

## **Clinical effects of recombinant human BNP in treating acute heart failure and study on its effects On TWEAK and nT-pro BNP.**

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### **Abstract**

**Objective:** To observe the level changes of tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP) of Acute Heart Failure (AHF) patients and re-evaluate the clinical effects and safety of recombinant human brain natriuretic peptide (rhBNP) in treating AHF.

**Methods:** 89 cases with AHF in our hospital and 40 healthy volunteers were recruited as the control group. The differences of TWEAK and NT-pro BNP of patients in two groups were observed and compared. Patients in AHF group were divided into subgroup. 24 cases in routine subgroup given routine anti-HF and anti-basic disease treatment. 47 cases in rhBNP subgroup given routine treatment and rhBNP treatment over 72 h.

**Results:** TWEAK and NT-pro BNP level of serum of patients in AHF group were ( $157.6 \pm 69.7$  pg/ml) and ( $3124.2 \pm 2713.5$  pg/ml) separately, significantly higher than the control group, there were statistical differences,  $P < 0.01$ . TWEAK and NT-pro BNP level of patients in routine subgroup and rhBNP subgroup before treatment were similar, there were no statistical differences,  $P > 0.05$ . After treatment, various detection indexes of patients in AHF group significantly improved compared with before treatment. TWEAK and NT-pro BNP level of serum of patients in TWEAK and NT-pro BNP level were ( $72.8 \pm 34.5$  pg/ml) and ( $769.2 \pm 518.5$  pg/ml) separately, there were statistical differences compared with patients in routine subgroup,  $P < 0.05$ . The total effective rate of patients in routine subgroup was 71.43%, obviously lower than rhBNP subgroup (89.36%), there were statistical differences,  $P < 0.05$ . There were 4 patients adverse events and 5 death patients in routine subgroup. There were 2 cases with hypotension and 2 death cases in rhBNP subgroup.

**Conclusion:** Recombinant human BNP can effectively treat CHF, rapidly improve clinical symptoms of patients and laboratory biochemical indexes such as TWEAK and NT-pro BNP etc. Compared with routine treatment methods, it has significant effects and high safety. It is worthy of clinical promotion.

**Keywords:** Recombinant human BNP, CHF, Clinical effects, TWEAK, NT-pro BNP.

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### **Introduction**

Acute Heart Failure (AHF) is a kind of clinical syndrome with acute failure or CHF sudden aggravation in short time caused by sudden myocardial severe injury or sudden aggravation of heart load [1]. The most common is acute left heart failure. The main manifestations are decreased myocardial contractility, increased heart load and decreased blood discharge volume caused by abnormal left heart function, it induces pulmonary circulation congestion and severe symptoms such as cardiogenic shock [2].

With the acceleration of population aging in China, the incidence rate of AHF increases year by year. Therefore, AHF brings an increasingly social and medical pressure. With the depth of study on HF in recent years, it is found that activation of endogenous neurological system plays an important role in

the progress of AHF and rebuild of ventricular rebuild. At the end of last century, Japanese specialists Sudoh et al. [3] first separate BNP from pig brain. Through long time study, it is found that BNP has functions such as dilating vessels, discharging sodium and urine, reducing retention of water sodium, inhibiting myocardial fibrosis and RAAS system etc. [4]. BNP exits mainly in myocytes of ventricle. Its cell volume has close relations with ventricular pressure and volume load. When tension of ventricular wall increases, BNP secretion increases, thus maintaining balance of artery, vein vasoconstriction and dilation, regulating vascular tension and improving ventricle rebuild. It also can block RAAS, cause abnormal activation antagonistic myocardial cells, toxin activity of vascular smooth muscle cells in heart fiber original nucleus, thus regulating ventricle contractility and heart load specifically [5]. Recombinant human Brain Natriuretic Peptide

(rhBNP) is a kind of biological agents synthesized by recombinant technology artificially, it has 32 amino acid sequences and biological activity the same to endogenous BNP. It has been approved by America FDA to appear on the market. Through multiple studies and clinical experience at abroad, it has shown rhBNP can effectively improve clinical symptoms and hemodynamics conditions of AHF patients, thus reducing death rate. In 2015, European and American heart disease society had listed BNP into Diagnosis and Treatment Guide of Chronic Heart Failure in Adults and had been regarded as only serum markers for diagnosing heart failure. Diagnosis and Treatment Guide of Acute Heart Failure in 2010 had been published by editorial board of Chinese Journal of Cardiology [6], it shows NT-pro BNP can be the objective indexes of additional AHF diagnosis and prognosis.

In addition, tumor necrosis factor-like weak inducer of apoptosis (TWEAK) belongs to one of superfamily members in tumor necrosis factor [7]. It combines with Fibroblast growth factor-inducible 14 (Fn14) promote secretion of inflammatory factors and induce cell apoptosis by complex cell signal transduction pathway. There are studies shows that TWEAK concentration in AHF patients *in vivo* obviously increases compared with healthy adults [8]. But at present, reports at home and abroad on relevance study of TWEAK and NT-pro BNP are rare.

Therefore, this study evaluates the clinical effects and safety of rhBNP by observing relevant indexes such as TWEAK and NT-pro BNP of CHD patients after using rhBNP. Now it reported as follows.

## Materials and Methods

### Clinical data

89 cases with CHD in cardiology in our hospital from June, 2014 to June, 2016 were recruited, consisting of 51 males and 38 females. Ages were from 43 to 75 y. Mean age was 60.5 ± 6.3 y. There were 34 cases with coronary heart diseases, including 3 heart infarction cases, 15 dilated myocardial disease cases, 9 single hypertension patients, 5 rheumatic valvular heart disease cases and 26 patients with hypertension accompanied with other complications. They were randomly divided into two groups. There were 42 AHF patients in routine treatment group and 47 cases in the observation group with rh-BNP treatment on the basis of routine treatment. Other 40 healthy volunteers were recruited as the control group. Hypertension, diabetes and coronary heart disease were excluded through examination.

### Inclusive criteria of patients

First, through basic heart function examination, grading of heart function can be divided into III and IV grades (NYHA); second, UCG has demonstrated that left ventricle ejection fraction was 50% or less than 50%; third, patients had signed informed consent form.

### Exclusive criteria of patients

The exclusion criteria includes patients who were not met the above mentioned inclusive criteria; systolic pressure was 90 mmHg or less than 90 mmHg; patients who had cardiogenic shock or contradictions of vascular dilation of venous injection; patients who had liver and kidney deficit; patients who had malignant tumor, immune system diseases, hematological system diseases and mental diseases; and patients who had poor compliance.

### Treatment methods

All AHF patients were patients of hospitalization and given routine anti-HF treatment. All were patients given routine treatment such as diuretic and vessel dilation according to Diagnosis and Treatment Guide of Heart Failure in China. Patients who had taken calcium blocker or ACEI or ARB, could continue medication whereas patients who had taken  $\beta$  receptor antagonist, should reduce medication or stop medication. Patients in the observation group were added rhBNP (provided by Tibet chengdurhodiola pharmaceutical holding limited company, trade name was rh-BNP on the basis of routine treatment. 1.5  $\mu$ g/kg load dosage were given for venous injection according to 0.0075  $\mu$ g (kg/min) for constant venous infusion at least 72 h until the heart function of patients have been improved obviously. Conditions of patients should be monitored closely during medication. If there were any abnormalities, medication dosage should be adjusted promptly.

### Observation indexes

Disease history of patients has been asked after admitted into hospital. They were given routine examination. Medication, injection conditions, changes of clinical symptoms during treatment were observed and recorded in detail. Blood pressure, heart rate, pulmonary rale were recorded. Biochemical indexes such as TWEAK, NT-pro BNP and Scr were detected by extracting venous blood.

### Evaluation criteria of clinical effects

First, obvious effects: the clinical symptoms of patients disappeared. The improvement of heart function were 2 grade or over. Second, validity: clinical symptoms improved in a certain degree. The improvement of heart function was 1 grade or less than 2 grade. Third, invalidity: clinical symptoms not improved even got worse. The improvement of heart function less than 1 grade or 1 grade in deterioration even death.

### Statistical management

SPSS 19.0 software was used to do t-test,  $\chi^2$  test and ANOVA etc. between two groups. Measurement data were done with t test and comparison between two groups. Enumeration data were done with  $\chi^2$  test. Statistical significance was assumed at  $P < 0.05$ . Statistical differences were significant at  $P < 0.01$ .

**Results**

**Comparison of basic data of study subjects before treatment**

Before treatment, general data such as mean age, sex, BMI etc. of patients in AHF group were in accordance with the control group basically, there were no statistical differences. Left ventricle ejection fraction of patients in AHF patients was

(40.9 ± 1.8%), lower than the control group, there were statistical differences, P<0.05. Scr level of patients in AHF group was (82.6 ± 7.9 μmol/l), higher than the control group, there were statistical differences, P<0.05. TWEAK and NT-pro BNP in serum were (157.6 ± 69.7 pg/ml) and (3124.2 ± 2713.5 pg/ml) separately, obviously higher than the control group, there were significant statistical differences, P<0.01. It is shown in the Table 1.

**Table 1.** Analysis of general clinical data of study subjects before treatment.

Group	Cases (number)	Mean age (y)	Sex (number)		BMI (kg/m <sup>2</sup> )	Left ventricle ejection fraction (%)	Scr (μmol/l)	TWEAK (pg/ml)	NT-pro BNP (pg/ml)
			Male	Female					
The control group	40	58.7 ± 7.1	25	15	22.7 ± 3.9	66.7 ± 2.1	61.5 ± 3.3	55.2 ± 27.1	32.1 ± 19.4
AHF group	89	60.5 ± 6.3	51	38	23.0 ± 4.1	40.9 ± 1.8*	82.6 ± 7.9*	157.6 ± 69.7**	3124.2 ± 2713.5**

Note: \*Compared with the control group, P<0.05; \*\*compared with the control group, P<0.01

**Comparison of basic data of patients in AHF subgroup before treatment**

Before treatment, general data such as mean age, sex, BMI, left ventricle ejection fraction, Scr, TWEAK and NT-pro BNP etc.

of patients in routine subgroup and in AHF subgroup were in accordance with the control group basically, it had comparability, there were no statistical differences, P>0.05. It is shown in the Table 2.

**Table 2.** Analysis of general clinical data of patients in AHF group before treatment.

Group	Cases (Number)	Mean age (y)	Sex (number)		BMI (kg/m <sup>2</sup> )	Left ventricle ejection fraction (%)	Scr (μmol/l)	TWEAK (pg/ml)	NT-pro BNP (pg/ml)	BNP
			Male	Female						
The routine group	42	59.1 ± 7.2	26	16	22.9 ± 3.9	38.7 ± 3.3	83.4 ± 8.0	159.2 ± 72.7	3111.5 ± 2897.2	
rhBNP group	47	61.6 ± 7.0	25	22	23.3 ± 3.8	39.9 ± 2.1	80.9 ± 7.7	157.1 ± 80.6	3131.2 ± 2755.9	

**Comparison of detection indexes of patients in AHF subgroup after treatment**

After treatment, various detection indexes of patients in AHF group improved greatly compared with before treatment. Its left ventricle ejection fraction, Scr and TWEAK in serum compared with before treatment, there were statistical differences, P<0.05. NT-pro BNP level in serum had

significant statistical differences compared with before treatment, P<0.01. In addition, left ventricle ejection fraction, TWEAK in serum and NT-pro BNP level in serum of patients in rh BNP were (59.3 ± 2.1%), (72.8 ± 34.5 pg/ml) and (769.2 ± 518.5 pg/ml) separately. Compared with routine treatment subgroup, there were statistical differences, P<0.05. It is shown in the Table 3.

**Table 3.** Comparison of detection indexes of patients in AHF subgroup after treatment.

Group	Case (number)	Left ventricle ejection fraction (%)		Scr (μmol/l)		TWEAK (pg/ml)		NT-pro BNP (pg/ml)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Routine group	42	38.7 ± 3.3	46.6 ± 1.8#	83.4 ± 8.0	69.9 ± 9.4#	159.2 ± 72.7	115.4 ± 59.7#	3111.5 ± 2897.2	± 1295.1 ± 817.7###
rhBNP group	47	39.9 ± 2.1	59.3 ± 2.1**	80.9 ± 7.7	67.6 ± 6.1#	157.1 ± 80.6	72.8 ± 34.5**	3131.2 ± 2755.9	± 769.2 ± 518.5###

Note: \*Compared with group, P<0.05; #compared with before treatment, P<0.05; ##compared with before treatment, P<0.05; ###compared with before treatment, P<0.01.

### Comparison of clinical effects of patients in various subgroup

After treatment, the total effective rate of patients in routine subgroup was 71.43%, obviously lower than rhBNP subgroup (89.36%), there were statistical differences,  $P < 0.05$ . It is shown in the Table 4.

**Table 4.** Comparison of clinical effects of patients in subgroup.

Group	Case (number)	Obvious effects	Validity	Invalidity	The total effective rate
Routine group	42	19 (45.23)	11 (26.19)	12 (28.57%)	30 (71.43)
rhBNP group	47	26 (55.32)	16 (34.04)	5 (10.64%)	42 (89.36)*

Note: \*Compared with routine group,  $P < 0.05$

### Analysis of safety and death conditions of patients in various subgroup

After treatment, there were two cases (4.76%) with headache and two cases (4.76%) with hypotension; there were one case (2.13%) with hypotension. The blood pressure of patients with hypotension recovered to over 90/60 mmHg after stopping medication. Other patients had no other relevant drug adverse reactions. In addition, death conditions of AHF patients within 30 d were compared. There were 5 death cases in routine subgroup, 4 cases (9.52%) caused by AHF, one case (2.38%) caused by non-cardiogenic death. There were two death cases in rhBNP group caused by AHF.

### Discussion

AHF has sudden decreased heart function and sudden decreased cardiac output caused by multiple factors. It causes insufficiency of tissue perfusion, thus leading to cardiogenic shock, severe arrhythmia even sudden death. It belongs to clinical emergent and severe disease. Effective treatment measures must be adopted promptly, otherwise it will cause relatively high death rate of patients.

At present, the main treatment methods for AHF include sodium and urine discharge, vascular discharge and myocardial contractility enhance etc. [9]. With transformation of cognition on AHF treatment modes, the purpose of treatment is not only to improve clinical symptoms of patients, also pay more attention to prevent and relieve myocardial rebuild of patients in order to lower death rate and recurrence rate of HF.

Though single use of ACE inhibitor/ARBs, calcium ion antagonist, diuretic and  $\beta$  receptor blocker can improve clinical symptoms of patients. Under the high rate of death rate and hospitalization rate, it has relations with these drugs not produce inhibition effects on neurological hormone of excessive activation, but produce activation effects. With the deep study of incidence rate of HF, the influences of nerve-endocrine-cell factor system activation and ventricular rebuild on HF has received attention widely, it includes RAAS system

and brain natriuretic peptide system [10]. BNP is one of family members in natriuretic peptide of vascular activity. It is mainly synthesized and secreted by ventricular myocytes, has positive correlations with ventricular load and ventricular wall tension [11]. The rhBNP occurrence and application both improve hemodynamics of AHF patients in clinic and inhibit endocrine hormone secretion of nerve. Recombinant human brain natriuretic peptide (rhBNP) is a kind of biological agents synthesized by recombinant technology artificially, it has sequence and biological activity the same to endogenous BNP. It has functions such as dilating vessels, reducing heart load, inhibiting RAAS system, rebuilding myocardial cells etc. [12]. In this study, on the basis of routine treatment, 47 patients in the observation group are given constant venous instillation of rhBNP over 72 h. The results find that HF symptoms of patients significantly improve. The treatment effective rate is 89.36%, obviously higher than the treatment effective rate (71.443%) of AHF patients in routine treatment group, there are statistical differences,  $P < 0.05$ . In addition, adverse reaction rate of patients in rhBNP is relatively low. There are only one case with hypotension. It recovers after stopping medication; there are two death cases (4.26%) because of AHF.

Multiple studies show that BNP level of patients with AHF obviously higher than normal people, it can be one of specific markers for diagnosing HF. But BNP level in blood is extremely low, cannot be detected easily [13]. NT-pro BNP forebody is the N end segment after slit up of BNP hormone. The level in them has correlations [14]. Comparing with BNP, NT-pro BNP is more stable. Half-time period is longer, which can reflect conditions of heart function injury. Since the year 2002, there is an international agreement that BNP forebody NT-pro BNP is a specific marker for detecting HF [15,16]. Furthermore, TWEAK as one of family members in tumor necrosis factors can combine with different receptors and start a series of signal transduction pathway, thus inducing corresponding genetic activation [17,18]. In recent years, there are studies show that TWEAK plays an important role in the occurrence and development of HF. Like BNP, circulation TWEAK level of HF patients also one of detection index for reflecting prognosis. Results of this study show that comparing with subjects in the normal control group, TWEAK and NT-pro BNP level in serum of AHF patients are ( $157.6 \pm 69.7$  pg/ml) and ( $3124.2 \pm 2713.5$  pg/ml) separately, obviously higher than the control group, there are significant statistical differences,  $P < 0.01$ . After treatment, various detection indexes of patients in AHF group improve greatly compared with before treatment. Its left ventricle ejection fraction, Scr and TWEAK in serum compared with before treatment, there are statistical differences,  $P < 0.05$ . NT-pro BNP level in serum has significant statistical differences compared with before treatment,  $P < 0.01$ . In addition, left ventricle ejection fraction, TWEAK in serum and NT-proBNP level in serum of patients in rhBNP are ( $59.3 \pm 2.1\%$ ), ( $72.8 \pm 34.5$  pg/ml) and ( $769.2 \pm 518.5$  pg/ml) separately. Comparing with routine treatment subgroup, there were statistical differences,  $P < 0.05$ .

In conclusion, recombinant human BNP effectively treat CHF, rapidly improve clinical symptoms of patients and laboratory

biochemical indexes such as TWEAK and NT-pro BNP etc. Compared with routine treatment methods, it has significant effects and high safety. It is worthy of clinical promotion.

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