Research Paper

Outcomes of Irbesartan Hydrochlorothiazide Combined with Recombinant Human Brain Natriuretic Peptide on Cardiac Function, Immune Function and Intestinal Flora in Acute Heart Failure

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Wang *et al.*: To Investigate the Effects of Irbesartan Hydrochlorothiazide with Recombinant Human Brain Natriuretic Peptide

To investigate the effects of irbesartan hydrochlorothiazide combined with recombinant human brain natriuretic peptide on cardiac function, immune function and intestinal flora in subjects with acute heart failure. 100 subjects with acute heart failure admitted to our hospital from March 2021 to March 2022 were divided into 50 subjects in each group according to different intervention methods. The monotherapy group was handled with conventional therapy, and the combination therapy group was handled with irbesartan hydrochlorothiazide combined with recombinant human brain natriuretic peptide, clinical efficacy, cardiac function, serum myocardial enzymes, cardiac troponin I, immunological functioning, change of intestinal flora and adverse reactions in two groups were contrasted. The monotherapy group *vs.* the total effective rate of the combination therapy group was higher (92.00 % *vs.* 74.00 %) ($p<0.05$). The monotherapy group *vs.* left ventricular ejection fraction in the combination therapy group was notably higher ($p<0.05$). Left ventricular end diastolic diameter, left ventricular end systolic diameter and serum creatine kinase, creatinine kinase myocardial band, aspartate transaminase, lactate dehydrogenase, troponin I levels were notably lower than those in the monotherapy group ($p<0.05$). Comparing the intestinal flora of the two groups, the abundance of *Bacteroides* in the combination therapy group was notably increased *vs.* the monotherapy group ($p<0.05$). The abundance of *Fusobacterium*, *Actinomyces*, Proteus and *Firmicutes* was notably lower than that of the monotherapy group ($p<0.05$). There was no notable difference in the incidence of adverse reactions between the two groups ($p>0.05$). Irbesartan hydrochlorothiazide combined with recombinant human brain natriuretic peptide can improve the therapeutic effect of acute heart failure, improve the subject's cardiac function, reduce the myocardial injury, improve the body immunity, and regulate the intestinal flora structure, so as to promote the subject's recovery.

Key words: Heart failure, irbesartan hydrochlorothiazide, recombinant human brain natriuretic peptide, cardiac function, immunity, intestinal flora

Heart failure is a clinical syndrome caused by abnormal cardiac structure and (or) function, including chronic heart failure and acute heart failure, of which the latter is more critical, and is one of the main reasons for subjects over 65 y old to stay in hospital[1,2]. According to the report[3], the incidence rate of heart failure among people over 35 y old in China is about 1.3 %, which has increased in recent years, bringing heavy disease burden to the country. The main clinical manifestations of acute heart failure are pulmonary congestion/edema, decreased cardiac output, hypoperfusion of tissues and organs, and even cardiogenic shock, respiratory failure, etc.,[4,5]. The early therapy of acute heart failure is mainly to stabilize hemodynamics, correct hypoxia and maintain organ perfusion. Later, symptomatic therapy is carried out according to the etiology. Common drugs include vasodilators,

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diuretics, positive inotropic drugs, etc., but the effect is average[6].

Irbesartan hydrochlorothiazide is a new type of angiotensin II receptor antagonist, in which hydrochlorothiazide can activate renin-angiotensin system and sympathetic nervous system, reduce blood pressure level while lowering blood potassium; irbesartan has strong diuretic effect, quickly corrects symptoms of heart failure, and is mainly used for the therapy of hypertension[7]. Subjects with heart failure were accompanied by increased plasma B-Type Natriuretic Peptide (BNP). Studies have shown that recombinant human Brain Natriuretic Peptide (rhBNP) can play a series of effects after binding with its receptor, such as expanding blood vessel, reducing blood pressure, filling left ventricle and maintaining heart function effectively. It can be used alone or in combination[8,9]. In addition, a study has shown that irbesartan can regulate body immunity and improve vascular endothelial function[10]. BNP has immunomodulatory function in unidirectional mixed lymphocyte reaction[11]. Recent study has found that there are many links between intestinal microbiota and their metabolites and immune system[12]. At the same time, the changes of intestinal flora in patients with cachexia will lead to the disturbance of intestinal barrier function, resulting in the increase of bacterial toxin translocation and systemic inflammation[13]. A study has found that heart failure is closely related to changes in intestinal flora, but the specific mechanism is unknown[14].

In view of this, this study took subjects with acute heart failure as the research object, to explore the therapeutic effect of irbesartan hydrochlorothiazide combined with rhBNP and its influence on the heart function, immune function and intestinal flora of subjects as shown in fig. 1.

MATERIALS AND METHODS

General information:

This was a double-arm cohort trial with repeated measurements from March 2021 to March 2022. In this retrospective analysis trial, the eligibility and exclusion criteria of subjects were evaluated according to the inclusion situation. After screening, the participants were assigned according to the intervention method. This study was approved by Nanjing University of Chinese Medicine Ethics Committee (Approval No: 2023-KY-106-02).

Inclusion criteria: The age was 18 y to 80 y; conformed to the diagnostic criteria related to acute heart failure[15], and it was left heart failure; New York Heart Association (NYHA) classification ≥grade II and the clinical data was complete.

Exclusion criteria: Patients with other types of heart failure or congenital heart disease; patients with severe liver and kidney dysfunction; patients with concurrent severe infection or blood system disease; patients with malignant tumors; patients with severe neurological disease and patients who did not tolerate the therapy drug.

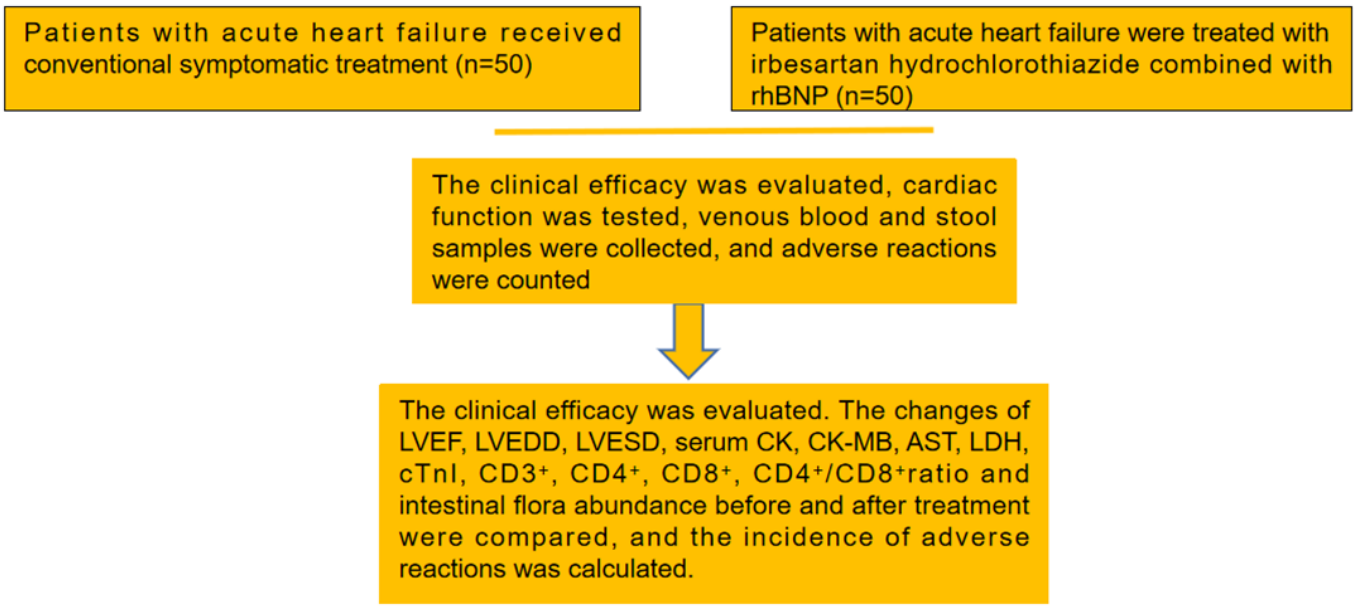

Fig. 1: Study on combined drug use

Therapy methods:

The monotherapy group was given routine symptomatic therapy such as mask oxygen inhalation, Electrocardiogram (ECG) monitoring, cardiotonic therapy, diuresis, etc. The combination therapy group added irbesartan hydrochlorothiazide tablets (GYZZ H20058709, Zhejiang Huahai Pharmaceutical Co., Ltd., irbesartan 150 mg+hydrochlorothiazide 12.5 mg/tablet, Zhejiang, China) and rhBNP (GYZZ S20050033, Chengdu Nordicam Biopharmaceutical Co., Ltd., 0.5 mg/500 U/bottle, Chengdu, China). Irbesartan hydrochlorothiazide tablets were taken orally. The dose was 162.5 mg/time and 1 time/d. RhBNP was injected intravenously with 1.5 μg/kg dose, completed in 3~5 min, and then pumped continuously according to 7.5 ng/(kg/min) for 3 d-7 d.

Observation indicators:

Cardiac function: The cardiac function of the subjects was tested by color Doppler ultrasound (Philips iu22, Amsterdam, Netherlands). The indexes include Left Ventricular Ejection Fraction (LVEF), Left Ventricular End Diastolic Diameter (LVEDD), and Left Ventricular End Systolic Diameter (LVESD).

Serum myocardial enzymes and cardiac Troponin I (cTnI) levels: 5 ml of venous blood was collected before and after therapy, and serum samples and cell samples were collected after centrifugation. The levels of serum Creatine Kinase (CK), CK-Myocardial Band (CK-MB), Aspartate Transaminase (AST), Lactate Dehydrogenase (LDH) and cardiac cTnI were detected with an automatic biochemical analyzer (Hitachi 7020, Prang Medical, Beijing, China).

Immunological functioning: The above cell samples were selected, and the levels of Cluster of Differentiation 3^+ ($CD3^+$), $CD4^+$, and $CD8^+$ were detected by flow cytometry, and the ratio of $CD4^+$/$CD8^+$ was calculated[16].

Change of intestinal flora: The stool samples of subjects before and after therapy were collected, and the fecal bacteria Deoxyribonucleic Acid (DNA) were extracted. *Bacteroides*, *Fusobacterium*, Actinomycetes, Proteus and *Firmicutes* were detected by gene sequencing.

Adverse reactions: The adverse reactions such as hypotension and headache were compared between the two groups.

Efficacy evaluation criteria:

Remarkable effect: The clinical symptoms and signs basically disappeared *vs.* those before therapy, and the improvement level of cardiac function ≥grade II or recovered to grade I. In effective, the clinical symptoms and signs are relieved *vs.* those before therapy, and the improvement grade of cardiac function was grade I. In ineffective, the clinical symptoms and signs were not improved or aggravated *vs.* those before therapy, and the cardiac function grade was not improved.

Remarkable efficiency+effective efficiency=total effective efficiency

Data statistics:

Statistical Package for the Social Sciences (SPSS) 24.0 software (IBM, Amonk, New York, United States of America (USA)) was selected as the analysis software to analyze the data. The measurement data conformed to the normal distribution and had the same variance. It was described by (x±s) and tested by t-value. Counting data were described by (n, %) and tested by Chi-square (χ^2)/Fisher exact probability method. The standard of statistically notable difference was $p<0.05$.

RESULTS AND DISCUSSION

There were 26 males and 24 females with the age of 51 y~78 y, average (67.25±7.39) y. In NYHA classification; 11 cases of grade II, 25 cases of grade III and 14 cases of grade IV; in past medical history; 17 cases of hypertension, 8 cases of coronary heart disease and 13 cases of diabetes. In monotherapy group; 28 males and 22 females were there and age was 48 y~79 y, average (68.31±7.55) y; NYHA classification with 14 cases of grade II, 24 cases of grade III, 12 cases of grade IV. In past medical history; 15 cases of hypertension, 10 cases of coronary heart disease and 12 cases of diabetes. There were no significant differences in general data between the two groups ($p>0.05$) (Table 1).

In the combination therapy group, the ineffective rate was 8.00 %, whereas 26.00 % in the monotherapy group *vs.* the total effective rate of the monotherapy group (74.00 %), the total effective rate of the combination therapy group (92.00 %) was higher ($p<0.05$). As corroborated in Table 2 and fig. 2.

Before therapy, there was no difference in LVEF, LVEDD and LVESD between the two groups ($p>0.05$). After therapy, the LVEF in both groups were higher than baselines with statistical significances, LVEDD

and LVESD were lower (all p<0.05) as shown in Table 3.

Before therapy, there was no difference in serum CK, CK-MB, AST, LDH and cTnI levels between the two groups (p>0.05). After therapy, the above indexes in both groups were lower than baselines with statistical significances (all p<0.05). And the decrease in the combination therapy group was greater (p<0.05) as shown in Table 4.

Before therapy, there was no difference in $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ ratio between the two groups (p>0.05). After therapy, $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ ratio in both groups were higher than baselines with statistical significances, $CD8^+$ was lower (all p<0.05). And the change range of the combination therapy group was greater (p<0.05) as shown in Table 5.

Before therapy, there was no difference in the abundance of intestinal flora between the two groups (p>0.05). After therapy, the abundance of intestinal *Bacteroides* in both groups were higher than baselines with statistical significances, the abundance of *Fusobacterium*, *Actinomyces*, Proteus and *Firmicutes* was lower (all p<0.05). And the change range of the combination therapy group was more notable (p<0.05) (Table 6).

During the therapy, 3 subjects in the combination therapy group had hypotension, 2 subjects had headache symptoms, and the incidence of adverse reactions was 10.00 % (5/50). In the monotherapy group, there were 2 cases of hypotension and 1 case of headache, respectively. The incidence of adverse reactions was 6.00 (3/50). The comparison between groups corroborated that there was no difference in the incidence of adverse reactions (Fisher's exact probability=0.715) (fig. 3).

TABLE 1: GENERAL INFORMATION IN TWO GROUPS

	Combination therapy group	Monotherapy group	χ^2/t	p
Gender				
Male	26	28	0.161	0.288
Female	24	22		
Age	67.25±7.39	68.31±7.55	0.709	0.479
NYHA classification				
Grade II	11	14		
Grade III	25	24	0.534	0.765
Grade IV	14	12		
Past medical history				
Hypertension	17	15		
Coronary heart disease	8	10	2.45	0.294
Diabetes	13	12		

TABLE 2: CLINICAL EFFICACY (n, %)

Category	n	Remarkable effect	Effective	Ineffective	Total effective efficiency
Combination therapy group	50	27 (54.00)	19 (38.00)	4 (8.00)	46 (92.00)
Monotherapy group	50	21 (42.00)	16 (32.00)	13 (26.00)	37 (74.00)
χ^2		2.885	3.099	11.481	5.741
p		0.089	0.078	<0.001	0.017

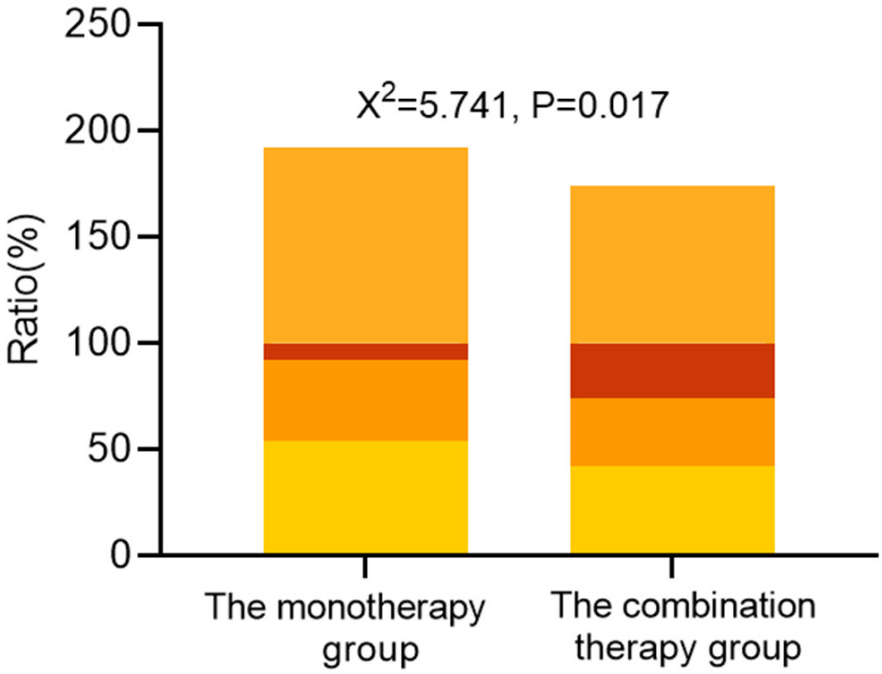

Fig. 2: Clinical efficacy between the two groups
Note: ( ): Total effective efficiency; ( ): Ineffective; ( ): Effective and ( ): Remarkable effect

TABLE 3: CARDIAC FUNCTION INDEXES (x̄±s)

Category	n	LVEF (%) (mm)		LVEDD (mm)		LVESD (mm)	
		Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
Combination therapy group	50	36.59±6.45	47.03±7.25[a]	61.58±9.43	51.74±7.81[a]	56.35±8.11	48.87±6.50[a]
Monotherapy group	50	36.71±6.30	41.86±7.34[a]	62.01±9.22	55.96±8.04[a]	55.79±8.35	52.61±6.77[a]
t		0.094	3.543	0.231	2.662	0.340	2.818
p		0.925	0.001	0.818	0.009	0.734	0.006

Note: [a]p<0.05 *vs.* the same group before therapy. In the combination therapy group, LVEF [a]p<0.001, LVEDD ap<0.001 and LVESD [a]p<0.001. In the monotherapy group, LVEF [a]p<0.001, LVEDD [a]p<0.001 and LVESD [a]p=0.039

TABLE 4: LEVELS OF SERUM MYOCARDIAL ENZYMES AND CTNI (x̄±s)

Category	n	CK (U/l)		CK-MB (U/l)		AST (U/l)		LDH (U/l)		cTnI (ng/ml)	
		Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
Combination therapy group	50	220.15± 30.42	134.88± 15.70a	14.63± 1.97	8.29± 1.53a	53.68± 7.20	29.01± 4.56a	308.57± 48.31	168.33± 32.64a	0.24± 0.07	0.11± 0.03a
Monotherapy group	50	221.67± 31.82	195.26± 18.30a	14.55± 2.08	10.86± 2.24a	52.79± 7.34	36.45± 5.39a	310.20± 50.15	217.63± 41.75a	0.25± 0.08	0.16± 0.05a
t		0.244	17.707	0.197	6.699	0.612	7.452	0.166	6.578	0.665	6.063
p		0.808	<0.001	0.844	<0.001	0.542	<0.001	0.869	<0.001	0.508	<0.001

Note: [a]p<0.05 *vs.* the same group before therapy. In the combination therapy group, CK [a]p<0.001, CK-MB ap<0.001, AST ap<0.001, LDH [a]p<0.001 and cTnI ap<0.001. In the monotherapy group, CK [a]p<0.001, CK-MB ap<0.001, AST [a]p<0.001, LDH ap<0.001 and cTnI [a]p<0.001

TABLE 5: IMMUNE FUNCTION INDEXES ($\bar{x}$±s)

Category	n	$CD3^+$ (%)		$CD4^+$ (%)		$CD8^+$ (%)		$CD4^+/CD8^+$	
		Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
Combination therapy group	50	48.26±4.31	56.74±6.48[a]	32.85±3.54	38.41±3.80[a]	28.01±2.56	22.45±1.92[a]	1.17±0.30	1.71±0.35[a]
Monotherapy group	50	49.55±4.22	53.14±6.05[a]	32.29±3.38	35.94±3.61[a]	27.83±3.40	25.37±2.16[a]	1.16±0.32	1.42±0.33[a]
t		1.512	2.871	0.809	3.332	0.299	7.145	0.161	4.263
p		0.134	0.005	0.421	0.001	0.766	<0.001	0.872	<0.001

Note: [a]p<0.05 *vs.* the same group before therapy. In the combination therapy group, $CD3^+$ [a]p<0.001, $CD4^+$ [a]p<0.001, $CD8^+$ [a]p<0.001 and $CD4^+/CD8^+$ [a]p<0.001. In the monotherapy group, $CD3^+$ [a]p<0.001, $CD4^+$ [a]p<0.001, $CD8^+$ [a]p<0.001 and $CD4^+/CD8^+$ [a]p<0.001

TABLE 6: ABUNDANCE OF INTESTINAL MICROFLORA (x±s, %)

Category	n	*Bacteroides*		*Fusobacterium*		*Actinomyces*		*Proteus*		*Firmicutes*	
		Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
Combination therapy group	50	28.74±3.15	45.86±6.20[a]	0.93±0.18	0.72±0.13[a]	14.36±2.90	6.53±1.74[a]	8.73±1.59	6.39±1.20[a]	63.15±5.78	29.36±4.15[a]
Monotherapy group	50	28.26±3.30	33.08±4.27[a]	0.95±0.17	0.84±0.15[a]	14.22±2.75	10.05±1.96[a]	8.80±1.55	7.26±1.44[a]	63.40±6.03	48.95±4.27[a]
t		0.744	12.004	0.571	4.275	0.248	9.497	0.223	3.282	0.212	23.264
p		0.459	<0.001	0.569	<0.001	0.805	<0.001	0.824	0.001	0.833	<0.001

Note: [a]p<0.05 *vs.* the same group before therapy. In the combination therapy group, *Bacteroides* [a]p<0.001, *Fusobacterium* [a]p<0.001, *Actinomyces* [a]p<0.001, Proteus [a]p<0.001 and *Firmicutes* [a]p<0.001. In the monotherapy group, *Bacteroides* [a]p<0.001, *Fusobacterium* [a]p<0.001, *Actinomyces* [a]p<0.001, Proteus [a]p<0.001 and *Firmicutes* [a]p<0.001

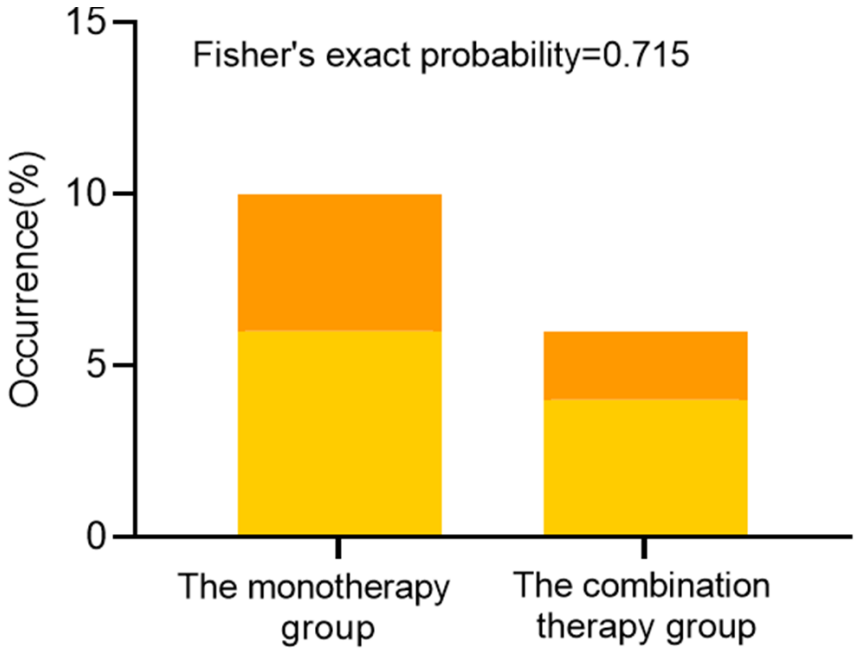

Fig. 3: Adverse reactions in two groups
Note: ( ): Hypotension and ( ): Headache

The vast majority of cardiovascular diseases will eventually develop into heart failure, and its prevalence rate will increase year by year with the growth of age. With the aggravation of the aging process in China, heart failure has become an important disease burden in China, seriously affecting the development of society[17,18]. There are many inducements for heart failure, such as myocardial injury, heart valve disease, mechanical obstruction, excessive resistance or volume load, etc. Among them, acute myocardial ischemia, acute poisoning, acute heart valve dysfunction, severe infection, etc., are the main causes of acute left heart failure, while acute right heart failure is relatively rare in clinical practice[19]. For acute left heart failure, the clinical therapy strategy is to evaluate the respiratory, circulatory and conscious state and provide supportive therapy[20].

The results of this study corroborated that the total effective rate of the combination therapy group was notably higher than that of the monotherapy group, and LVEF of the combination therapy group was notably higher than that of the monotherapy group, LVEDD and LVESD were notably lower than that of the monotherapy group, it shows that irbesartan hydrochlorothiazide combined with rhBNP can improve the clinical efficacy of acute left heart failure, reduce cardiac load and improve cardiac function. Based on the pathological characteristics of acute heart failure, diuretics, positive inotropic drugs and vasodilators are mainly used in clinical therapy, which can alleviate the symptoms of heart failure and stabilize the condition, but the prognosis is not notably beneficial[21]. Obviously, conventional supportive therapy can no longer meet the needs of subjects with acute heart failure. Elevated BNP level is a recognized plasma marker for clinical diagnosis of heart failure. The study shows that BNP is mainly synthesized by cardiomyocytes and stored in myocardial secretory granules in the form of precursors[22]. Once the ventricular wall tension increases and the myocardium is damaged, it will be released, some of which will be decomposed into active BNP and the other into inactive N-terminal BNP, resulting in an increase in plasma BNP concentration, and the more serious the degree of heart failure, the higher the BNP concentration. On the other hand, BNP has the effects of diuresis, vasodilation, natriuretic, inhibition of sympathetic nerve and renin-angiotensin-aldosterone system, and can be used in the therapy of heart failure[23]. Previous studies have confirmed that intravenous drip of rhBNP can improve the clinical symptoms of subjects and reduce the risk of rehospitalization in subjects with short-term heart failure[24,25]. As a compound preparation, irbesartan hydrochlorothiazide has the dual effects of irbesartan and hydrochlorothiazide, which cannot only dilate blood vessels and reduce ventricular wall tension, but also resist hypotension and reduce blood potassium level[26]. rhBNP combined with irbesartan and hydrochlorothiazide can play a synergistic therapeutic effect, and the effect is more notable. Myocardial zymogram and cTnI are serum markers for evaluating myocardial injury[27]. In this study, the lower levels of serum CK, CK-MB, AST, LDH and cTnI in the combination therapy group also corroborated that the combination of them was more effective in the therapy of acute heart failure, which could improve the cardiac function of subjects and promote the recovery of myocardial injury.

Through the analysis of the incidence characteristics of heart failure in the elderly, this disease is related to the deterioration of cardiovascular structure and function, or to the decrease of immune function[28]. In recent years, more and more evidence shows that the immune system plays an important role in the occurrence and development of heart failure. Abnormal T cell subsets can cause ventricular remodeling and aggravate the process of heart failure[29]. Intestinal microflora refers to microorganisms living in human intestine, including beneficial bacteria, harmful bacteria and neutral bacteria. Under normal circumstances, their number and types are in dynamic balance. If the balance is damaged, many diseases will occur, including heart failure[30,31]. This study found that after therapy, the $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ ratio and the abundance of *Bacteroides* in the combination therapy group were notably higher than those in the monotherapy group, while $CD8^+$, the abundance of *Fusobacterium*, *Actinomyces*, Proteus and *Firmicutes* was notably lower than that in the monotherapy group. It is suggested that irbesartan hydrochlorothiazide combined with rhBNP can improve immune function and regulate intestinal flora balance in subjects with acute heart failure. Inflammatory response is another important mechanism leading to heart failure. rhBNP and irbesartan hydrochlorothiazide can reduce the inflammatory response, and their immune enhancement effect on the body may be related to reducing the expression of proinflammatory factors[32,33]. Yu *et al*.[34] have suggested that the

synthesis and secretion of adhesion molecules and chemokines in subject's body with coronary heart disease complicated with heart failure increased. Probiotic intervention can regulate intestinal flora, increase myocardial hypoxia tolerance, increase cardiac output, reduce inflammation. It also suggests that reducing inflammation can improve intestinal flora[35]. In this study, it was found that there was no difference in the incidence of adverse reactions between the two groups, indicating that the combination of drugs had higher safety, which was consistent with the results of previous safety studies[36,37].

To sum up, for subjects with acute heart failure, the combination of irbesartan hydrochlorothiazide and rhBNP is more effective on the basis of routine therapy, which can improve subject's cardiac function, increase body immune function, and regulate the balance of intestinal flora, which is worthy of clinical application. However, the number of cases in this study is small, the observation time is short, and the specific mechanism of heart failure and intestinal flora has not been discussed, which needs to be demonstrated by large sample size and multicenter research.

Irbesartan hydrochlorothiazide combined with rhBNP can improve the therapeutic effect of acute heart failure, improve the subject's cardiac function, reduce the myocardial injury, improve the body immunity, and regulate the intestinal flora structure, so as to promote the subject's recovery.

Conflict of interests:

The authors declared no conflict of interests.

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