EFFECTS OF RECOMBINANT HUMAN BRAIN NATRIURETIC PEPTIDE COMBINED WITH NICORANDIL ON CARDIAC FUNCTION, NT-PROBNP, LP-PLA2 AND OXIDATIVE STRESS INDICATORS IN PATIENTS WITH ISCHEMIC HEART FAILURE

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ABSTRACT

Objective*: To analyze the effects of recombinant human brain natriuretic peptide combined with nicorandil on cardiac function, N-terminal pro-B-type natriuretic peptide (NT-proBNP), lipoprotein-related phospholipase A2 (Lp- PLA2) and oxidative stress indicators.*

Methods: *Eighty-six patients with ischemic heart failure who visited the outpatient clinic or were hospitalized from June 2018 to March 2020 were randomly divided into a conventional control group and a treatment group, with 43 patients in each group. The control group was given recombinant human brain natriuretic peptide, and the treatment group was given nicorandil on the basis of the control group. The clinical efficacy and cardiac function after treatment (left ventricular end systolic volume [LVESV], left ventricular end diastolic diameter [LVEDD], and left ventricular ejection fraction [LVEF]) and levels of NT-proBNP, Lp-PLA2 and oxidative stress changes as well as adverse reactions of patients in the two groups were compared.*

Results: *After treatment, the total effective rate of the treatment group was 93.02%, which was significantly higher than the rate of the control group (P<0.05). The levels of LVESV, LVEDD, NT-proBNP, Lp-PLA2 and MDA in the two groups were significantly decreased after treatment compared to levels before treatment. Additionally, the levels of LVEF and SOD were significantly increased after treatment compared to before treatment, and the improvement in the treatment group was significantly better than that in the control group (P<0.05). The incidence rate of adverse reactions in the treatment group and the control group were 13.95% and 23.26%, respectively, a difference that was statistically significant (P<0.05).*

Conclusion: *Recombinant human brain natriuretic peptide combined with nicorandil demonstrates good efficacy in treating ischemic heart failure. This treatment can effectively improve the patient's heart function, regulate and reduce the levels of NT-proBNP and Lp-PLA2, and improve oxidative stress indicators.*

Keywords: *Recombinant human brain natriuretic peptide, nicorandil, ischemic keart failure, NT-proBNP, Lp-PLA2, oxidative stress index, impact.*

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Introduction

Ischemic heart failure (ischemic cardiomyopathy, ICM) is the end-stage manifestation of various types of organic heart disease. ICM, which occurs at a high incidence rate, is a complex clinical syndrome in which cardiac filling or ejection ability is impaired as a result of a structural or functional heart disease and is a common outcome of various cardiovascular diseases. According to data released by the World Health Organization, the number of heart failure patients worldwide has reached 22.5 million or more and is growing at a rate of 2 million per year. In addition, patients with heart failure are generally middle-aged and elderly. The etiology of heart disease and age is closely linked with social economy, environmental factors, and lifestyle. However, since no effective treatments for heart failure currently

exist, research on heart failure has become an area of intense focus within cardiovascular medicine[1, 2]. With the continuous improvement of medical technology in China, research studies have found that the combination of recombinant human brain natriuretic peptide and specific natriuretic peptide receptor (coupled to guanylate cyclase) can promote an increased concentration of intracellular loops guanosine cyclic monophosphate (cGMP) and induce relaxation of smooth muscle cells[3].

Nicorandil is a potassium channel activator. An increasing number of experimental results have shown that potassium channel activators can play a direct role in cell protection by enhancing the normal physiological process of protecting the heart from ischemia. However, few reports exist on cardiac function, N-terminal B-type natriuretic peptide (NT-proBNP), lipoprotein associated phospholipase A2 (Lp-PLA2) and oxidative stress indicators. This study used recombinant human brain natriuretic peptide combined with nicorandil to treat patients with ischemic heart failure, with the goal of exploring the effects of natriuretic peptide and nicorandil on cardiac function, NT-proBNP, Lp-PLA2 and oxidative stress indicators.

Materials and methods

General information

From June 2018 to March 2020, a total of 86 patients who came to our hospital for outpatient treatment or hospitalization and were willing to participate were enrolled in the study.

The study participants consisted of 48 males and 38 females aged 45 to 84 years. Of the 86 patients with ischemic heart failure (all patients excluded other diseases), 23 had cardiac function at grade II, 37 had cardiac function at grade III, and 26 had cardiac function at grade IV.

Using a method of random assignment, the patients were divided into the treatment group and the control group, each group consisting of 43 patients. Comparing the gender, age, and cardiac function classification of the participants in the two groups revealed that the levels of patients in the two groups were equal, with no statistically significant differences (P>0.05).

Inclusion criteria

The diagnostic criteria for heart failure was determined from the "Interpretation of the 2008 European Guidelines for the Diagnosis and Treatment of Heart Failure." Strictly in accordance with the New York Heart Association's Heart Function Classification Standard (NYHA)[4], the heart function of each patient was graded from I to IV, and the clinical manifestations were obvious symptoms of heart failure.

The results of coronary angiography met the clinical diagnostic criteria for patients with ischemic cardiomyopathy and heart failure.

Group	Case	Age	NYHA heart function grading		
		(year)	II grade	III grade	IV grade
The treatment group	43	61.45±1.78	12	19	13
The control group	43	61.32±1.96	11	18	13
$\chi^2/t/Z$		0.322			
P		0.748			

Table 1: Comparison of the general information of patients in the two groups.

Exclusion criteria

- Severe liver and kidney dysfunction or failure;
- Acute cerebrovascular disease;
- Severe primary diseases of the hematopoietic system or the endocrine system;
- Severe hypertension, arrhythmia, cardiogenic shock, obstructive cardiomyopathy;
- Severe primary diseases of the hematopoietic system or the endocrine system;
- Drug allergies;
- Pregnancy or lactation in women.

Method

Patients in both groups received the same routine treatment after admission. For general treatment, water restriction, diet control, and antidepressants were administered. The drug treatment consisted of diuretics, angiotensin II receptor antagonists, aldosterone antagonists and for routine treatment were given. The control group additionally received recombinant human brain natriuretic peptide (drug specification: 0.5mg*500u, Chengdu Nuodi Biopharmaceutical, production batch number: 20180033) based on the above.

A bolus injection of 1.5 μg/kg was given across a time period of two or three minutes, followed by intravenous pumping of 0.01 μg/(kg·min) for 24 to 48 hours. On the basis of the control group, the treatment group was given nicorandil, 5 mg orally each time, three times a day. Patients in the two groups were checked regularly during treatment, and if any abnormalities were present, symptomatic

treatment was given in a timely manner. Patients in both groups were treated for two consecutive months.

Observation indicators

• Clinical efficacy was indicated as either markedly effective, effective, or invalid using the following criteria: markedly effective: after treatment, heart function was improved by more than level 2, with a normal heart rate, reduced dyspnea, absence of edema, and absence of wet rales in either lung; effective: the heart function was improved by level 1, and symptoms of discomfort were reduced; invalid: the discomfort had not improved or become worse.

• The six-minute walk measurement (6MWT) was used to assess cardiac function[5]. The six-minute walk measurement was an exercise test used to determine the functional status of patients with moderate and severe cardiopulmonary diseases. (Contraindications: absolute contraindications included unstable angina or myocardial infarction in the past one month; relative contraindications included resting heart rate >20/min, systolic blood pressure >180mmHg, and diastolic blood pressure >100mmHg).

• Determination of markers: 2ml of fasting venous blood was extracted in the morning, and the serum was separated. The NT-proBNP level was detected using a two-way flow immunoassay. The level of Lp-PLA2 was detected with the immunoenhanced turbidimetric method, and the level of superoxide dismutase (SOD) was determined using the xanthine oxidase method.

• Adverse reactions were observed during treatment of patients in two groups.

Statistical methods

SPSS 14.0 statistical software was used for analysis. Enumeration data was expressed as rate (%), and an χ^2 test was performed. Rank data was analyzed with the rank sum (Z) test. Measurement data was expressed as (x±s), and a t-test was performed. P<0.05 was considered statistically significant.

Results

Comparison of clinical efficacy between the two groups

After treatment, the total effective rate of the treatment group was 93.02%, and the total effective rate of the control group was 86.04%. This difference in the total effective rate of the treatment was statistically significant (P<0.05). See Table 2.

Group	Markedly effective	Effective	Invalid	The total effective rate
The observation group (n=43)	24 (55.81)	16 (37.21)	3 (6.98)	40 (93.02)
The control group (n=43)	17 (39.53)	14 (32.56)	12 (27.91)	31 (72.09)
χ^2				6.540
P				0.011

Table 2: Comparison of clinical efficacy between the two groups [n (%)].
*Note: *indicates P<0.05 compared with the control group after treatment.*

Comparison of cardiac function of patients between two groups before and after treatment

Before treatment, there was no significant difference between the groups in the levels of LVESV, LVEDD, and LVEF (P>0.05). After treatment, the levels of LVESV and LVEDD in the two groups were significantly lower than before treatment, and the LVEF levels were significantly higher than before treatment.

The degree of improvement of the treatment group was significantly better than that of the control group, a difference which was statistically significant (P<0.05). See Table 3.

Group		LVESV (*mm*)	LVEDD (*mm*)	LVEF (%)
The treatment group	Before treatment	83.51±9.61	69.43±5.58	24.36±4.23
	After treatment	66.33±5.23*#	51.67±3.45*#	38.41±5.35*#
The control group	Before treatment	81.47±8.14	58.73±5.36	24.15±4.14
	After treatment	76.22±6.32*	50.25±5.07*	30.28±4.39*

Table 3: Improvement of heart function in the two groups before and after treatment (x±s).
*Note: *indicates P<0.05 compared with the control group after treatment, #means P<0.05 compared with the control group after treatment.*

Comparison of the level of markers in the two groups before and after treatment

Before treatment, the levels of NT-proBNP and Lp-PLA2 in the two groups were not statistically different (P>0.05). After treatment, NT-proBNP and Lp-PLA2 levels in the two groups were significantly decreased compared with before treatment, and the degree of improvement was significantly better in the treatment group compared to the control group (P<0.05).

Group	Case	Time	NT-proBNP	Lp-PLA2
The treatment group	43	Before treatment	568.45±106.81	253.31±18.25
		After treatment	209.32±17.12*#	161.06±15.42*#
The control group	43	Before treatment	574.17±112.23	250.21±19.78
		After treatment	285.98±20.13	211.46±16.35

Table 4: Comparison of NT-proBNP and Lp-PLA2 between the two groups.
*Note: *indicates P<0.05 compared with the control group after treatment, #indicates P<0.05 compared with the control group after treatment.*

Comparison of changes in oxidative stress index levels between the two groups

Before treatment, the levels of superoxide dismutase (SOD) and malondialdehyde (MDA) were not significantly different patients in the two groups (P>0.05). After treatment, the levels of SOD in both groups increased significantly. The MDA level was significantly reduced, and the improvement in the treatment group was significantly better than that of the control group, the difference was statistically significant (P<0.01), see Table 5.

Group	Case	SOD (U/ml)		MDA (nmol/ml)	
		Before treatment	After treatment	Before treatment	After treatment
The treatment group	43	94.62±8.32	155.45±9.53*#	6.96±1.64	5.02±0.31*#
The control group	43	96.38±9.29	115.04±9.34	7.52±1.86	6.23±0.53*
t		0.925	19.858	1.481	12.923
P		0.357	<0.001	0.142	<0.001

Table 5: Comparison of oxidative stress index levels between the two groups ($\bar{x}\pm s$).
*Note: *indicates P<0.05 compared with the control group after treatment, #indicates P<0.05 compared with the control group after treatment.*

Comparison of adverse reactions

Adverse reactions observed in the two groups were nausea, headaches, ulcers, and elevated blood creatinine (6). The incidence rate of adverse reactions in the treatment group and the control group were 13.95% and 23.26%, respectively. This difference in the incidence rate was statistically significant (P<0.05). See Table 6.

Group	Case	Headache	Elevated blood creatinine	Nausea and vomiting	Ulcers	The total incidence rate
Treatment group	43	2 (4.65)	1 (2.33)	1 (2.33)	2 (4.65)	6 (13.95)
Control group	43	8 (18.60)	3 (6.98)	4 (9.30)	0 (0.00)	15 (23.26)
χ^2						4.590
P						0.032

Table 6: Comparative analysis of the occurrence of adverse reactions between the two groups.

Discussion

Ischemic heart failure is primarily caused by coronary artery multivessel disease or even diffuse disease. In clinical practice, heart failure is more commonly observed in the elderly. Long-term myocardial ischemia leads to localized or diffuse myocardial fibrosis, degeneration, necrosis, and myocardial frustration. These outcomes result in impaired systolic and/or diastolic function, further leading to additional undesirable consequences such as heart enlargement or stiffness and arrhythmia[7, 8]. Long-term insufficient blood supply to the myocardium can also cause diseases like left ventricular aneurysm and mitral insufficiency[9]. In recent years, the incidence rate of ischemic heart failure in China has been on the rise. Heart failure, a group of clinical symptoms that presents in the late stage of coronary heart disease, is based on coronary atherosclerosis, and long-term extensive myocardial ischemia produces myocardial fibrosis or multiple myocardial infarctions. According to epidemiological research surveys, risk factors for heart failure include hypertension, hyperlipidemia, smoking, diet, obesity, diabetes, personality and social factors, abnormal coagulation factors, lack of high microelements, and increased levels of homocysteine in the blood.

Studies have shown that recombinant human brain natriuretic peptide can balance the expansion of the lungs. After binding to the corresponding receptors in ICM patients, this peptide promotes diuresis and excretion of natriuresis and reduces the burden on the myocardium, thus ultimately relieving heart failure. Furthermore, recombinant human brain natriuretic peptide has an inhibitory effect on the proliferation of fibroblasts and smooth muscle cells, which can improve the early heart function of patients with acute decompensated heart failure. The results of the study in this group showed that the heart function of two groups of patients was significantly improved after treatment compared to before treatment. Nicorandil (Nicotinamide, chemical name ethoxynicotinamide nitrate) is an ATP-sensitive potassium channel opener[10, 11], which is composed of partial structures of nicotinamide vitamins and organic nitrates. Nicotinamide nitrate can activate guanylate activating enzyme, relax and dilate vascular smooth muscles, thus treating patients with heart failure can significantly increase the LVEF value, 6MWT, and reduce LVEDD, LVESD, PCWP, BNP, thereby improving the patient's heart function,

improving the patient's cardiac microvascular circulation, improving the quality of life, improving myocardial contractility, preventing and delaying the development of ventricular remodeling, and reducing the mortality and hospitalization rate of patients with heart failure, which is same to results in this study. NT-proBNP is a cardiogenic neurohormone synthesized in ventricular myocytes, which is related to vasodilation, stable blood pressure, and cardiac compensatory function. Additionally, NT-proBNP promotes diuretic and sodium excretion and antagonizes the renin-angiotensin-aldosterone system; levels of this hormone can also be monitored to detect cardiac dysfunction in healthy people at early stages[12]. Studies have found that the concentration of serum NT-proBNP in the early stages of heart failure is specifically increased and is both negatively correlated with the LVEF value and positively correlated with the NYHA grading[13]. Lp-PLA2 is a vascular-specific inflammatory factor and a newly discovered marker of cardiovascular disease, which can catalyze a variety of oxidized phospholipids, produce free fatty acids and lysophospholipids, and generate pro-inflammatory substances[14, 15]. In this study, the levels of NT-proBNP and Lp-PLA2 were decreased significantly following treatment ($P<0.05$), further demonstrating that recombinant human brain natriuretic peptide combined with nicorandil had a positive effect on patients with ischemic heart failure.

In conclusion, recombinant human brain natriuretic peptide combined with nicorandil demonstrated good efficacy for treating ischemic heart failure, effectively improving the patient's heart function, regulating and reducing the levels of NT-proBNP and Lp-PLA2, and improving oxidative stress indicators. This effectively improved the response rate. However, additional samples will be collected for further analysis in the future due to the limited number of samples in this study.

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