difference between the two groups was not statistically significant (X^2=0.698, P= 0.403) (**Figure 1**).

Cardiac function

Group 1 before treatment: LVEF, 0.34±0.12%; LVEDD, 68.52±9.49 mm; LVESD, 55.43±8.19 mm; SV, 45.24±7.60 ml/beat; Group 2 before treatment: LVEF, 0.33±0.11%; LVEDD, 67.19± 9.22 mm; LVESD, 54.93±8.33 mm; SV, 45.91± 7.18 ml/beat. There were no differences between the two groups (all *P*>0.05). 3 days after treatment, Group 1: LVEF, 0.65±0.15%; SV, 68.12±8.13 ml/beat; LVEDD, 58.21±7.36 mm; LVESD, 47.62±7.31 mm; Group 2: LVEF, 0.51±0.10%; SV, 60.34±6.97 ml/beat; LVEDD, 64.32±8.43 mm; LVESD, 52.16±7.91. Both

Table 3. Adverse reactions occurred after treatment in the two groups [n (%)]

Group	Gastrointestinal reactions	Postural hypotension	Dizziness & headache	Reduced serum creatinine	Reduced serum potassium	Total incidence
Group 1 (n=48)	4 (8.33)	3 (6.25)	1 (2.08)	1 (2.08)	2 (4.17)	11 (22.92)
Group 2 (n=45)	2 (4.44)	2 (4.44)	2 (4.44)	0 (0.00)	3 (6.67)	9 (20.00)
X^2						0.117
P						0.732

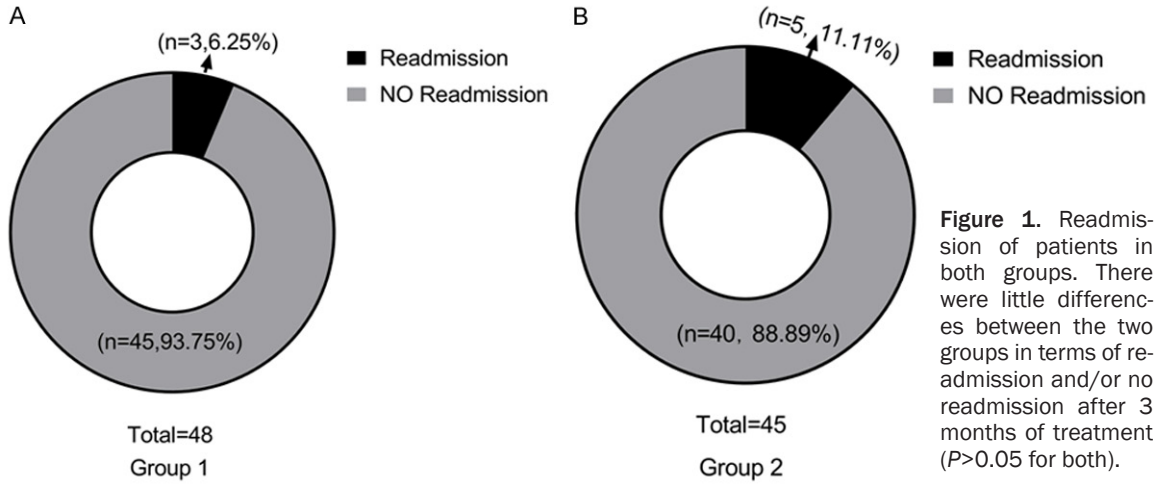

Figure 1. Readmission of patients in both groups. There were little differences between the two groups in terms of readmission and/or no readmission after 3 months of treatment (*P*>0.05 for both).

LVEF & SV 3 days after treatment in Group 1 were higher than those in Group 2, but LVEDD and LVESD in Group 2 were superior (P<0.05) (**Figure 2**).

Humoral factors

Group 1 before treatment: renin activity, 6.38±1.75 pmol/L; angiotensin I, 6.53±2.18 ng/ml; angiotensin II, 4.11±0.38 μg/L; aldosterone, 440.31±152.37 pmol/L, all were slightly different from those in Group 2 before treatment: renin activity, 6.50±1.82 pmol/L; angiotensin I, 6.48±2.11 ng/ml; angiotensin II, 3.95±0.41 μg/L; aldosterone, 429.62±138.79 pmol/L. After 3 days of treatment, the individual indicators in the same order in Group 1 were 3.12±1.08 pmol/L, 4.60±1.23 ng/ml, 3.12±0.26 μg/L, & 220.32±102.28 pmol/L, all were significantly higher than those in Group 2 (P<0.05) (**Figure 3**).

Quality of life

MLHFQ score before treatment in Group 1, 75.56±12.34, was not obviously different from 78.31±13.19 in Group 2 (P>0.05). However, at 1, 2, and 3 months after treatment, the MLHFQ scores in Group 1, 63.48±8.91, 53.35±6.83, 41.19±4.79, respectively, were significantly inferior to those in Group 2, which were 70.42±10.13, 61.39±8.79, 50.34±6.45, respectively] (P<0.05) (**Figure 4**).

Discussion

In addition to newly-presented HF, AHF also includes acute exacerbation of CHF, which is also known as acute decompensated heart failure [14]. Regarding the pathogenesis of HF, it is considered that neuro-humoral regulation plays important roles, first, in increased sympathetic excitability: the onset of HF is followed by reduced cardiac output, stimulated aortic arch and carotid sinus baroreceptors that increases sympathetic excitation, and elevated blood noradrenaline which have an effect on the norepinephrine receptor to increase the heart rate as well as the peripheral vasoconstriction that further steps up cardiac afterload and therefore myocardial oxygen consumption [15, 16]; second, increased humoral factors: following the occurrence of HF, some humoral factors is increased, such as arginine vasopressin, endothelin, and natriuretic peptides, where arginine vaso-

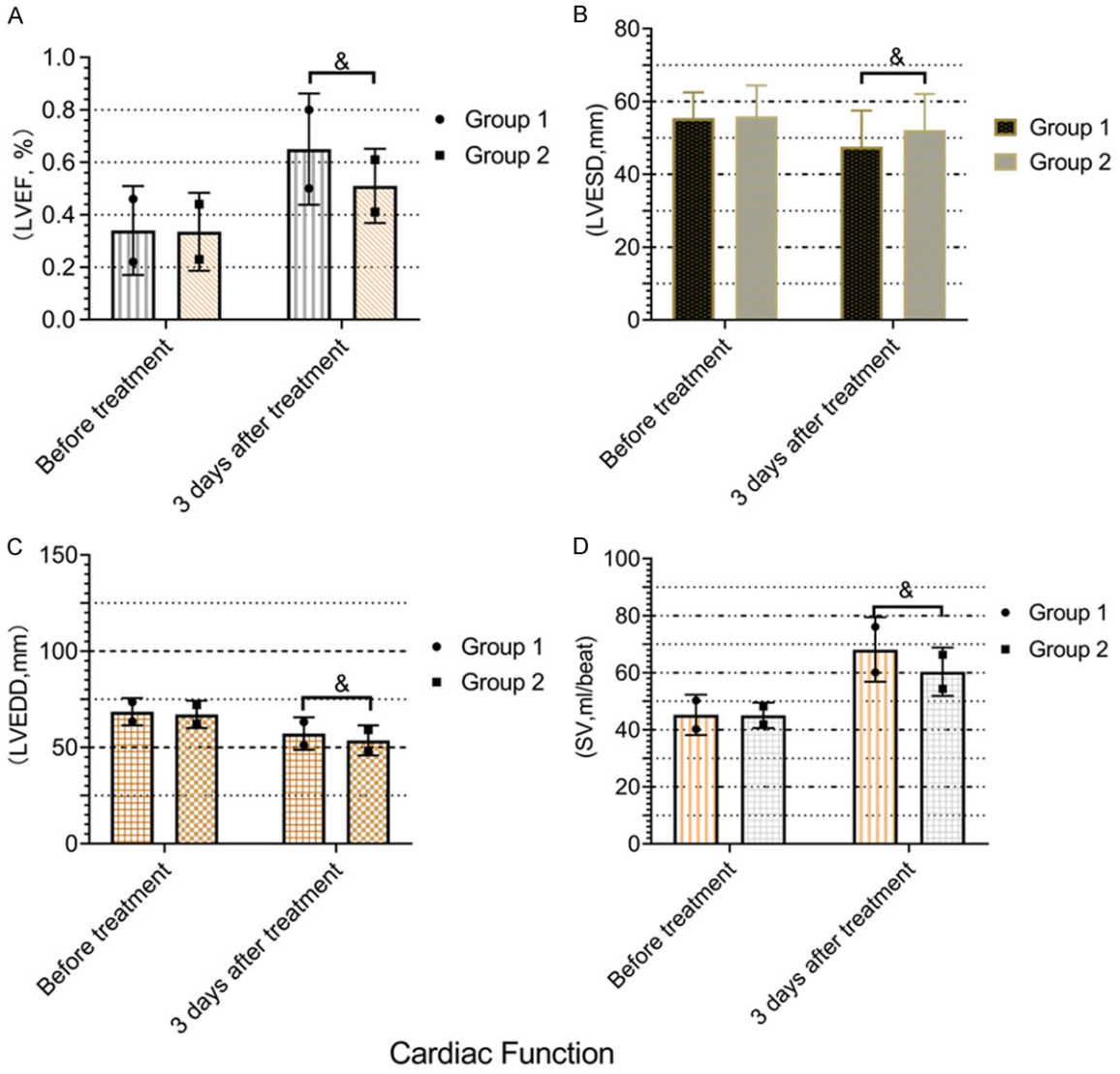

Figure 2. Cardiac functions of patients in both groups. Before treatment, there were little differences in levels of LVEF (A), LVESD (B), LVEDD (C), and/or SV (D) between the two groups ($P>0.05$). 3 days after treatment, LVEF (A), and SV (D) levels in Group 1 were higher than those in Group 2 ($P<0.05$) yet LVEDD (C) and LVESD (B) in Group 2 were superior ($P<0.05$). & indicated $P<0.05$ between the groups.

pressin causes more cardiac preload and afterload by promoting vasoconstriction and lowering the clearance of free water to water retention, endothelin increases vascular resistance by vasoconstriction, whilst brain natriuretic peptide, one of the natriuretic peptides, increases itself [17, 18]; and third, RAAS activation: hypoperfusion of the kidney induces activated RAAS system which raises angiotensin and aldosterone levels of which the angiotensin imposes ventricular afterload by triggering vasoconstriction and accelerates the release of aldosterone, which has an effect on water and sodium retention leading to lifted preload and afterload of the heart, and/or norepinephrine [19, 20].

Although basic measures including diuresis, cardiotonic, and vasodilation are essential to the treatment of AHF, they, alone, would not offer desired improvement. Isosorbide dinitrate applied in the Group 2 is one type of vasodilator that induces small veins to evident dilation. Intravenously injected isosorbide dinitrate also alleviates cardiac preload and ventricular filling pressure so as to present improved hemodynamics [21]. However, isosorbide dinitrate alone has little effect on im-

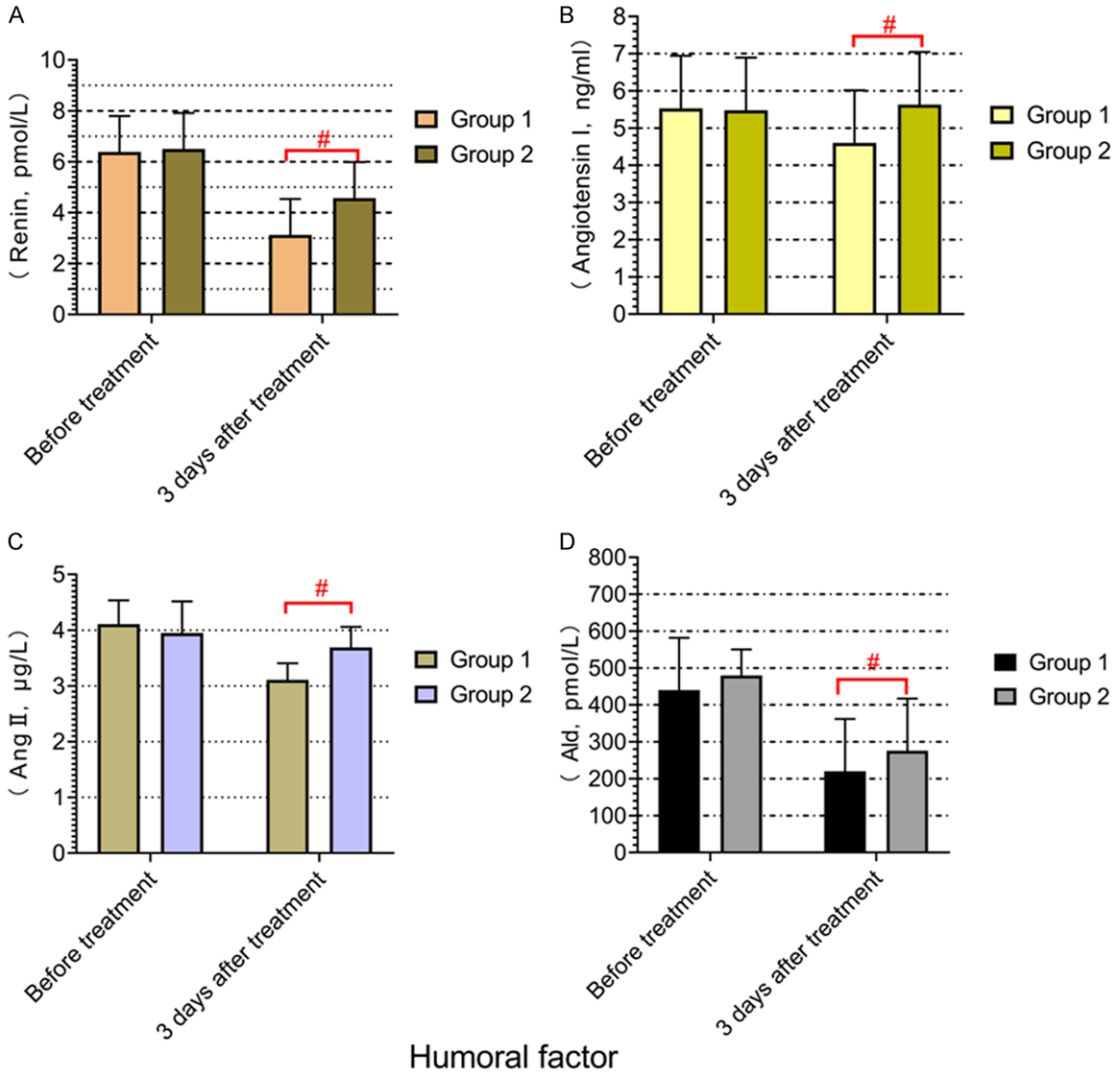

Figure 3. Humoral factor levels in both groups. Before treatment, there were little differences in levels of renin (A), angiotensin I (B), angiotensin II (C) and/or aldosterone (D) between the two groups ($P>0.05$). 3 days after treatment, all these individual levels in Group 1 were notably lower as compared with those in Group 2 ($P<0.05$). # indicated $P<0.05$ between the groups.

paired cardiac function, let alone the quality of life of patients. In Group 1, the rhBNP refers to the biological preparation synthesized by recombinant DNA technology. The molecular weight is 3464 Da. It shares the same sequence consisting of 32 amino acids with endogenous polypeptides released by ventricular muscles. Their mechanism of actions could be basically consistent [22]. A prospective study by Zhao et al. [23] found that rhBNP more quickly relieved the clinical symptoms of HF patients. In this study, the overall response rate of Group 1 was higher than that of Group 2 after 3 days of treatment; yet the incidence of adverse reactions as well as readmission within 3 months after treatment were not notably different from those of Group 2. It was suggested that rhBNP could be preferable to ensure more effective and safe treatment, together with good prognosis, as compared to isosorbide dinitrate. It may be explained by the fact that rhBNP increases cGMP by binding to natriuretic peptide A and B receptors, that rhBNP causes small arteries and veins dilated to greatly reduce the pulmonary capillary wedge pressure and right atrial pres-

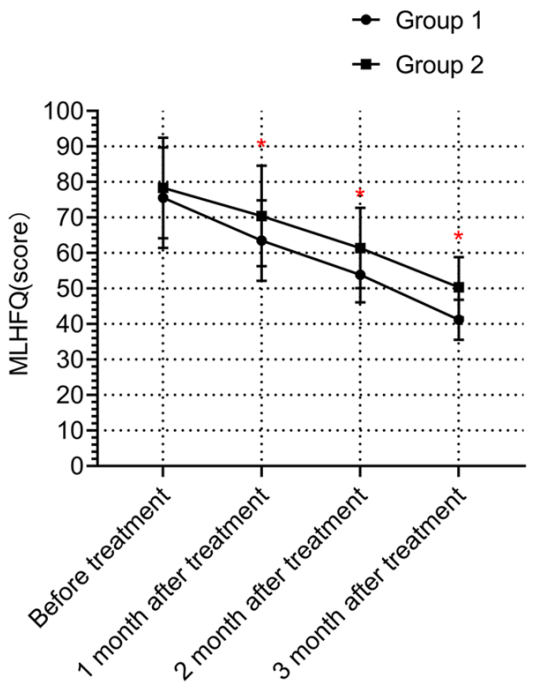

Figure 4. Quality of life of patients in both groups. Before treatment, there were little differences in the quality of life scores between the two groups ($P>0.05$). At 1, 2, and 3 months, respectively, after treatment, the quality of life scores of patients in Group 2 were remarkably superior to those of patients in Group 1 ($P<0.05$). * indicated $P<0.05$ between the groups.

sure and therefore cardiac preload, and that rhBNP cuts down peripheral vascular resistance to offer lower cardiac afterload [24]. Song et al. [25] showed that LVEF increased in HF patients treated with rhBNP. In this paper, as compared with those reported by Group 2, superior cardiac function and humoral factors, along with better quality of life scores tested at 1, 2, and 3 months after treatment in Group 1 indicated that rhBNP is more efficient with respect to controlling body fluid and improving the cardiac function, and quality of life of the patients. Among all related reasons, it should be noted that rhBNP inhibits the release of angiotensin II and aldosterone, lowers glomerular filtration, suppresses sodium reabsorption by the collecting duct in medulla nephrica, exerting good sodium excretion and urination [26]. In addition, rhBNP may lower the activity of neurohormone to reverse cardiac remodeling; it could effectively inhibit central and peripheral sympathetic nerves, directly decompose myocardial cells to be antagonistic to vascular fibrosis and/or tissue proliferation [27].

To sum up, rhBNP could be more effective in the treatment of acute heart failure than isosorbide dinitrate on the account of evident neuro-humoral regulation, lower readmission rate and improved quality of life of patients. The small sample size, however, plus incomplete design on the mechanism of actions, likely produce the bias of the results in this study. Future researches focusing on larger sample size, extensive range and perspectiveness to provide scientific evidences for the treatment of AHF were warranted.

Disclosure of conflict of interest

None.

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