

# Effect of levosimendan combined with recombinant human brain natriuretic peptide on diuretic resistance

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## ABSTRACT

Levosimendan is a calcium sensitizer used for managing heart failure (HF) because of its inotropic and vasodilatory effects. As many patients do not respond to levosimendan as a monotherapy, it may be necessary to combine it with other diuretic agents such as recombinant human brain natriuretic peptide (rhBNc P). The aim of this study was to investigate efficacy of levosimendan when combined with rhBNP in patients with diuretic resistance and low ejection fraction (EF) rate.

The study included HF patients with diuretic resistance and low EF. Before grouping, patients with a 24-hour urine volume of <0.5 mL/kg/h were administered with furosemide injection. Treatment group was administered levosimendan injection based on the original diuretic and rhBNP.

One hundred twenty-eight patients were included, with 64 patients each in the control and treatment arms. 24-hour urine volume of the treatment group was significantly higher than that of the control group. Moreover, dyspnea score of the treatment group significantly improved compared with control group. In the treatment group, 12.5% of patients had no significant changes in the urine volume, weight, and dyspnea score before and after the treatment, indicating poor curative effect of the treatment, whereas in the control group, 23.4% of patients had poor curative effect ( $P < .05$ ). No significant change was observed in the systolic blood pressure, heart rate, and serum creatinine level before and after treatment in both groups.

Levosimendan in combination with rhBNP can effectively relieve diuretic resistance, reduce body weight, improve dyspnea, and ensure safety in the treatment process.

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Volume overload; dyspnea score; heart disease; inotropic effect; combination diuretic therapy

## 1. Introduction

Heart failure (HF) is a progressive disorder with an estimated prevalence of 64.3 million people worldwide [1]. An important pathophysiologic process of HF is volume overload, which is conventionally treated with diuretics. However, their prolonged use can lead to diuretic resistance, which affects approximately 20% to 30% of patients with HF, increasing short- and long-term mortalities [2–5]. Inotropic drugs improve cardiac output by enhancing cardiac contractility, and has been considered as an attractive approach to provide improvements in HF symptoms [6]. Compared with other inotropes, levosimendan promotes sensitization of cardiomyocyte to calcium ions without increasing intracellular calcium levels, which may prevent an increased risk of cardiac arrhythmia [7]. Levosimendan also acts as a vasodilator by regulating ATP-dependent potassium channels. By acting via both inotropic and vasodilatory approaches, the drug enhances cardiac output without increasing myocardial oxygen demand [8]. In most of the reported studies, the application of levosimendan on refractory HF has been mainly

focused on the treatment of diuretic resistance [9,10]. However, despite advances in HF therapy, many patients do not respond to a levosimendan as a monotherapy and experience clinical deterioration [11]. To accelerate and improve its effects to lower diuretic resistance, levosimendan can be used in combination with other diuretic agents such as natriuretic peptides.

Natriuretic peptides have been widely known to enhance diuresis by increasing cardiac output, inhibiting renin-angiotensin-aldosterone system (RASS), and improving diastolic function [12]. The levels of plasma brain natriuretic peptide (BNP) are significantly enhanced in patients with more severe HF and are presently listed as an established biomarker for heart disease in international guidelines [13,14]. Although high levels of BNP are already present in patients with HF, they have a lower protective efficacy when compared with the immunoreactive effects of exogenous recombinant human brain natriuretic peptide (rhBNP). Thus, the administration of rhBNP has shown to

improve symptoms and hemodynamic conditions [15]. The combination of rhBNP with levosimendan has been reported to improve clinical outcomes in terms of pulmonary congestion, edema, and New York Health Association (NYHA) functional class for the treatment of acute decompensated HF [16]. However, the effect of these two agents to specifically relieve diuretic resistance and decrease volume load in patients with HF is currently unknown.

Levosimendan and rhBNP act via different mechanisms to improve diuretic resistance, where the former is a positive inotropic agent and the latter inhibits the RASS. In theory, their combination may offer synergistic effects and better improved outcomes when compared with those of a single drug. Hence, the aim of this study was to investigate the effects of levosimendan administered in conjunction with rhBNP in patients with diuretic resistance and low ejection fraction (EF) rate.

## 2. Methods

### 2.1. Study population

This single-center, interventional study included patients with HF with diuretic resistance and low EF from cardiac care unit of Xinjiang Uygur Autonomous Region Hospital of traditional Chinese medicine, from June 2017 to June 2019. Diuretic resistance was defined as in need of more than two loop diuretic units per day. The diagnostic criteria of HF were those of the Chinese guidelines for diagnosis and treatment of HF 2018 [17]. The study protocol was approved by Xinjiang Uygur Autonomous Region Hospital of traditional Chinese medicine ethical committee (ethical approval number: XUATM2015Y034) and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before participation in the study.

### 2.2. Inclusion and non-inclusion criteria

The inclusion criteria were HF patients with a EF <40%, and those who have one or more of the following: dyspnea score  $\leq 4$  points (dyspnea scale developed according to the recommendations of the European Society of Cardiology International Working Group on acute HF [14], Box 1), lung moist rales, paroxysmal nocturnal dyspnea, orthopnea, hepatomegaly or ascites, jugular vein distension, pulmonary edema, or pleural effusion. All patients were classified according to their symptoms based on NYHA classification system [18] into class I–IV. Non-inclusion criteria were patients with acute coronary syndrome, estimated glomerular filtration rate (eGFR)

$\leq 30$  mL/min/1.73 m<sup>2</sup>, systolic blood pressure  $\leq 90$  mmHg, systemic infection, and blood potassium <3.5 mmol/L and those who participated in other clinical trials. At the time of study, the average BNP level of patients was 3000 pg/mL.

### 2.3. Grouping and treatment

Eligible patients were randomized using a computer-generated random number table in a 1:1 ratio and allocated into either control group or treatment group. According to the guidelines for diagnosis and treatment of HF, both groups were given comprehensive drug treatment for HF, including thiazide diuretics, cardiotoxic drugs, and vasodilators, to actively control the primary disease and eliminate incentives. During admission, all patients had a 24-hour urine volume of <0.5 mL/kg/h and were administered with furosemide injection at a dose of 80 mg/d. All patients rendered a urine output of more than 0.5 ml/kg/h. The patients in control group were administered with rhBNP (1.5  $\mu$ g/kg for 5 minutes, 0.0075  $\mu$ g/kg/min was continuously pumped), maintaining a 24-hour urine volume of <0.5 mL/kg/h. The dosage of natriuretic peptide was the same as before. The patients in the treatment group were given levosimendan injection (0.1  $\mu$ g/kg/min using micropump) based on the original diuretic and rhBNP and were observed for 24 hours.

### 2.4. Study outcomes

The efficacy was assessed within the group, and also between the groups in terms of 24-hour urine volume (mL), changes in body weight (kg), and changes in dyspnea score before and after 24 hours of treatment in both groups also between the two groups. Safety outcomes included changes in the systolic blood pressure (mmHg), heart rate (beats/min), and serum creatinine levels ( $\mu$ mol/L) before and after the treatment.

### 2.5. Statistical analysis

The statistical analysis was performed using SPSS22.0 software. Chi-test or Fischer's exact test was independent *t* test used for comparison between the two groups if the data were distributed normally and variance was homogenous. Mann-Whitney test was used if the data was not normally distributed. To compare the values within the individual treatment group, paired *t*-test was applied.  $P < .05$  was considered to be statistically significant.

## 2.6. Sample size

A sample size calculation was done considering the effect size of the two groups. The effect size was calculated using the standardized difference – the absolute difference divided by the standard deviation. Using conventional values of  $\alpha = 0.05$  and 80% power, median effect size = 0.5 the required sample size was calculated as 64 per group [19].

## 3. Results

### 3.1. Demographic and baseline characteristics

The study included 128 patients divided into two groups (treatment and control) of 64 patients each (Figure 1). Of the total patients enrolled, 74 were males, with a mean age of  $61.4 \pm 10.8$  years. The patients had an average BNP level of 3000 pg/mL, and based on the NYHA guidelines, 52 patients had NYHA class III and 76 had NYHA class IV. The average course of disease was  $4.70 \pm 1.40$  years (Table 1). Statistically, no significant difference was observed in sex, age, weight, course of disease, dyspnea score, NYHA cardiac function classification, and combined diseases between the 2 groups ( $P > .05$ ).

### 3.2. Efficacy outcomes

All three measured outcomes (*ie*; urine volume, weight, and dyspnea score), rendered improvement in the treatment group when compared with the control group ( $P < .05$ ; Table 2).

Within the treatment group, a significant mean increase of  $1168 \text{ mL} \pm 170 \text{ mL}$  was observed after the administration of levosimendan, whereas an increase of  $499 \text{ mL} \pm 42 \text{ mL}$  was observed in the control group ( $P < .05$ ; Table 2). The average body weight of the patients significantly decreased by  $3.2 \pm 0.26 \text{ kg}$  in the treatment group. However, no significant change was observed in the control group. The mean dyspnea score of the treatment group increased significantly by  $4.2 \pm 1.5$  [4,5,20] points (Table 2). The control group also showed a significant increase in dyspnea score by  $1.45 \pm 0.7$  ( $P < .05$ ).

There was no significant change in the urine volume, body weight and dyspnea scores in 23 patients before and after treatment in both groups. The mean eGFR was  $38.4 \pm 4.7 \text{ mL/min/1.73 m}^2$ , and the mean EF was  $24.6 \pm 4.9\%$ , including 8 (12.5%) patients in the treatment group and 15 (23.4%) patients in the control group. The proportion of patients with poor efficacy in the treatment group (2%) was significantly lower than that in the control group (21%) ( $P < .05$ ).

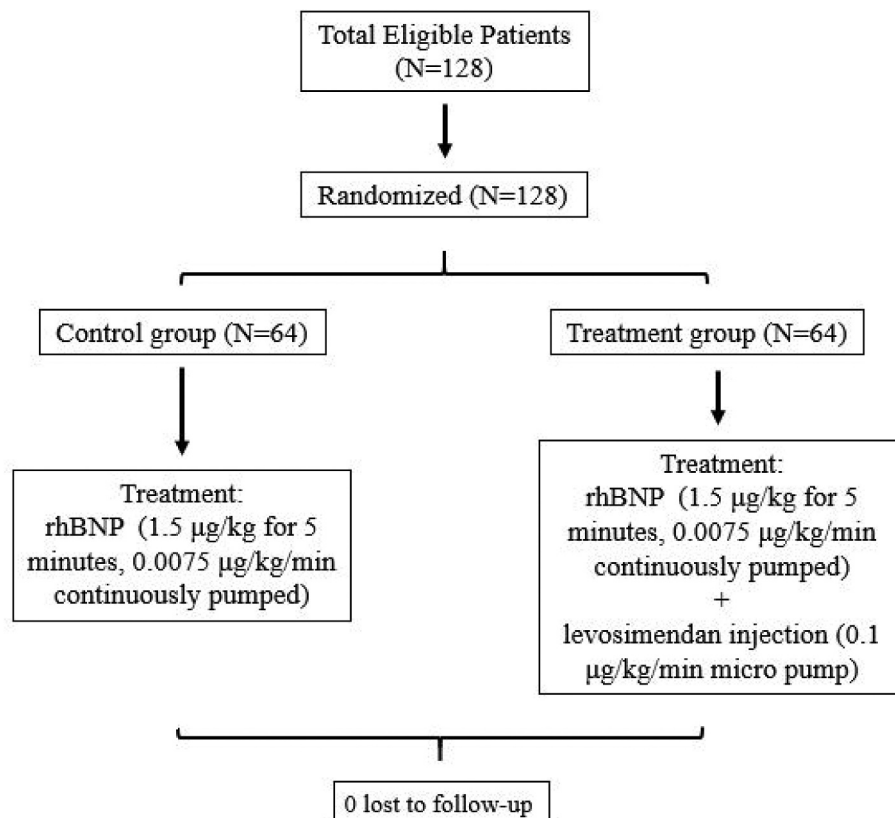


Figure 1. Patients' flowchart.

rhBNP: recombinant human brain natriuretic peptide.

**Table 1.** Demographics and baseline characteristics of patients.

Parameters	Control group (n = 64)	Treatment group (n = 64)	P-Value
Sex (n [%]): male	34 (53.1)	40 (62.5)	0.08
Age (years; mean $\pm$ SD)	58.60 $\pm$ 9.60	57.70 $\pm$ 10.40	0.61
Course of disease (years; mean $\pm$ SD)	4.40 $\pm$ 1.70	3.9 $\pm$ 1.90	0.12
Weight (kg; mean $\pm$ SD)	75.30 $\pm$ 9.20	76.70 $\pm$ 11.20	0.45
ACE/ARB	60 (93.8)	57 (89.1)	0.16
Beta-blockers	59 (92.2)	62 (96.9)	0.16
Aldosterone receptor antagonists	58 (90.6)	61 (95.3)	0.16
NYHA cardiac function class (n [%])	25 (39.1)	27 (42.2)	0.13
Class III	39 (60.9)	37 (57.8)	
Class IV			
EF (%; n [%])	46 (71.9)	42 (65.6)	0.11
30–40	18 (28.1)	22 (34.4)	
15–30			
eGFR (mL/min/1.73 m <sup>2</sup> ; n [%])	56 (87.5)	54 (84.4)	0.18
$\geq$ 45	8 (12.5)	10 (15.6)	
30–45			
Combined diseases (n [%])	24 (37.5)	20 (31.3)	0.11
Dilated heart disease	29 (45.3)	24 (37.5)	0.10
Coronary heart disease	2 (3.1)	2 (3.1)	0.5
Rheumatic heart disease	8 (12.5)	12 (18.8)	0.12
Atrial fibrillation	16 (25)	19 (29.7)	0.13
Arterial-hypertension			

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; EF = ejection fraction; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association.

### 3.3. Safety outcomes

No significant differences were observed in the mean systolic blood pressure, heart rate or serum creatinine between the treatment and control groups ( $P > .05$ ; Table 3). Although a decrease in systolic blood pressure, heart rate, and serum creatinine levels was observed in the treatment group before and after treatment, these changes were not statistically significant ( $P > .05$ ; Table 3). Within the control group, the heart rate and serum creatinine levels were increased, and the systolic blood pressure was observed to decrease. Nevertheless, these changes were also not statistically significant ( $P > .05$ ; Table 3).

## 4. Discussion

In this study, we investigated the combined effects of levosimendan and rhBNP in patients with diuretic resistance. The results showed a significant increase in the

24-hour urine volume and dyspnea score and a significant reduction in the body weight, indicating better diuretic effects with the combination of levosimendan and rhBNP. Upon treatment with rhBNP, Colucci et al. [21] reported an increase in the urine volume and dyspnea compared with placebo. Furthermore, in a study by He et al. [22], a significant increase in the 24-hour urine volume after treatment with rhBNP was reported when compared with that before treatment and also when compared with control. In another study, the effect of rhBNP in ST-segment elevation myocardial infarction and HF was evaluated [23]. The study reported increased urine volume with rhBNP compared with nitroglycerine [23].

Levosimendan has previously reported to demonstrate a significant increase in the 24-hour urine output compared with that before treatment [24,25]. In par with the previous studies, the present study also reported a significant increase in the 24-hour urine volume and dyspnea score in the treatment group compared with control, and also when compared within the group (before treatment and after treatment), a significant increase was observed after treatment in both groups.

On one hand, levosimendan is able to inhibit the reabsorption of NaCl in the thick wall segment of renal tubular medullary loop, whereas rhBNP helps in antagonizing the RASS [26]. These stimulatory effects of both levosimendan and rhBNP synergistically help in reducing the diuretic resistance, and such combined treatment strategies seem promising in future HF therapies.

Although patients with eGFR  $<$ 30 mL/min/1.73 m<sup>2</sup> were excluded from the study, there were still a certain proportion (17.9%) of patients with poor curative effect. These patients showed poor EF and/or renal function even with other diuretics, which may be due to individual patient's sensitivity to drugs but the exact underlying reason for poor curative effect is unknown.

The mean systolic blood pressure, heart rate, and serum creatinine level decreased after treatment with levosimendan and rhBNP, but not statistically significant. The results from the present study are in accordance with reported studies. A study by Pan et al. [27] reported no significant change in the heart rate and serum creatinine levels during the treatment with rhBNP. Similarly, no significant decrease in the mean systolic blood pressure was reported with levosimendan

**Table 2.** Comparison of efficacy outcomes between the 2 groups.

Index	Control group (n = 64)		Treatment group (n = 64)	
	Before treatment	After treatment	Before treatment	After treatment
Urine volume (mL)	751 $\pm$ 128	1250 $\pm$ 116 <sup>a</sup>	782 $\pm$ 112	1950 $\pm$ 124 <sup>ab</sup>
Weight (kg)	75.30 $\pm$ 9.20	74.9 $\pm$ 10.7	76.70 $\pm$ 11.20	73.5 $\pm$ 5.7 <sup>ab</sup>
Dyspnea score	2.84 $\pm$ 1.58	4.37 $\pm$ 2.15 <sup>a</sup>	2.75 $\pm$ 1.68	6.38 $\pm$ 2.27 <sup>ab</sup>

Data were mean  $\pm$  standard deviation.

Before treatment vs. after treatment for the same group: <sup>a</sup> $P < .05$ .

Control group vs. treatment group for the same time: <sup>b</sup> $P < .05$ .

**Table 3.** Comparison of safety indexes between the 2 groups before and after treatment.

Index	Control group (n = 64)		Treatment group (n = 64)	
	Before treatment	After treatment	Before treatment	After treatment
Systolic blood pressure (mmHg)	123.2 ± 11.4	121.8 ± 13.9	124.4 ± 14.2	121.9 ± 19.3
Heart rate (beats/min)	76 ± 18	81 ± 14	79 ± 15	74 ± 18
Serum creatinine (μmol/L)	83.43 ± 17.74	86.43 ± 16.59	81.45 ± 19.87	78.75 ± 20.47

Data were mean ± standard deviation.

Before treatment vs. after treatment for the same group:  $P > .05$ .

and rhBNP in a study by Bocchi et al. [28]. In another study, it was reported that the application of levosimendan in the patients with advanced HF was safe with no significant difference in the systolic blood pressure, heart rate, and serum creatinine values between the treatment and control groups [29, 30]. In addition, the present study reported no all-cause deaths in the two groups during the treatment process. Hence, from the results, combined use of levosimendan and rhBNP is not only effective in treating patients with HF with diuretic resistance, but it is also safe.

#### 4.1. Study limitations

Major limitations of the study include short end point analysis of the 24-hour urine volume, and single-center study, implicating that the data may not be generalized for a larger population. Nevertheless, to the best of the authors' knowledge, this is the first study that investigates the combination of levosimendan and rhBNP in treating patients with HF with diuretic resistance and low EF, and provides a rationale to develop more in-depth studies with multicenter, randomized, controlled clinical trials with larger patient cohorts and follow-up timelines.

## 5. Conclusion

Levosimendan when combined with rhBNP can effectively relieve diuretic resistance, increase urine volume, reduce body weight, improve dyspnea, and ensure safety in the treatment process.

### Data availability statement

All data used in this study will be available from the corresponding author upon reasonable request.

### Disclosure statement

No potential conflict of interest was reported by the author(s).

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Ethics approval and consent to participate

The study protocol was approved by Xinjiang Uygur Autonomous Region Hospital of traditional Chinese medicine ethical committee (ethical approval number: XUATM2015Y034) and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before participation in the study.

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