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Effects of recombinant human brain natriuretic peptide on serum NPY and galectin-3 in patients with acute heart failure: A preliminary study

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Heart failure (HF) is the main cause of death in patients with cardiovascular diseases (CVDs), such as coronary atherosclerotic heart disease, and hypertension. It is prevalent (1.5-2.0%) in the global population, and in China it is 0.9%. Recombinant human brain natriuretic peptide (RH-BNP) is known to improve the clinical symptoms of HF patients. As the serum Neuropeptide-Y (NPY) is positively correlated with the development and improvement of HF, it is used to evaluate the prognosis of HF patients. As the biomarker of fibrosis and inflammation, Galectin-3, a multifunctional β-galactoside binding protein, has a considerable predictive effect on the development of HF and the occurrence of cardiovascular complications. Here, we investigated the therapeutic effect of RH-BNP on acute heart failure (AHF) and the effects on neuropeptide-Y (NPY) and Galectin-3. Sixty patients with AHF were selected and randomly rolled into an experimental group (Exp group, 30 cases, conventional treatment + RH-BNP treatment) and a control group (Ctrl group, 30 cases, conventional treatment). The functions of heart, lung, liver, and kidney of patients in different group were compared, and the changes in serum NPY and Galectin-3 in the Exp group were analysed. After 7 days of treatment, the level of amino terminal pre-B type natriuretic peptide (NT-proBNP) in the Exp group was significantly lower and the blood oxygen partial pressure (PaO_2) was much higher to those in the Ctrl group, showing great differences with P <0.05. The glomerular filtration rate (GFR) and urine volume (UV) of patients in the Exp group were obviously higher (P <0.05). 90% of the patients in the Exp group were effectively treated, which was more than 73.33% in the Ctrl group (P <0.05). The post-treatment NPY and Galectin-3 were down regulated compared with the levels in the first two tests (P <0.05). It has been found that compared with the conventional treatment, the application of RH-BNP effectively improved the heart and lung function of patients, reduced the liver and kidney toxicity, showed the diuretic effect, and enhanced the treatment efficiency. In addition, it promoted the decrease of serum NPY and Galectin-3 levels in patients, which was beneficial to better the prognosis of patients.

Keywords: Cardiovascular diseases (CVDs), Diastolic dysfunction, Glomerular filtration rate

Heart failure (HF) is a clinical syndrome of ventricular systolic and/or diastolic dysfunction caused by multiple causes, with patients usually suffering from dyspnea, skin edema, fatigue, etc.[1]. Acute heart failure (AHF) refers to acute clinical syndrome with sudden or acute exacerbation of HF symptoms and signs, and its pathogenesis is complex[2]. AHF includes acute decompensated heart failure (ADHF)[3]. China has a large population, and with the increase of "three high levels", the incidence of cardiovascular adverse events is gradually increasing, and the HF prevalence rate as well[4]. Globally, HF has a prevalence of about 1.5-2.0%, and China, 0.9%. Number of patients with HF has reached >4 million and is still increasing. At present, HF is still the main cause of death in patients with cardiovascular diseases (CVDs), such as coronary atherosclerotic heart disease, and hypertension[5]. Hence, there is a strong need to prevent the number of such incidences and treat HF. At present, HF treatment is mainly divided into drug therapy, electro-mechanical therapy, and surgical therapy[6-8].Due to various factors such as cost, invective, surgical risk, operation difficulty, donor source and effective rate, electro-mechanical therapy and surgical treatment are limited, and drug therapy is still the main treatment for HF[9,10].

Recombinant human brain natriuretic peptide (RH-BNP) that improves the clinical symptoms of HF patients, is the only new drug approved for HF treatment globally in the past two decades[11]. RH-BNP has similar spatial structure and biological activity to endogenous BNP, and plays various roles in the treatment of HF, including coronary artery dilation, arterial and venous dilation, cardiac afterload relief, and cardiac output enhancement. Without positive inotropic effect, it can also produce diuretic effect, improve glomerular filtration rate (GFR) and inhibit renin-angiotensin-aldosterone system (RAAS)[12]. Firstly, it inhibits the RAAS system by antagonizing the aldosterone and endothelin secreted by smooth muscle cells, improving the sodium excretion ability of HF patients, and thereby achieving the diuretic effect. Secondly, it blocks the endothelial cell guanylate cyclase to smooth the muscle relaxation. Thirdly, it reduces the smooth synthesis of collagen fibers, effectively inhibits the myocardial fibrosis, and maintains the normal elasticity of myocardial tissue. Further, it can dilate arteriovenous and coronary arteries, reduce the load before and after the heart, and improve the cardiac output[13,14].

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Similarly, Neuropeptide-Y (NPY), widely distributed in central and peripheral nerves, mainly in sympathetic nerves, coexists with norepinephrine[15]. NPY can also directly affect neutrophils and mast cells, resulting in cell degranulation reaction, promote platelet aggregation, leukocyte adhesion, and macrophage activation, and play a regulatory role in the whole immune response[16,17]. Patients with HF have significantly increased serum NPY level compared to the normal population which gets reduced after a period of treatment. It indicates a close relationship between serum NPY and HF, and studies have shown that the level of serum NPY is positively correlated with the development and improvement of HF[18,19]. Therefore, serum NPY level can be used to monitor the progression of the disease or to evaluate the prognosis of HF patients. Galectin-3, a multifunctional β-galactoside binding protein, produced by macrophages, vascular smooth muscle cells and endothelial cells, actively participates in regulating the behaviour of inflammatory cells and thereby plays a non-negligible role in inflammation, fibrosis, immunity, cardiac remodeling, tissue repair and other aspects[20,21]. It is associated with the adverse clinical events after myocardial infarction. As a biomarker of fibrosis and inflammation, Galectin-3 has been widely studied and has a good predictive effect on the development of HF and the occurrence of cardiovascular complications[22,23].

Therefore, in this work, we used recombinant human brain natriuretic peptide (RH-BNP) to treat patients with acute heart failure (AHF) and compared with those receiving conventional treatment to explore its therapeutic effect and its influence on serum Neuropeptide-Y (NPY) and Galectin-3, thus providing reference for AHF treatment.

Methodology

Selection Criteria

According to the exclusion criteria, 60 patients with AHF admitted to our hospital-Panjin Central Hospital from 01-01-2022 to 30-12-2023 were selected, including 34 males and 26 females with the average age of63.4±5.7 years. They were rolled into an Exp group (30 cases, conventional treatment + RH-BNP treatment) and a Ctrl group (30 cases, conventional treatment).

The patients enrolled for the study voluntarily had to satisfy all the following conditions (Inclusion criteria) : (i) clinically diagnosed as AHF; (ii) with left ventricular ejection fraction (LVEF) ≤40%; (iii) with New York Cardiac Function Scale (NYHA Scale) of grades III to IV; and (iv) with informed consent and being voluntarily participate in the study. However, the patients had to be excluded from this work if they had any of below conditions (Exclusion criteria): (i) with systolic/diastolic blood pressure (SBP/DBP) of 90/60 mmHg; (ii) with severe valvular heart disease, cardiomyopathy (dilated cardiomyopathy and hypertrophic cardiomyopathy), malignant arrhythmia, acute myocarditis, pericardial disease, or cardiogenic shock, etc.; (iii) suffering from neurological disorders and unable to communicate normally; and (iv) with liver and kidney diseases.

The Framingham diagnostic criteria for HF were as follows. diagrnostic 7 major and 7 minor criteria, and at least two major criteria must be met for HF diagnosis, or one major criterion plus two minor criteria must be met[24]. The primary (major) criteria are (i) jugular vein rage; (ii) lung wet rales; (iii) acute pulmonary edema; (iv) the third heart sound galloping horse rhythm; (v) enlarged cardiac boundary; (vi) paroxysmal dyspnea at night; and (vii) abnormal increase of central venous pressure. The secondary (minor) criteria include (i) subcostal palpability and liver enlargement; (ii) pitted edema in the ankle; (iii) dyspnea after activity; (iv) rapid heart rate (HR) (>120 beats/min); (v) paroxysmal cough at night; (vi) pleural effusion; and (vii) reduced vital capacity (only the maximum vital capacity of 1/3). If the patient experienced significant weight loss (≥4.5 kg) during the study period, it could be classified as primary or secondary.

The New York Heart Association (NYHA) grading criteria[25] has four grades. (1) Grade I: patients with CVDs were not restricted in physical activities, and normal light activities such as walking would not cause fatigue, dyspnea, and other manifestations. (2) Grade Ⅱ: patients with CVDs had mild physical activity restriction, no symptoms of HF at rest, however, but normal daily activities can appear mild HF manifestations. (3) Grade Ⅱ I: the physical activity of patients with CVDs was significantly limited, and the symptoms of HF could appear in normal daily activities, and the symptoms would be improved after rest. (4) Grade IV: patients with CVDs would have HF manifestations when performing any activities, and there was still no sign of improvement after rest, and the symptoms become worse after activities.

Treatment methods

In the Ctrl group, the patients had undergone electrocardiogram monitoring, blood pressure measurement, oxygen inhalation, and other general treatment, diuresis, blood pressure control, β-blocker, angiotensin converting enzyme inhibitors, and other conventional anti-HF treatment.

In the Exp group, on the basis of the above treatment, lyophilized RH-BNP (trade name: Neoxin; Specification 0.5 g/PCS; approval number: 520050033; manufacturer: Chengdu Nordicon Biological Pharmaceutical Co., LTD.) was intravenously micro-pumped 0.0075/ug/kg/min for 3-7 days. The pump speed was adjusted at any time according to the HR, blood pressure, and clinical symptoms of patients.

Efficacy observation indexes

The level of NT-proBNP, HR, LVEF, left ventricular end-diastolic inner diameter (LVEDD), PaO_2 and $PaCO_2$ were compared for patients before and 7 days after they were treated differently.

Serum creatinine (Scr), blood urea nitrogen (BUN), GFR, AST and ALT levels of patients in different groups were compared before and 7 days after they were treated.

In addition, UV, length of stay (LOS), treatment efficiency, and incidence of adverse reactions were compared between patients receiving the conventional treatment alone and conventional treatment + RH-BNP before and 7 days after treatment.

The curative effect was evaluated as follows: (i) obviously effective: symptoms and signs disappeared or basically disappeared; NYHA grade ≥2 or reduction of NT-proBNP ≥50%; (ii) effective: symptoms and signs were relieved, NYHA grade = 1 or reduction of NT-proBNP ≥30%; and (iii) ineffective: symptoms and signs were not changed or did not meet the above standards before basic treatment, and cardiac function did not change significantly or further aggravate.

Detection of NPY and Galectin-3

Plasma samples were collected from patients in the Exp group patients at 1, 3 and 7 days after treatment. The fasting elbow venous blood of patients was collected and placed into the EP tube containing ethylene diamine tetraacetic acid (EDTA). After collection, the test tube was slightly shaken to prevent blood agglutination. After mixing, the test tube was centrifuged for half an hour, and the supernatant was kept at a centrifugation rate of 3,000 r/min. After sealing, the test tube was stored in the refrigerator at –80℃ for later use. Plasma NPY levels were determined by radioimmunoassay (RIA). Galectin-3 levels were determined by enzyme-linked immunosorbent assay (ELISA) according to the kit (JiangsuSofia Biotechnology Co., LTD.).

Methods for statistics

SPSS23.0 was used for data processing. Measurement and count data were expressed with mean ± standard deviation ($\bar{x} \pm s$) and percentage (%), respectively. Analysis of variance, paired sample t test or independent sample 't' test were utilized for inter/intra-group comparison, and P <0.05 was considered statistically significant.

Results and Discussion

Functions of heart and lung before and after patients treatment

The cardiac function indexes (NT-proBNP, HR, LVEF, and LVEDD) and lung function indexes (PaO_2 and $PaCO_2$) are depicted in Fig. (1A & 1B), respectively. No great difference was observed in all indicators of patients before they were treated (P >0.05). The post-treatment NT-proBNP (3084.24±535.72) ng/L, HR (81.73±10.28) times/min, and LVEDD (5.41±0.43) mm in the Exp group were lower to those in the Ctrl group, which were 4158.27±638.41 ng/L, 83.59±11.37 times/min, and 5.44±0.46 mm, respectively(P <0.05). In the Exp group, the LVEF and PaO_2 were (44.73±3.29)% and (12.03±1.15) kPa, respectively; while those in the Ctrl group were (44.16±3.38)% and (10.57±1.42) kPa, respectively. Based on the pretreatment LVEF and PaO_2 levels, those after the treatment were greatly increased (P <0.05). In addition, the patients in the

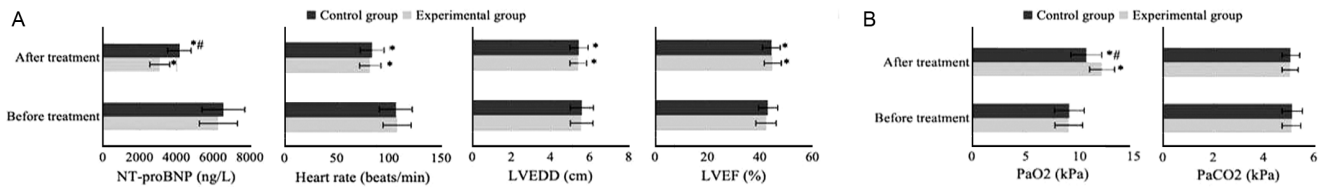

Fig. 1 — The (A) cardiac; and (B) lung function indexes of patients before and after different treatments. [* and # means significance difference with P <0.05 to the values before the treatment and those in the Exp group, respectively]

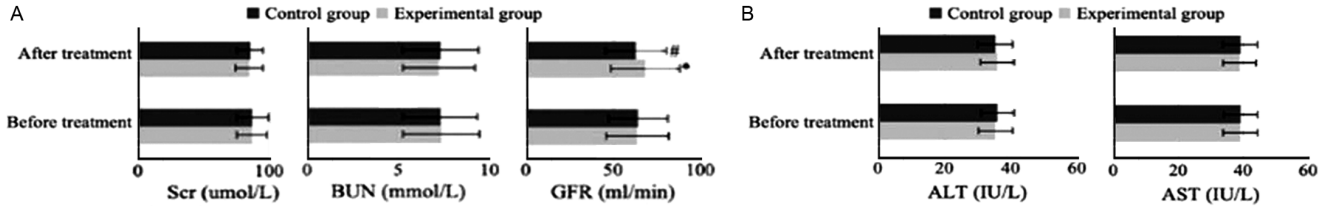

Fig. 2 — (A) The kidney function; and (B) liver function indexes of patients before and after different treatments. [* and # Significant difference with P <0.05 to the values before the treatment and those in the Exp group, respectively]

Exp group showed decreased NT-proBNP and elevated PaO_2 to the Ctrl group (P <0.05), and the $PaCO_2$ level did not show much change (P >0.05).

Functions of liver and kidney before and after patients treatment

The changes in functions of kidney and liver before and after the patients were treated are shown in Fig. 2 (A & B) respectively. No great differences were observed in pretreatment Scr, BUN, GFR, AST and ALT of patients in different groups (P >0.05). After treatment for seven days, patients in the Exp group had the Scr of (84.29±10.64) umol/L, the BUN of (7.21±1.96) mmol/L, the GFR of (68.17±19.65) mL/min, the ALT of (35.81±5.14) IU/L, and the AST of (38.74±5.06) IU/L. At the same time point, those in the Ctrl group were (85.08±10.05) umol/L, (7.29±2.11) mmol/L, (62.79±17.53) mL/min, (35.13±5.26) IU/L and (38.93±5.29) IU/L, respectively. Compared with the pretreatment levels, changes in all indexes of patients in the Ctrl group were not obvious (P >0.05). Meanwhile, the GFR was sharply increased in the Exp group, showing an obvious difference with P <0.05. In addition, GFR in the Exp group was much higher based on that in the Ctrl group (P <0.05).

Comparison of other indicators of patients before and after treatment

Before the patients were treated, UV of them in different groups was not greatly different (P >0.05).After 7 days of treatment, UV values were (1329.48±257.86) mL in the Exp group and (890.15±294.72) mL in the Ctrl group, showing that it increased greatly after treatment (P <0.05). In addition, there was more UV for patients in the Exp group and exhibited a remarkable difference to that in the Ctrl group (P <0.05). The above results are illustrated in Fig. 3. The occurrence of adverse reactions (transient hypotension, headache and nausea or vomiting) of patients in various groups after they were treated differently (P >0.05), as illustrated in Fig. 4. Fig. 5 compares the LOS of patients treated differently. Patients in the Exp group were

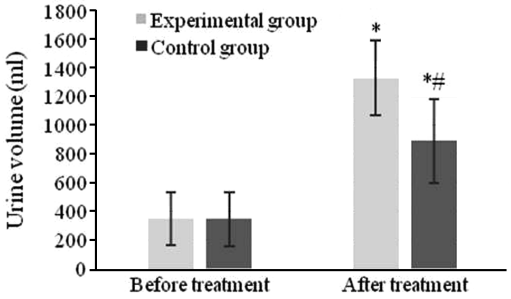

Fig. 3 — Comparison of UVs of patients before and after different treatments. [* and # Significant difference with P <0.05 to the values before treatment and those in the Exp group, respectively]

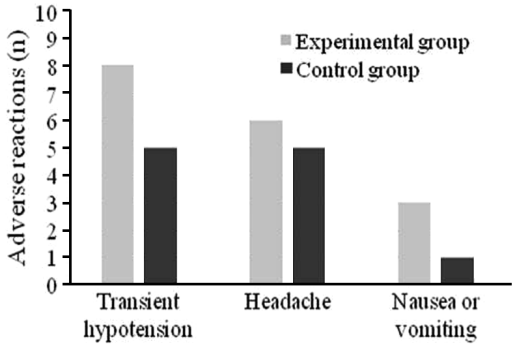

Fig. 4 — Incidences of postoperative adverse reactions

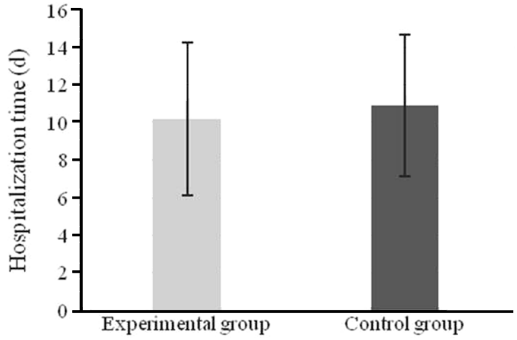

Fig. 5 — LOS of patients in different groups

hospitalized for an average of (10.19±4.05) days, which had no remarkable difference based on that in the Ctrl group (10.88±3.77) days (P >0.05). 27 patients (90%) in the Exp group were effectively treated, which was significantly more than that of the Ctrl group (22 patients, 73.33%) (Fig. 6).

Changes in post-treatment serum NPY level

The serum NPY levels in the Exp group patients were (215.38±17.27) ng/L, (184.29±13.44) ng/L, and (116.38±8.95) ng/L on post-treatment day 1, 3 and 7, respectively. The overall trend was downward, and the difference compared with the previous measured value was statistically significant (P <0.05) (Fig. 7A).

Changes in serum Galectin-3 levels before and after patients treatment

The serum Galectin-3 levels in the Exp group patients were (61.39±11.87) ng/mL, (54.28±10.06) ng/mL, and (42.32±8.49) ng/mL on post-treatment day 1, 3 and 7, respectively. The overall trend was downward, and the value on the day 7 was greatly reduced to the levels in the first two tests, showing obvious differences (P <0.05) (Fig. 7B).

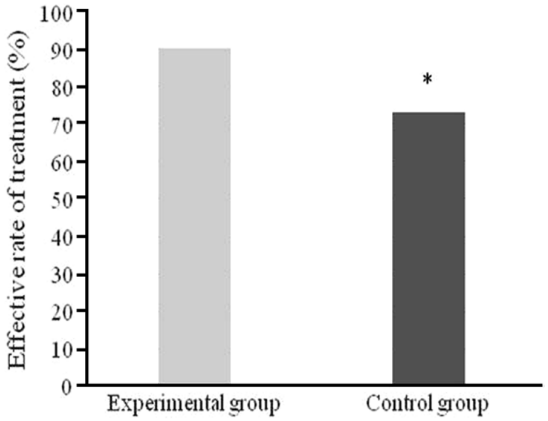

Fig. 6 — Comparison of treatment efficiencies of patients before and after different treatments. [* Significant difference with P <0.05 to the values in the Exp group]

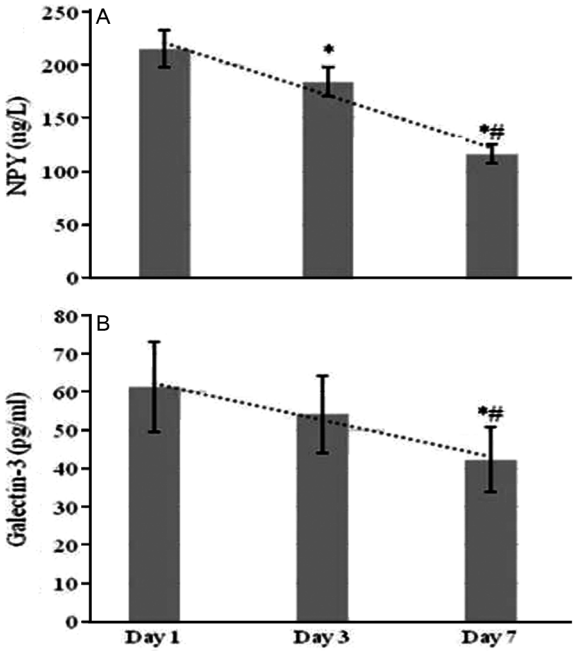

Fig. 7 — Changes in posttreatment serum (A) NPY; and (B) Galectin-3 level before and after the treatment. [* and # Significant difference with P <0.05 to the values on the post-treatment day 1 and day 3, respectively]

Heart failure is a clinical syndrome caused by cardiovascular diseases such as coronary atherosclerotic heart disease and hypertension. As a result, cardiac function or structure is damaged, resulting in decreased ventricular filling volume or ejection volume, which cannot meet the normal needs of body tissue and cell metabolism[26]. HF patients are mainly affected by circulatory system disorders, especially venous blood stasis and insufficient blood perfusion in peripheral organs, resulting in dyspnea, internal fluid deposition and difficulty in discharging, and normal activities, such as walking[27]. AHF refers to the decompensated state of cardiac function, mainly characterized by volume overload and pulmonary edema[28]. For patients with AHF, the prognosis is very poor despite intensive combination therapy during hospitalization[29]. It has been reported that the combined outcome of death or re-hospitalization within 3 months of discharge remains as high as 50 per cent. Although the diagnosis and treatment of HF have been improved obviously, it still fails to change its high morbidity and mortality[30]. Since RH-BNP was marketed in China in 2005, many clinical studies have shown that RH-BNP can greatly improve the dyspnea and other symptoms in HF patients. In this work, RH-BNP was applied to treat patients with AHF, and its efficacy was compared with that of conventional treatment.

The results revealed that compared with the conditions before the patients were treated, other cardiac and lung indexes except $PaCO_2$ were greatly improved in both the groups (P <0.05). The NT-proBNP in the Exp group was much lower and the PaO_2 was sharply higher to those in the Ctrl group (P <0.05). A previous study[31] has shown that NT-proBNP is an independent predictor of mortality in patients with right ventricular dysfunction caused by acute pulmonary embolism, so RH-BNP is effective for AHF treatment. Xu *et al*.[32] also showed that LVEF increased, and the level of NT-proBNP decreased sharply compared with that in the Ctrl group. RH-BNP can protect myocardial cell damage, improve cardiac function, shorten the LOS, and reduce the incidence and mortality of delayed encephalopathy after carbon monoxide poisoning. Such findings are consistent with the results of this

work. Based on the conditions before treatment, the indexes of liver and kidney function had no great changes except an obviously increased GFR (P >0.05), and GFR in the Exp group was much higher and presented an obvious difference with that in the Ctrl group (P <0.05). Zhang *et al*.[33] also showed that the creatinine clearance and eGFR increased at 48 and 72 h in the RH-BNP treatment group, and early application of RH-BNP could protect the kidney function. Xiangli *et al*.[34] also found that levosimendan combined with RH-BNP could effectively relieve the diuretic resistance, reduce the weight, improve the dyspnea, and ensure the safety of the treatment process. Recently, Zhou *et al*.[35] has observed that treatment with levosimendan and rhBNP for acute heart failure is superior and monotherapy in early clinical improvement keep the incidence of adverse reactions under control. In addition, this work suggested that the post treatment UV increased greatly, and that in the Exp group was higher (P <0.05). There were no remarkable differences in the LOS and the occurrence of adverse reactions of patients receiving different treatments (P >0.05), and the treatment efficiency in the Exp group was much better (P <0.05).The study of Fang *et al*.[36] showed that RH-BNP can observably improve clinical efficacy and myocardial function, shorten the LOS, and does not increase the incidence of adverse reactions such as hypotension, headache, low HR, and renal insufficiency. Similar to the present study, no obvious difference was observed in the LOS of patients receiving the conventional treatment alone and the conventional treatment + RH-BNP treatment, which may also be due to the small number of patients enrolled, so further research is needed.

Finally, the effects of RH-BNP on serum levels of NPY and Galectin-3 were analysed in this work. An animal study by Qin *et al*.[37] showed that NPY can reduce myocardial infarction in mice, inhibit cardiac inflammation and fibrosis, and enhance angiogenesis but reduce apoptosis, which may be the potential mechanism for NPY to reduce cardiac remodeling and functional deterioration after myocardial infarction. A foreign study[38] has also shown that high serum NPY level is associated with increased HF incidence and mortality, and may be a useful prognostic marker. This work indicated that the serum NPY level of patients treated by the conventional method combined with RH-BNP showed a downward trend after treatment (P <0.05) compared with the previous measurement. It indicates that RH-BNP could hinder the development of HF and improve the prognosis of patients. Previous studies[39-41] have shown that Galectin-3 is a biomarker to evaluate the predictors of adverse HF outcomes. Sygitowicz *et al*.[42] reported elevation of Galectin-3 in both acute and chronic HF, and demonstrated its involvement in the inflammatory pathway after injury, leading to myocardial tissue remodeling. In this work, serum Galectin-3 levels in the Exp group patients showed a decreased trend after treatment, and the values on day 7 were greatly decreased to those obtained in the first two tests (P <0.05). It indicates that Galectin-3 can delay or improve the progression of HF, which has application value.

Conclusion

This work showed that compared with conventional treatment, the application of Recombinant human brain natriuretic peptide (RH-BNP) can effectively improve the heart and lung function of patients, have less toxicity to liver and kidney, has diuretic effect, and improve the treatment efficiency. It can promote the decrease of serum NPY and Galectin-3 levels in patients, which was beneficial to improve the prognosis of patients. However, the number of patients included was not large, and some experimental results were biased, which had a certain impact on the research results. In the future, it needed to increase the sample size for further confirmation.

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