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Clinical Study on Self-Made Lixin Granules Combined with Natriuretic Peptide in the Treatment of Refractory Heart Failure

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Abstract: *Objective:* To analyze the clinical effects of the combined application of self-made Lixin Granule and natriuretic peptide in treating refractory heart failure. *Methods:* From January 2022 to June 2023, 40 patients with refractory heart failure were randomly divided into groups using the envelope method. A reference group (n = 20) received conventional Western medicine treatment, while an observation group (n = 20) received self-made Lixin Granules and natriuretic peptide. Clinical efficacy, heart failure scores, traditional Chinese medicine (TCM syndrome scores, inspection indicators, and adverse reactions of the two groups were compared. *Results:* The effective treatment rate in the observation group was significantly higher than that in the reference group ($P < 0.05$). There were no significant differences in heart failure scores and traditional Chinese medicine (TCM) syndrome scores between the two groups before treatment ($P > 0.05$). However, both scores in the observation group were lower than those in the reference group after treatment ($P < 0.05$). Before treatment, there were no significant differences in the inspection indicators between the two groups ($P > 0.05$). After treatment, the left ventricular ejection fraction (LVEF) of the observation group was higher than that of the reference group, while the N-terminal pro b-type natriuretic peptide (NT-proBNP) level and fractional shortening (FS) of the observation group were lower than those of the reference group ($P < 0.05$). There were no apparent adverse reactions in either group during treatment. *Conclusion:* The combined application of self-made Lixin Granules and natriuretic peptide in treating refractory heart failure improved clinical efficacy, alleviation of clinical symptoms, and enhanced cardiac function. This approach is deemed safe and holds high application value.

Keywords: Self-made Lixin Granules; Natriuretic peptide; Refractory heart failure; Clinical efficacy

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1. Introduction

Chronic heart failure has persistently posed clinical challenges, remaining a refractory disease. Despite the application of neuroendocrine blockers and the continuous progress in medical technology and concepts over the past few decades, the mortality rate of this disease has decreased. However, the 5-year mortality rate following its onset remains high, ranging from 60% to 80%, akin to that of malignant tumors. It stands as one

of the most severe cardiovascular diseases [1,2].

Refractory heart failure denotes patients whose clinical symptoms persist uncontrollably or worsen despite routine treatment interventions. Natriuretic peptide, a lyophilized recombinant human brain natriuretic peptide, has been substantiated by studies to expand blood vessels, induce diuresis, and significantly impact anti-heart failure measures [3,4]. According to traditional Chinese medicine (TCM), heart failure results from heart qi deficiency. Lixin Granule, a self-made prescription fostering blood circulation, eliminating blood stasis, and promoting yang warmth and diuresis, is believed to alleviate refractory heart failure symptoms. A group of 40 patients with refractory heart failure admitted to Gaoyou Hospital of Traditional Chinese Medicine from January 2022 to June 2023 were observed in this study.

2. Materials and methods

2.1. General information

This study was conducted from January 2022 to June 2023, encompassing 40 subjects, all of whom were refractory heart failure patients admitted to Gaoyou Hospital of Traditional Chinese Medicine within this period. There were ten male and ten female patients in the reference group, with their age ranged from 63 to 81 years and an average of 72.29 ± 4.35 years. The primary diseases included nine patients with coronary heart disease, six with dilated cardiomyopathy, three with high heart disease, and two with rheumatic heart disease. There were twelve male and eight female patients in the observation group, with their age ranged from 62 to 83 years and an average of 72.96 ± 4.47 years. The primary disease included eight patients with coronary heart disease, six with dilated cardiomyopathy, three with high heart disease, and three with rheumatic heart disease. The baseline data of both patient groups were balanced and comparable ($P > 0.05$).

Inclusion criteria included all patients who met the diagnostic criteria for refractory heart failure, utilizing sufficient doses of diuretics, aldosterone antagonists, angiotensin-converting enzyme receptor antagonists/inhibitors, and beta-receptor blockers, symptoms persisted despite routine heart failure treatment, and all volunteered and signed the consent form.

Exclusion criteria included patients with severe heart valve disease, cerebral infarction or cerebral hemorrhage within the last six months, acute coronary syndrome within the last three months, co-infection, malignant tumor, autoimmune system diseases, recent major trauma or surgery history, hepatic and renal insufficiency, thyroid disease, uncorrected electrolyte imbalance, atrial fibrillation with a permanent pacemaker of a history of blood embolism within the past six months, pulmonary heart disease, and allergy to any drug component in the treatment plan.

2.2. Diagnostic criteria

The diagnostic criteria for chronic heart failure outlined in the “Guidelines for the Diagnosis and Treatment of Chronic Heart Failure” (2014 edition) were followed [5]: in addition to the original heart disease-related symptoms, dyspnea, decreased activity tolerance, chest tightness, and wheezing gradually appeared. The situation was confirmed by echocardiography, and the cardiac function was analyzed using the New York Heart Association (NYHA) criteria.

Additionally, TCM diagnostic criteria from the “Guiding Principles for Clinical Research of New Drugs of Traditional Chinese Medicine (Trial)” on Qi and Yang Deficiency and Water-damp Internal Stop Syndrome were considered [6]: main symptoms included palpitations, shortness of breath, face/limb edema, chest tightness, chest pain, fear of cold, cold limbs, lack of urination; secondary symptoms included abdominal fullness, spontaneous sweating, irritability; tongue examination revealed white and greasy tongue coating, dark red/dull

tongue; pulse examination revealed thready and rapid pulse or intermittent pulse.

2.3. Methods

The reference group was treated with conventional Western medicine according to the "Guidelines for the Diagnosis and Treatment of Chronic Heart Failure" (2014 edition). The observation group received self-made Lixin Granules and natriuretic peptide (Chengdu Nuodikang Bio-Pharmaceutical Co., Ltd., S20050033) in addition to routine Western medicine treatment. The initial treatment amount was 1.5 μg/kg, adjustable to 0.075 μg/kg, and continued for three days. The full prescription of self-made Lixin Granules included 30 g of *Astragalus membranaceus*, 30 g of motherwort, 15 g of polygonatum, 12 g of psoralen, and 12 g of descurainia seed. Self-made Lixin Granules were taken once a day, one bag each time, for 14 days as a course of treatment, with continuous treatment for three courses.

2.4. Observation indicators

(1) Clinical efficacy comparison: Evaluated based on criteria. Edema resolution, liver size reduction (> 2 cm), disappearance of jugular venous distension, complete or significantly weakened pulmonary moist rales, dyspnea disappearance, and improved heart function (Grade 2 or above) as markedly effective. Edema subsidence, liver shrinkage (≤ 2 cm), relief of jugular venous distension, reduced lung moist rales, improved dyspnea, tolerable side effects, and improved heart function (Grades 1–2) as effective; No improvement in heart function of clinical-related symptoms as ineffective. The effective rate of treatment was calculated as 100.00% - (number of ineffective cases / 20 × 100.00%).

(2) Heart failure points and TCM syndrome points comparison: Assessed using Lee's treatment integral method (1982). Higher heat failure and TCM syndrome scores indicated more severe heart failure [6].

(3) Relevant inspection indicators comparison: N-terminal pro-b-type natriuretic peptide (NT-proBNP) detection using an automatic fluorescent immunoassay analyzer, and echocardiography for left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (FS).

(4) Incidence of adverse reactions comparison.

2.5. Statistical methods

Data were processed using SPSS 24.0 statistical software. Descriptive statistics included [*n* (%)] for clinical curative effect and adverse reaction incidence, while heart failure score, TCM syndrome score, and heart function indexes were presented as mean ± standard deviation (SD). Group comparisons were conducted using *t*-tests and χ^2 tests, with $P < 0.05$ considered statistically significant.

3. Results

3.1. Comparison of clinical efficacy

The treatment's effective rate was 90.00% (18/20) in the observation group, with 60.00% (12/20) markedly effective, 30.00% (6/20) effective, and 10.00% (2/20) ineffective. In the reference group, the effective rate was 55.00% (11/20), including 25.00% (5/20) markedly effective, 30.00% (6/20) effective, and 45.00% (9/20) ineffective. The treatment efficiency in the observation group was significantly higher ($P = 0.033$, $\chi^2 = 4.514$).

3.2. Comparison of heart failure points and TCM syndrome points.

Before treatment, no significant difference existed in heart failure and TCM syndrome scores between the two groups ($P > 0.05$). After treatment, both scores in the observation group were significantly lower than those of

the reference group ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of heart failure and TCM syndrome scores before and after treatment (mean ± SD, points)

Group	Heart failure score		TCM Syndrome Points	
	Before	After	Before	After
Reference group ($n = 20$)	12.51 ± 1.49	7.84 ± 1.23*	29.45 ± 3.94	15.38 ± 4.32*
Observation group ($n = 20$)	12.63 ± 1.67	4.79 ± 1.65*	29.61 ± 4.14	8.09 ± 3.68*
t	0.239	6.627	0.125	5.744
P	0.811	< 0.001	0.901	< 0.001

* $P < 0.05$ compared with the group before treatment

3.3. Comparison of relevant inspection indicators

Prior to treatment, no significant differences were found in NT-proBNP, LVEF, and FS between the two groups ($P > 0.05$). Post-treatment, NT-proBNP and FS in the observation group were lower than those in the reference group, and LVEF was higher than that in the reference group ($P < 0.05$), as indicated in **Table 2**.

Table 2. Comparison of relevant inspection indicators before and after treatment (mean ± SD)

Group	NT-proBNP (pg/mL)		LVEF (%)		FS (%)	
	Before	After	Before	After	Before	After
Reference group ($n = 20$)	8,670.75 ± 125.34	6,214.54 ± 107.63*	28.89 ± 3.16	33.47 ± 3.53*	23.44 ± 2.61	26.73 ± 2.12*
Observation group ($n = 20$)	8,683.62 ± 126.51	3,213.79 ± 112.58*	28.31 ± 3.33	42.69 ± 2.85*	23.39 ± 2.58	28.48 ± 2.31*
t	0.323	86.161	0.565	9.088	0.060	2.496
P	0.748	< 0.001	0.575	< 0.001	0.951	0.017

* $P < 0.05$ compared with the group before treatment

3.4. Comparing the incidence of adverse reactions

No apparent adverse reactions were observed in either group during the treatment.

4. Discussion

With the aging of the population, the incidence of chronic diseases, such as hypertension, diabetes, and coronary heart disease, is on the rise. Consequently, the occurrence of heart failure is increasing, turning it into a significant ailment that poses a serious threat to human health and life safety, burdening patient's families and society. It has become a global public health concern [7].

Heart failure is characterized by the excessive activation of the renin-angiotensin system, sympathetic nervous system, continuous decline in cardiac function, and ventricular remodeling. It represents an inevitable consequence of abnormal expression of cardiomyocyte genes [8,9]. Refractory heart failure refers to a state where heart failure symptoms persist despite the use of digitalis, diuretics, vasodilators, and other medications. At this juncture, the primary objective of treatment should be to alleviate clinical symptoms, reduce the risk of mortality, and lower readmission rates.

Natriuretic peptide emerges as a therapeutic agent capable of dilating arterioles and venules, reducing arterial blood pressure, pulmonary capillary wedge pressure, atrial pressure, and peripheral vascular resistance [10,11]. This leads to increased stroke output and cardiac output, effectively alleviating dyspnea and improving

hemodynamic status without causing reflexive heart rate acceleration. Additionally, it promotes sodium excretion and diuresis.

In line with traditional Chinese medicine, the pathogenesis of chronic heart failure involves heart-qi deficiency. A mild heart yang potential is at the root, while water stagnation is the visible manifestation. If left unaddressed, it can lead to liver and kidney deficiency and damage. Treatment, therefore, should emphasize promoting blood circulation, benefiting water, nourishing qi, and moistening yang [12,13]. The self-made Lixin Granule incorporates medicinal materials that aid qi and warm yang, coupled with restorative components promoting blood circulation and dredging collaterals to invigorate qi and enhance blood flow. This combination also fosters water reduction and swelling alleviation. The prescription includes polygonatum and *Radix astragali*, both invigorating qi, invigorating the spleen, promoting diuresis, and reducing swelling; psoralen for warming yang, transforming qi, and invigorating heart and kidney qi; descurainia seed for relieving asthma, lung alleviation, and diuresis; and motherwort for promoting blood circulation and diuresis. These ingredients collectively warm yang, induce diuresis, relieve asthma, purge lungs, promote blood circulation, remove blood stasis, and protect the heart.

The study results demonstrated that the addition of self-made Lixin Granules and natriuretic peptide to conventional Western medicine treatment significantly improved clinical efficacy, TCM syndromes, heart failure scores, heart function, and NT-proGNP compared to the reference group ($P < 0.05$). This result suggesting the effectiveness and safety of this combined approach for refractory heart failure patients.

In conclusion, the combination of self-made Lixin Granules and natriuretic peptide in treating refractory heart failure exhibits substantial improvements in clinical efficacy, symptomatic relief, and safety.

Disclosure statement

The authors declare no conflict of interest.

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