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Original Article

Efficacy of Sacubitril Valsartan sodium tablets in patients with heart failure combined with pulmonary infection and long-term recurrence rate

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Abstract: Objective: To observe the therapeutic effect of Sacubitril Valsartan sodium tablets (SVST) on heart failure (HF) complicated by pulmonary infection (PI), and to provide a reference for future medication. Methods: A total of 89 patients with HF complicated by PI who were treated at Dongying People's Hospital from January 2019 to May 2020 were selected as study subjects in this retrospective study. The control group consisted of 41 patients who received conventional treatment, while the study group included 48 patients who received SVST in addition to conventional treatment. The time to disappearance/improvement of chest tightness, shortness of breath, cough, and moist rales in both groups were recorded. The levels of brain natriuretic peptide (BNP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and procalcitonin (PCT) were measured before and after treatment. Changes in cardiac function were observed, and the Clinical Pulmonary Infection Score (CPIS) and Sequential Organ Failure Assessment (SOFA) were used to assess PI. The clinical efficacy and adverse reactions were evaluated after treatment. Follow-up lasted 2 years, during which the readmission rate due to HF and mortality rate were calculated. Results: Patients in the study group experienced a shorter time to disappearance/improvement of chest tightness, shortness of breath, cough, and moist rales compared to the control group (all $P<0.05$). The study group also showed reduced levels of BNP, IL-6, TNF-α, and PCT, as well as lower CPIS and SOFA scores after treatment (all $P<0.05$), with significantly improved cardiac function ($P<0.05$). Additionally, the total effective rate was higher in the study group than in the control group ($P<0.05$), and there was no significant difference in adverse reactions between the two groups ($P>0.05$). Follow-up revealed no difference in mortality between the two groups ($P>0.05$), but the study group had a lower readmission rate ($P<0.05$). Conclusion: SVST is effective in treating HF complicated by PI, ensures a good prognosis for patients, and is recommended for clinical use.

Keywords: Heart failure, pulmonary infection, Sacubitril Valsartan sodium tablets, prognosis, recurrence, cardiac function

Introduction

Heart failure (HF) refers to a group of syndromes characterized by insufficient blood perfusion in organ circulation and tissues. This includes impaired ventricular filling and ejection function caused by various cardiac structural or functional diseases, as well as cardiac output falling short of meeting the metabolic needs of body tissues [1]. HF cannot be completely cured, and patients' long-term myocardial contraction and metabolic dysfunction can easily lead to pulmonary blood stasis, microcirculatory disorders, and bacterial deposition, which further trigger pulmonary infection (PI) [2]. HF complicated by PI is a common acute and severe clinical condition; patients are often weak, which in turn aggravates their condition, forming a vicious cycle and posing a serious threat to their lives [3]. Patients whose HF and PI are effectively and timely intervened tend to have better survival rates [4].

Sacubitril Valsartan sodium tablet (SVST) is a novel oral drug for the treatment of HF that contains the neprilysin inhibitor sacubitril and the angiotensin receptor antagonist valsartan. SVST inhibits neprilysin and reduces the degradation of natriuretic peptides through LBQ657, thus achieving vasodilation, lowering blood

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pressure, inhibiting myocardial hypertrophy, and suppressing the release of renin and aldosterone [5, 6]. The drug exerts a positive effect on reducing the preload and afterload of the heart and improving ventricular remodeling [7]. However, there are still few clinical studies on SVST for the treatment of HF complicated by PI, and its therapeutic efficacy and safety remain unclear. To further explore its therapeutic effects, this study was conducted to analyze the therapeutic effects and long-term prognosis of SVST use in HF complicated by PI.

Materials and methods

Data collection

In this retrospective analysis, 89 patients with HF complicated by PI who were treated at Dongying People's Hospital from January 2019 to May 2020 were selected as study subjects.

Inclusion criteria: Patients who were diagnosed by clinical examination and met the diagnostic criteria for chronic HF and PI [8, 9]; patients with complete data.

Exclusion criteria: Patients with mental disorders or unable to communicate normally; patients with concomitant gastrointestinal and visceral diseases; patients with other malignant tumors; patients with drug contraindications; patients with low compliance. The study was approved by the Ethics Committee of Dongying People's Hospital (DYYX-2023-130).

Patient grouping

The control group consisted of 41 patients who received conventional treatment, while the study group consisted of 48 patients who received SVST in addition to conventional treatment.

Treatment method

Control group [10]: All patients were on bed rest after admission and strictly monitored for vital signs. Their sodium intake was controlled. They received conventional cardiac stimulants, vasodilators, and diuretic anti-HF treatments, as well as anti-infection treatments including bronchodilators, antibiotics, and aerosol inhalation, to ensure water and electrolyte balance. One week was considered a course of treatment, for a total of 2 courses.

Study group: Patients received SVST (100 mg, 14 tablets/box, NMPA approval number: HJ 20170362) in addition to the treatment adopted in the control group, with an oral dose of 50-100 mg twice daily depending on their conditions. The dose was gradually increased to the maximum dose or maximum tolerated dose over 2-4 weeks. Note: Due to the potential risk of angioedema caused by SVST when combined with ACEI, SVST is prohibited to be used in combination with ACEI. If a patient was taking ACEI/ARB, SVST should be taken 36 hours after discontinuing the other drug. Patients in both groups were treated for 6 consecutive months.

Sample collection and testing

Before and after treatment, 3 mL of venous blood was collected from the patients' elbows in the fasting state and centrifuged for 20 minutes at room temperature to separate the plasma and serum. Brain natriuretic peptide (BNP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) levels were determined by enzyme-linked immunosorbent assay (ELISA), and procalcitonin (PCT) by immunoluminescence assay. Changes in left ventricular end-diastolic dimension (LEVDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF), and left ventricular end-systolic dimension (LVDs) were examined by cardiac ultrasound before and after treatment using the PHILIPS ultrasound system (EPIQ7C).

Efficacy assessment

At the end of the treatment period (6 months), patients were evaluated for clinical efficacy [11]. Markedly effective: patient's cardiac function was significantly improved, no shadow was observed on the lungs, and hematology parameters returned to normal. Effective: X-ray showed that most of the lung shadows were reduced, and the symptoms of HF were effectively controlled. Ineffective: HF and PI symptoms did not change or even worsened. Total effective rate = (Number of markedly effective cases + Number of effective cases)/total number × 100%.

Prognosis follow-up

Patients in both groups were followed up for 2 years. Follow-ups were carried out through reg-

Table 1. Comparison of general information

	Study group (n=48)	Control group (n=41)	χ^2 or t/P
Age	61.3±7.7	61.0±6.3	0.199/0.843
BMI (Kg/m^2)	22.7±2.4	23.3±2.1	1.245/0.217
Gender			0.084/0.772
Male	29 (60.42%)	26 (63.41%)	
Female	19 (39.58%)	15 (36.59%)	
Duration of HF disease (years)	3.3±1.2	3.5±1.5	0.699/0.487
Smoking			0.710/0.399
Yes	25 (52.08%)	25 (60.98%)	
No	23 (47.92%)	16 (39.02%)	
Living environment			0.254/0.614
Urban	34 (70.83%)	27 (65.85%)	
Rural	14 (29.17%)	14 (34.15%)	
Ethnicity			0.078/0.779
Han Chinese	45 (93.75%)	39 (95.12%)	
Ethnic Minority	3 (6.25%)	2 (4.88%)	

Note: BMI, Body Mass Index; HF, heart failure.

ular reviews, with an interval of no more than 2 months between visits.

Outcome measures

The timing of symptom improvement was recorded in both groups, including the disappearance/improvement of chest tightness, shortness of breath, cough, and moist rales.

The levels of inflammatory factors (BNP, IL-6, TNF-α, PCT) and cardiac function (LEVDD, LVESD, LVEF, LVDs) were compared before and after treatment between the two groups.

The clinical pulmonary infection score (CPIS) [12] and Sequential Organ Failure Assessment (SOFA) [13] were used to assess the PI of patients. The CPIS totals 12 points, with higher scores indicating more severe infection; the SOFA totals 24 points, with higher scores indicating more severe disease.

Other outcome measures were: clinical efficacy of patients in both groups; dverse reactions during treatment, such as hypotension and hypoglycemia; and rate of readmission due to HF and mortality rate in the two groups within 2 years.

Statistical analysis

Statistical analysis was performed using SPSS 23.0, and plots were generated using GraphPad Prism 7. Enumerated data were expressed as percentages, and comparisons between groups were made using the chi-square test. Measured data were expressed as mean ± standard deviation (SD), and comparisons between groups were made using the t-test, while paired t-tests were used for comparisons before and after treatment. A P value <0.05 was considered significant.

Results

Comparison of general information of patients

As shown in **Table 1**, there were no significant differences between the two groups regarding age, body mass index (BMI), gender, duration of HF, smoking status, living environment, and ethnicity (all P>0.05).

Comparison of time of improvement of symptoms

The time to disappearance/improvement of chest tightness, shortness of breath, cough, and moist rales was shorter in the study group compared to the control group (all P<0.05) (**Figure 1**).

Comparison of levels of inflammatory factors in vivo before and after treatment

There were no significant differences in BNP, IL-6, TNF-α, and PCT levels between the two

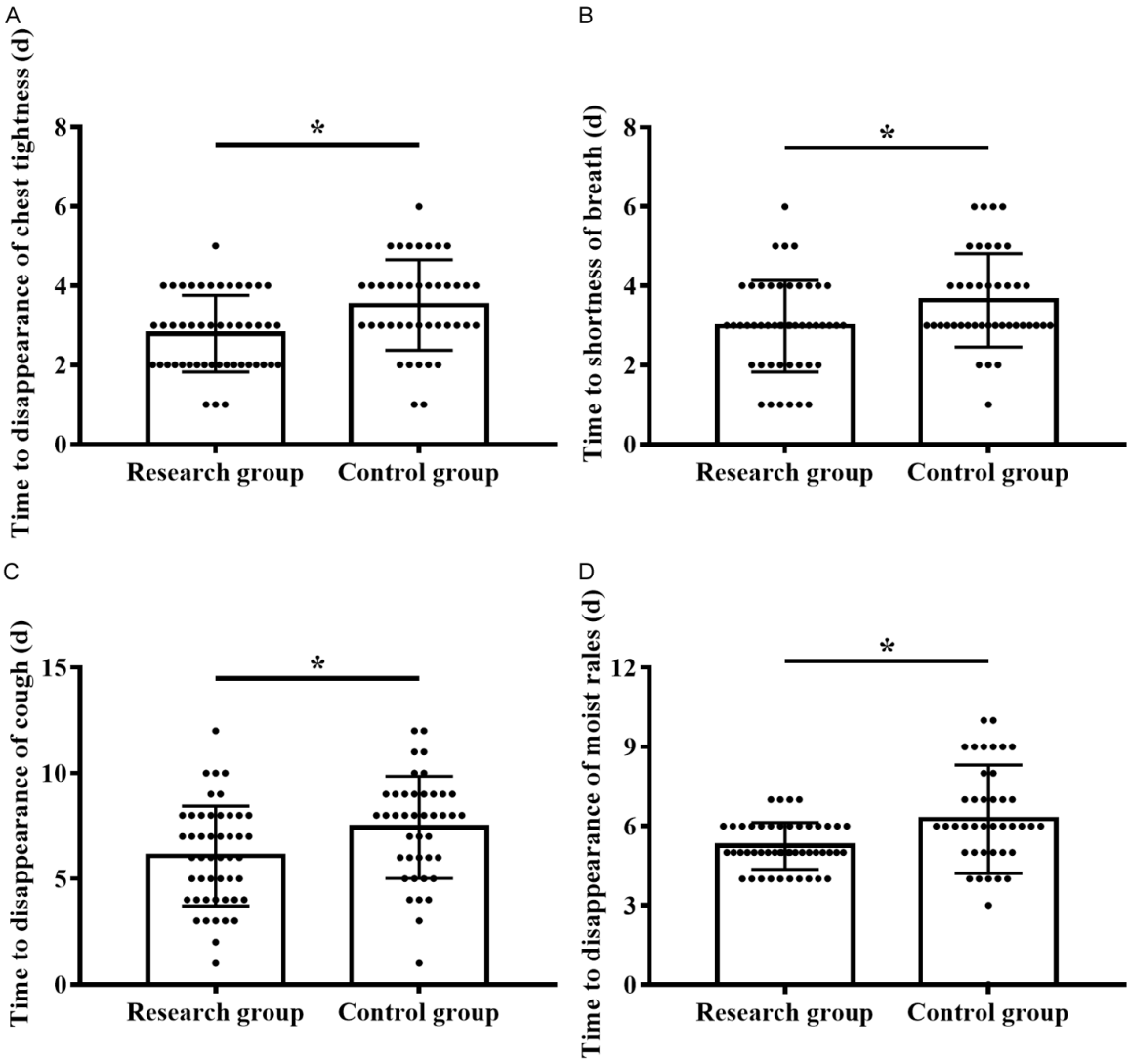

Figure 1. Comparison of time course of improvement of symptoms in both groups. A. Time to disappearance of chest tightness. B. Time to improvement of shortness of breath. C. Time to disappearance of cough. D. Time to disappearance of moist rales. * represents P<0.05.

groups before treatment (all P>0.05). After treatment, all these levels decreased in both groups and were lower in the study group than in the control group (all P<0.05) (**Figure 2**).

Comparison of levels of cardiac function indexes before and after treatment

There were no differences in cardiac function indexes between the two groups before treatment (all P>0.05). After treatment, the study group showed lower LVESD, LEVDD, and LVDs, and higher LVEF compared to the control group. Both groups exhibited decreased LVESD, LVDD, and LVDs, and increased LVEF after treatment (all P<0.05) (**Figure 3**).

Comparison of CPIS and SOFA scores before and after treatment

There were no differences in CPIS or SOFA scores between the two groups before treatment (both P>0.05). After treatment, both scores decreased in the two groups and were lower in the study group compared to the control group (both P<0.05) (**Figure 4**).

Comparison of clinical efficacy

After treatment, the total effective rate was 95.83% in the study group and 82.93% in the control group. The rate was significantly higher in the study group (P<0.05) (**Table 2**).

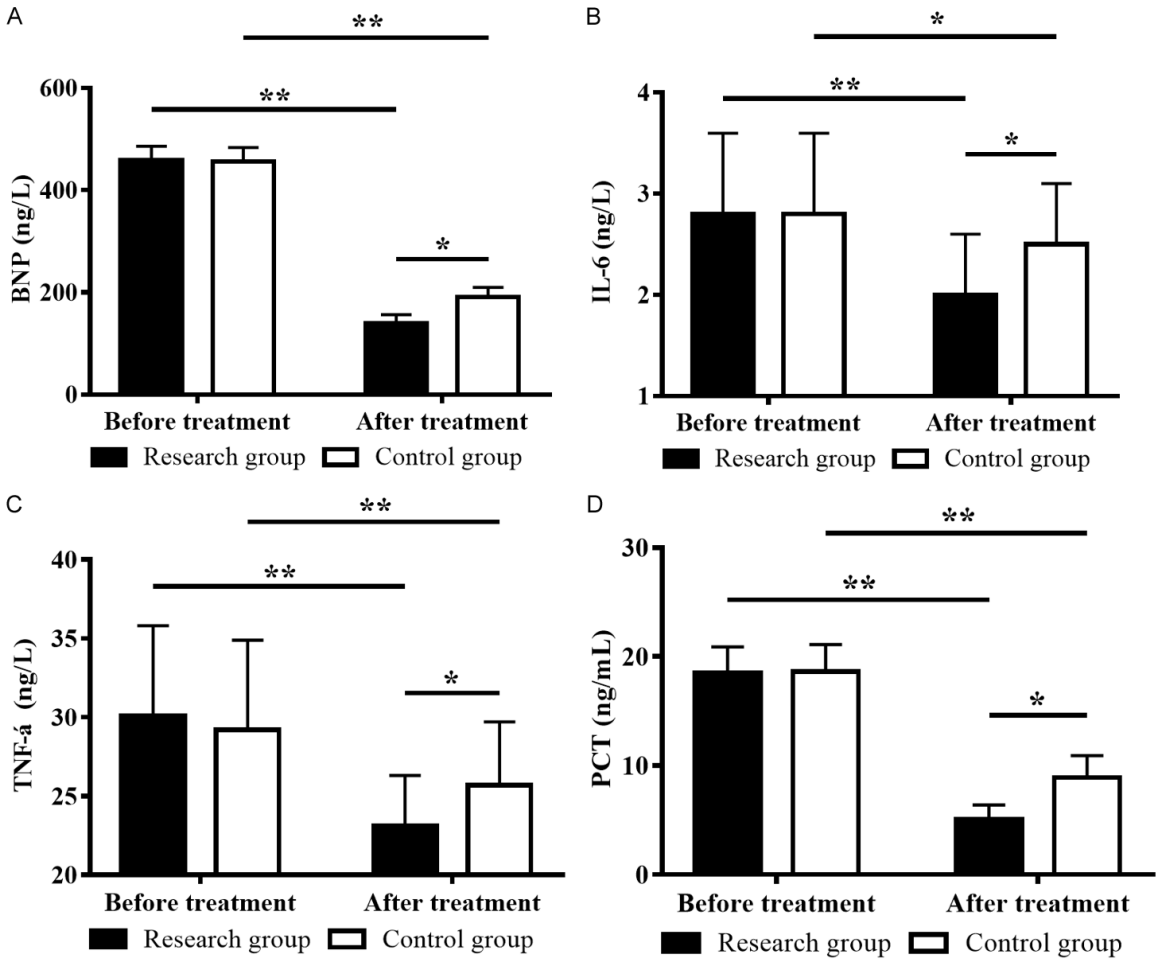

Figure 2. Comparison of levels of inflammatory factors in vivo before and after treatment. A. BNP level. B. IL-6 level. C. TNF-α level. D. PCT level. BNP, brain natriuretic peptide; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; PCT, procalcitonin. * represents P<0.05, and ** represents P<0.01.

Comparison of incidence of adverse reactions

During the treatment, adverse reactions such as hypotension, hypoglycemia, acute renal impairment, dizziness, and hyperkalemia were observed in both groups. The total incidence of adverse reactions was 8.33% in the study group and 14.63% in the control group, with no significant difference (P>0.05) (**Table 3**).

Comparison of prognosis

All patients were successfully followed up. There was no significant difference in mortality between the two groups (P>0.05). However, the study group showed a lower rate of readmission due to HF at 12.5% (P<0.05) (**Table 4**).

Discussion

Heart failure (HF) is a common clinical disease with a high prevalence in the elderly [14]. According to the latest epidemiological studies, the incidence of HF has been increasing year by year, with more than 600,000 new cases worldwide in 2020 [15]. Due to the decline in body function and respiratory system resistance in patients with HF, pulmonary bacterial retention and infection tend to occur, leading to a higher incidence of PI in the elderly [16, 17]. PI increases the cardiac load of patients and aggravates the severity of HF. Therefore, exploring treatment strategies for patients with HF complicated by PI is of great significance to ensure their safety and improve their prognosis. The natriuretic peptide system (NPS) serves as a physiologic compensatory mechanism, providing cardiorenal protective effects by activating the natriuretic peptide receptor and the second messenger cyclic guanosine monophosphate on the membrane. However, these effects are insufficient to counteract the impacts of the

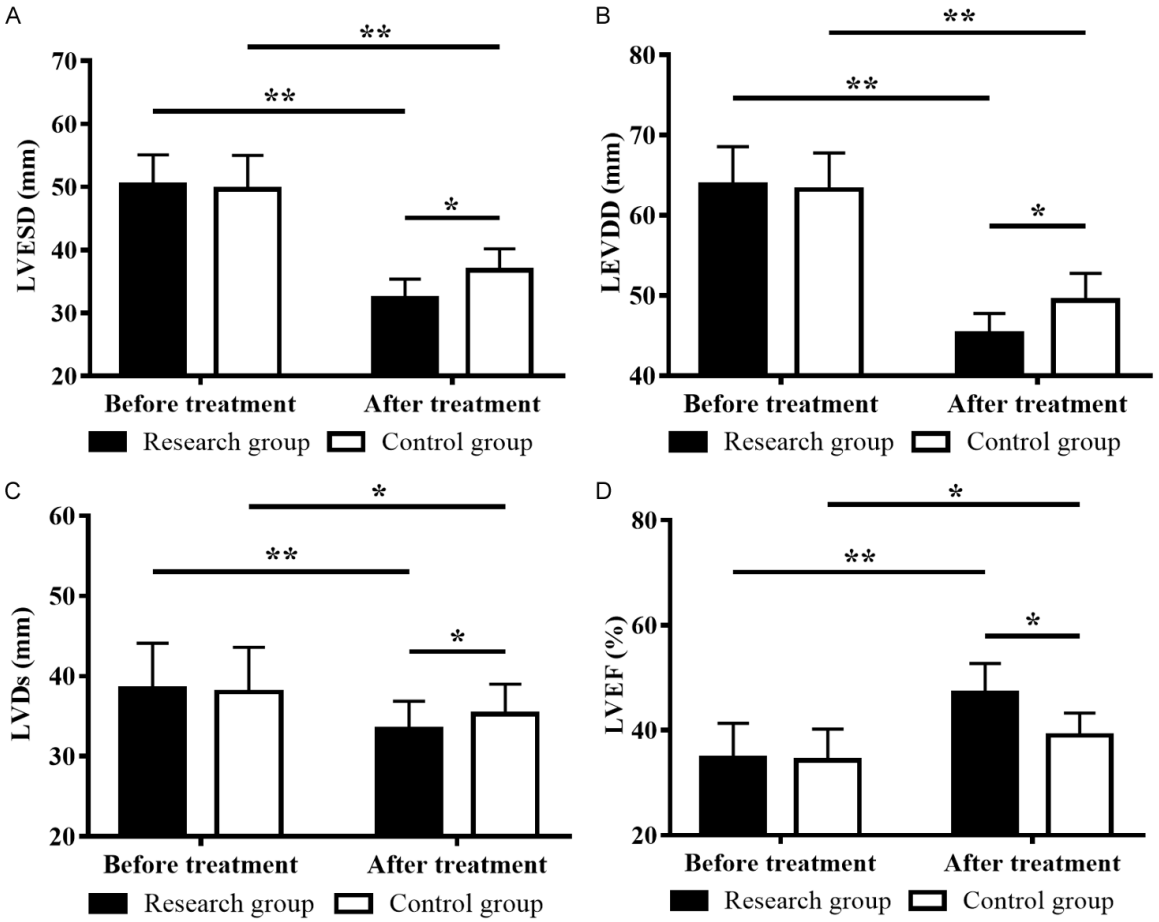

Figure 3. Comparison of levels of cardiac function indexes before and after treatment. A. LVESD level. B. LEVDD level. C. LVDs level. D. LVEF level. LVESD, left ventricular end systolic diameter; LEVDD, left ventricular end diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction. * represents P<0.05, and ** represents P<0.01.

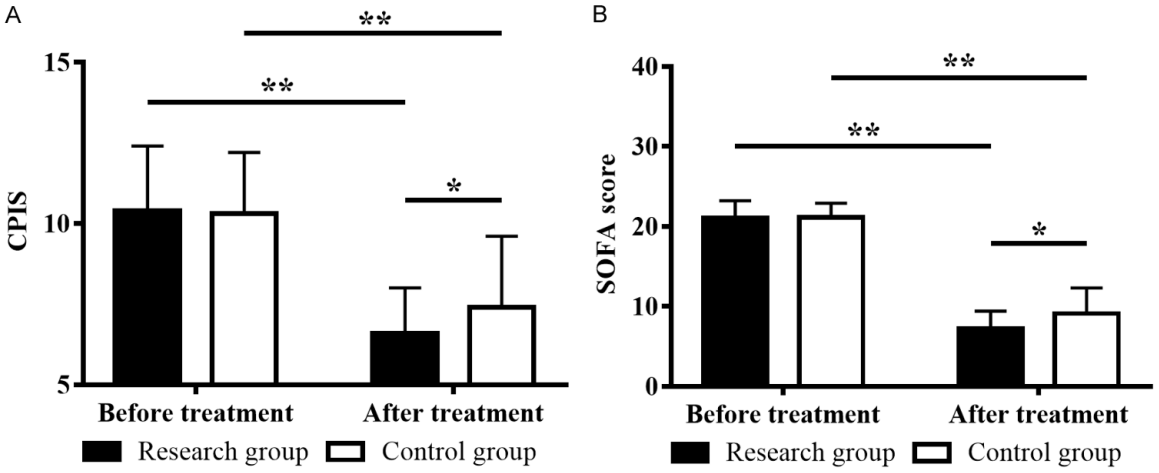

Figure 4. Comparison of CPIS and SOFA scores before and after treatment. A. CPIS. B. SOFA score. CPIS, clinical pulmonary infection score; SOFA, Sequential Organ Failure Assessment. * represents P<0.05, and ** represents P<0.01.

Table 2. Comparison of clinical efficacy

	Markedly effective	Effective	Ineffective	Total effective rate
Study group (n=48)	31 (64.58%)	15 (31.25%)	2 (4.17%)	46 (95.83%)
Control group (n=41)	14 (34.15%)	20 (48.78%)	7 (17.07%)	34 (82.93%)
χ^2				4.052
P				0.044

Table 3. Comparison of incidence of adverse reactions

	Hypotension	Hypoglycemia	Acute renal impairment	Dizziness	Hyperkalemia	Incidence of total adverse reactions
Study group (n=48)	1 (2.08%)	1 (2.08%)	0 (0%)	1 (2.08%)	1 (2.08%)	4 (8.33%)
Control group (n=41)	2 (4.88%)	1 (2.44%)	0 (0%)	1 (2.44%)	2 (2.44%)	6 (14.63%)
χ^2						0.880
P						0.348

Table 4. Comparison of prognosis

	Mortality rate	Rate of readmission due to HF
Study group (n=48)	4 (8.33)	6 (12.50)
Control group (n=41)	5 (12.20)	13 (31.71)
χ^2	0.363	4.858
P	0.547	0.028

Note: HF, heart failure.

renin-angiotensin-aldosterone system (RAAS) and the activation of the sympathetic nervous system. Enhancing NPS activity or combining it with a RAAS blocker can alleviate symptoms, reverse ventricular remodeling, and benefit HF treatment [18, 19]. Neprilysin hydrolyzes several endogenous vasoactive substances (such as natriuretic peptide, bradykinin, and adrenal medulla), which can exacerbate HF [20].

As the first angiotensin receptor-neprilysin inhibitor currently on the market, SVST operates through dual mechanisms: it inhibits neprilysin to increase bradykinin levels and suppresses the counteraction of angiotensin II on the RAAS system by blocking the activation of angiotensin type I receptors. This dual action helps resist vasoconstriction and water and sodium retention, and mitigates neurohormonal overactivation [21].

In this study, patients in the study group experienced a significantly shorter time to symptom improvement compared to the control group following SVST treatment. They also demonstrated more significant improvements in cardiac function and better clinical efficacy. These findings suggest that SVST is effective in treating patients with HF complicated by PI, aligning with results from several previous studies [22, 23], and supporting our conclusion. In patients with HF complicated by PI, SVST acts as an angiotensin receptor inhibitor to block angiotensin II receptors in the RAAS, lower blood pressure, and reverse left ventricular hypertrophy [24]. As a neprilysin antagonist, SVST facilitates the inhibition of NEP activity, increases blood natriuretic peptide levels, and promotes water excretion, sodium excretion, vasodilation, and cardiac load reduction. These two pathways synergize to dilate blood vessels more effectively, improve myocardial conditions, and reverse cardiac remodeling [25]. Additionally, it was found that the levels of inflammatory factors after treatment were lower in the study group than in the control group, suggesting that SVST significantly suppresses the inflammatory response. Similarly, Rezq et al. indicated that SVST effectively reduces inflammatory factor levels in patients with myocardial infarction [26], which is consistent with our findings. This may be related to the ameliorative effect of SVST on the hypoxic state of cardiomyocytes [27]. During the development of HF, severe hypoxic damage to cardiomyocytes is a typical pathological change, which also causes increased inflammatory responses and stress damage in tissues [28]. SVST can effectively improve inflammatory and stress reactions by expanding the cardiovascular system and protecting cardiomyocytes. This reduction in inflammatory response, in turn, improved the CPIS and SOFA scores of patients, providing a reliable founda-

tion for the recovery of patients with HF complicated by PI. Furthermore, no significant differences were observed in the comparison of adverse reactions between the two groups, indicating that SVST has a high safety profile for this purpose. Lastly, according to follow-up results, there was no significant difference in mortality between the two groups, while the readmission rate in the study group was significantly lower than that of the control group. This further suggests that SVST has a long-lasting and stable protective effect on the long-term prognosis of patients. Zhou et al. also suggested that SVST is suitable for the long-term treatment of patients with myocardial infarction [29], reaffirming the excellent long-term stability and safety of SVST.

However, due to the limited experimental conditions, only a small number of cases were included in this study, which may reduce the comprehensiveness and representativeness of the results. It is also not clear whether SVST has different effects on patients of different ages and genders, which warrants further study and analysis. Moreover, subjects involved in this study should be followed for a longer period to explore the long-term prognostic impact of SVST on patients with HF complicated by PI.

In conclusion, SVST can effectively improve cardiac function and suppress the inflammatory response in patients with HF complicated by PI, providing excellent therapeutic effect. Moreover, SVST ensures a safer prognosis and higher prognostic survival quality, and prevents the recurrence and deterioration of the HF.

Disclosure of conflict of interest

None.

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