ORIGINAL RESEARCH

Impact of Angiotensin Receptor–Neprilysin Inhibition Combined with Enteral Nutritional Therapy on Cardiac Performance and Inflammatory Burden in Hemodialysis-Associated Heart Failure: Clinical and Experimental Evidence

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Abstract

Background

Cardiovascular complications remain the leading cause of mortality in patients undergoing maintenance hemodialysis (MHD), with heart failure (HF) representing a major clinical challenge. Beyond neurohormonal dysregulation, malnutrition and chronic microinflammation contribute significantly to disease progression. This study investigated whether angiotensin receptor–neprilysin inhibition combined with enteral nutritional support could provide additive benefits in this high-risk population.

Methods

A randomized controlled clinical study was conducted involving 60 MHD patients with HF, allocated to standard therapy or combined intervention groups. The intervention consisted of sacubitril/valsartan administration together with structured enteral nutrition support. Cardiac structure and function, inflammatory markers, nutritional indices, immune parameters, and quality-of-life scores were evaluated over 6 months. In parallel, a rat model of post-infarction HF was established to validate mechanistic and physiological changes, including echocardiographic measurements and serum biomarker assessment.

Results

Patients receiving the combined regimen demonstrated superior improvement in left ventricular systolic performance, with greater reductions in LV dimensions and circulating BNP levels compared with conventional treatment. Inflammatory mediators including IL-1β, IL-6, and CRP were significantly attenuated, while serum albumin, total protein, hemoglobin, and immunoglobulin levels increased more prominently. Quality-of-life scores improved without excess adverse events. Experimental findings mirrored clinical observations: treated rats exhibited improved LVEF, reduced ventricular remodeling indices, and decreased BNP and pro-inflammatory cytokines relative to untreated HF controls.

Conclusion

The integration of sacubitril/valsartan therapy with enteral nutritional supplementation exerts synergistic effects on cardiac remodeling, inflammatory modulation, and metabolic recovery in MHD-associated HF. These findings support a multidimensional therapeutic strategy targeting both neurohormonal activation and nutritional-inflammatory imbalance.

Keywords: maintenance hemodialysis, heart failure, sacubitril/valsartan, enteral nutrition, microinflammatory status

Introduction

Maintenance hemodialysis (MHD) is an effective measure for the clinical therapy of uremia in patients with renal failure[1]. It excretes all kinds of toxins produced by physiological metabolism in the body through the hemodialysis instrument, and finally maintains the normal daily life of patients[2]. Due to the serious obstacles in the excretion of physiological metabolites in the body of patients, and the edema of gastrointestinal mucosal tissue, the total food intake of patients is significantly reduced, which leads to the deficiency of L-carnitine level of patients in the long term, and the limitation of physiological functions such as myocardial contraction and diastole, and eventually the significant weakening of cardiac physiological functions of patients, and the development of HF in severe cases[3].

Sacubitril/valsartan is a treatment drug for HF developed in recent years, which can effectively inhibit the function of human enkephalin and angiotensin type 1 (AT1) receptor, thereby accelerating the degradation rate of encephalin[4]. However, there are no clinical reports on sacubitril/valsartan in treating MHD patients with HF.

HF can cause congestion in the systemic and pulmonary circulation, reduce the appetite of patients, and affect normal eating in severe cases, resulting in malnutrition due to insufficient intake of nutrients, thus influencing the quality of life of patients[5]. Clinical researches have manifested that the nutritional status of HF patients is closely linked to their prognosis, and long-term malnutrition will reduce myocardial energy supply, which will further aggravate the disease of patients[6]. Therefore, in recent years, it has been advocated that planned nutritional support should be given in treating HF patients in order to promote the nutritional status of patients and promote the improvement of their conditions[7].

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Enteral nutrition support can deliver nutrients directly to the gastrointestinal tract through the feeding tube, which is not only consistent with the physiological state of the body, but also can effectively avoid the discomfort caused by parenteral nutrition support, which has a better effect on the intestinal function of patients as well as can reduce the risk of related complications. In addition, enteral nutrition support has low cost and high patient acceptance, and has been widely used in clinical treatment[8].

Based on this, our study was designed to assess the impacts of sacubitril/valsartan in association with enteral nutrition support on cardiac function as well as microinflammatory status in MHD patients or rats with HF.

Material and methods

General data

Sixty MHD patients with HF admitted to our hospital from January 2022 to December 2023 were chosen and separated into observation group (n=30) as well as control group (n=30) following the random number table method. To ensure allocation concealment, the random sequence was generated by an independent statistician using a computer random number generator, and the assignments were placed in sequentially numbered, opaque, sealed envelopes. The envelopes were opened only after each patient's enrollment and baseline assessments were completed. The control group contained 20 males along with 10 females, aged 52~70 years old, with a mean age of (60.72±8.53) years old; The duration of MHD treatment ranged from 3 to 10 years, with an average of (6.23±2.75) years. The dry weight was (56.23±7.16) kg, ranging from 48 to 64 kg. The observation group contained 19 males along with 11 females, aged 52~71 years old, with a mean age of (61.06±8.65) years old. The duration of MHD treatment ranged from 4 to 11 years with an average of (6.27±2.86) years. The dry weight was (55.87±7.12) kg, ranging from 47 to 63 kg. No significant difference was discovered in general data between 2 groups (P>0.05). This study was approved by the Ethics Committee of our hospital. Due to the open-label nature of the enteral nutrition intervention (tube feeding vs. routine diet), blinding of participants and treating physicians was not feasible. However, outcome assessors responsible for echocardiography measurements, laboratory tests (BNP, inflammatory markers, nutritional and immune parameters), and quality-of-life scoring were blinded to group allocation throughout the follow-up period. Inclusion criteria: (1) Patients met the diagnostic criteria of HF and the indications of MHD treatment; (2) Normal cognitive function, high degree of cooperation; (3) Regular hemodialysis ≥3 months; (4) New York Heart Association (NYHA) ≥ grade □; (5) Age ≥18 years old; (6) Patients signed informed consent. Exclusion criteria: (1) Previous history of drug allergy; (2) Patients with severe hyperkalemia, blood potassium ≥ 6.2 mmol/L; (3) Abnormal mood, previous history of taking antipsychotics; (4) Those who had language barriers and were unable to communicate in language; (5) Patients with renal artery stenosis; (6) Patients with tumors and tuberculosis; (7) Patients with severe liver dysfunction.

Treatment methods

The control group adopted conventional therapy. Patients were treated with ACEI or ARB, beta-blockers to slow ventricular rate, and nitrates to dilate vasodilators, depending on their previous use.

Based on the control group, the observation group accepted sacubitril/valsartan (Beijing Novartis Pharmaceutical Co., LTD.) orally. The initial dose of treatment was 50 mg/time, twice/day, followed by an increase of 50 mg/ time in the therapeutic dose of sacubitril/valsartan at 2-week intervals, until the final dose of drug therapy reached 200 mg/time.

Both groups received follow up for 6 months.

Nutrition support methods

The control group adopted conventional dietary intervention. The patients were initially instructed to eat easy digestible and light foods, mainly low-salt, liquid and low-fat foods, and strictly followed the principle of small and frequent meals. Later, the patients were gradually transferred to a general diet, and nasal feeding was given through a gastric tube for patients who could not eat independently.

Based on the control group, the observation group adopted enteral nutrition support. First, 250 mL of normal saline was injected into the naso-intestinal tube. If no discomfort was found, enteral nutritional suspension (SP, Nutricia Pharmaceutical (Wuxi) Co., LTD.) was applied. The dosage of SP was 125 ml on day 1, added to 250 ml on day 2 and 500 ml on day 3, and the dosage was maintained.

Both groups were treated continuously for 1 month.

Observation indicators

(1) Cardiac function. Echocardiography was implemented to examine left ventricular end systolic diameter (LVESD), left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), interventricular septum thickness (IVST) and left ventricular posterior wall thickness (LVPWT). For detecting the level of B-type natriuretic peptide (BNP), 2 mL of venous blood was taken from the patient under fasting state, the blood sample was placed in the dipotassium EDTA collection vessel, mixed upside-down for 8 times, centrifuge at low speed, centrifuge for 5 min, and then tested with ADVIA Centaur CP automatic chemiluminescence analyzer (manufactured by Siemens, Germany).

(2) Microinflammatory markers. Serum tumor interleukin-1β (IL-1β) together with interleukin-6 (IL-6) levels was examined by ELISA and serum C-reactive protein (CRP) levels were detected by immunoturbidity assay.

(3) Serum albumin (ALB), total protein (TP) as well as hemoglobin (Hb) levels was assessed by automatic biochemical analyzer.

(4) Serum immunoglobulin A (IgA), immunoglobulin G (IgG) as well as immunoglobulin M (IgM) levels was detected by immunoturbidimetry.

(5) Incidence of adverse reactions including hypotension, hyperkalemia, dizziness, and gastrointestinal reactions was recorded.

(6) The Kansas City Cardiomyopathy Questionnaire (KCCQ), which included a total of 15 questions and 23 items, was mainly to understand the quality of life of patients. The score was 0 to 100 points, and the higher the score was, the better the quality of life.

Animals

Forty SD rats with an average body weight of (190±10)

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g were acquired by Beijing Vital River Laboratory Animal Technology Co., Ltd., and 5 rats were kept in a constant temperature and humidity room at (22±2) □ and (55±5) % humidity.

Experimental drug and dosage

According to literature, rats were treated with a daily dose of 68 mg/kg of sacubitril/valsartan (Beijing Novartis Pharmaceutical Co., LTD.). Sacubitril/valsartan were dissolved in 0.9% sodium chloride and prepared into 2 mL solution.

Construction of rat HF model

First, the respiratory system was anesthetized in small animals and the respiratory anesthesia in rats was administered with isoflurane (isoflurane concentration of 5 mL/min × 5% to induce rapid anesthesia, continuous anesthesia at 3 mL/min × 3%). After full anesthesia, the chest was opened between the 5th and 6th ribs to fully expose the heart. 5.0 silk thread was used to pass through a small bundle of myocardia in the left ventricle, and the heart was slightly suspended by pulling the silk thread to fully expose the coronary artery. Ligation was performed at about 1.0 mm below the junction of the left atrial appendage as well as the pulmonary artery conus. The surface of the myocardium in the anterior descending blood supply area was pale by the naked eye, and the ECG showed that the ST segment continued to be elevated (>1/2 R wave), indicating that the ligation was successful. Left ventricular function was measured by color ultrasound 7 days after surgery. In the final study, rats with LVEF<60% were used as HF model rats.

Grouping and intervention

A total of 30 rats were modeled, and on the 7th day after operation, the model construction was evaluated by cardiac color ultrasound after inhalation anesthesia with isoflurane. Rats that did not meet the criteria for HF were excluded, and 20 remaining rats with HF model were randomly separated into 2 groups: model group as well as intervention group (n=10). The remaining 10 rats underwent thoracotomy without coronary artery ligation as sham operation group.

In the intervention group, rats were given enteral nutritional suspension (SP, Nutricia Pharmaceutical (Wuxi) Co., LTD.) by gavage with gavage needle (4 mL/time, 4 times/day) at 6 hours after modeling. At the same time, rats were gavaged with sacubitril/valsartan 68 mg/kg daily.

In the sham operation group and model group, rats adopted regular gavage with normal saline (4 mL/ time 4 times/day).

All groups were treated for 8 weeks.

Statistical analysis

SPSS 20.0 statistical software was adopted for data analysis. The measurement data were expressed as mean ± standard deviation (x±s), and t-test was implemented for comparison. Count data were expressed as rate, and $\chi 2$ test or Fisher's exact test was adopted for comparison. P<0.05 meant statistical significance.

A priori sample size calculation was performed using G*Power 3.1.9.7 software. The sample size estimation was based on the primary outcome of left ventricular ejection fraction (LVEF) change. From previous literature in similar patient populations (9), we assumed an expected difference in LVEF improvement of 5% between the observation group and the control group, with a common standard deviation of 5% (Cohen's d = 1.0). Using a two-sided independent t-test, with a Type I error (α) of 0.05 and a statistical power (1 β) of 0.80, the required sample size per group was calculated as 17 patients. To account for an anticipated dropout rate of approximately 20% during the 6 month follow-up period, we increased the sample size to 30 patients per group. Therefore, a total of 60 patients (30 per group) were enrolled, which provided adequate statistical power to detect a clinically meaningful difference in the primary cardiac function endpoint.

Results

Follow-up situation

After 6 months of follow-up, 3 cases died in the control group, 2 cases died in the observation group, and 1 case was lost to follow-up in each group. Therefore, there were 26 patients in the control group and 27 patients in the observation group.

To provide a clearer comparative summary of mortality between the two groups, we calculated mortality rates, risk ratio, and Fisher's exact test p value. The mortality rate was 10.0% (3/30) in the control group versus 6.7% (2/30) in the observation group, with a risk ratio of 0.67 (95% CI: 0.12-3.70, p = 1.00 by Fisher's exact test). The difference was not statistically significant, which is consistent with the fact that the study was primarily designed for cardiac function and inflammatory outcomes rather than powered for mortality detection.

Cardiac function in 2 groups

No difference was seen in LVEF, LVESD, LVEDD, IVST, LVPWT and BNP levels between 2 groups prior to intervention (P>0.05). Followed by intervention, LVEF was elevated while LVESD, LVEDD, IVST, LVPWT and BNP levels were declined in 2 groups, and relative to the control group, the improvements of these cardiac function indexes were more significant in the observation group (P<0.05, Figure 1).

Microinflammatory status in 2 groups

No difference was seen in IL-1β, IL-6 along with CRP levels between 2 groups previous to intervention (P>0.05). Followed by intervention, IL-1β, IL-6 along with CRP levels were declined in 2 groups, and relative to the control group, IL-1β, IL-6 along with CRP levels in the observation group presented reduction (P<0.05, Figure 2).

Nutritional status in 2 groups

No difference was seen in ALB, TP and Hb levels between 2 groups before intervention (P>0.05). Followed by intervention, ALB, TP as well as Hb levels were elevated in 2 groups, and relative to the control group, ALB, TP along with Hb levels in the observation group presented elevation (P<0.05, Figure 3).

Immune function in 2 groups

No difference was seen in IgA, IgG together with IgM levels between 2 groups before intervention (P>0.05). Followed by intervention, IgA, IgG as well as IgM levels were elevated in 2 groups, and relative to the control group, IgA, IgG together with IgM levels in the observation group were elevation (P<0.05, Figure 4).

Incidence of adverse reactions in 2 groups

Table 1 displayed that there was no significant difference

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Table 1 Incidence of adverse reactions in 2 groups

Groups	n	Hypotension	Hyperkalemia	Dizziness	Gastrointestinal reactions	Total incidence rate
Control group	26	2	2	2	1	7 (26.92%)
Observation group	27	1	1	1	1	4 (14.81%)
χ^2						1.181
P						0.277

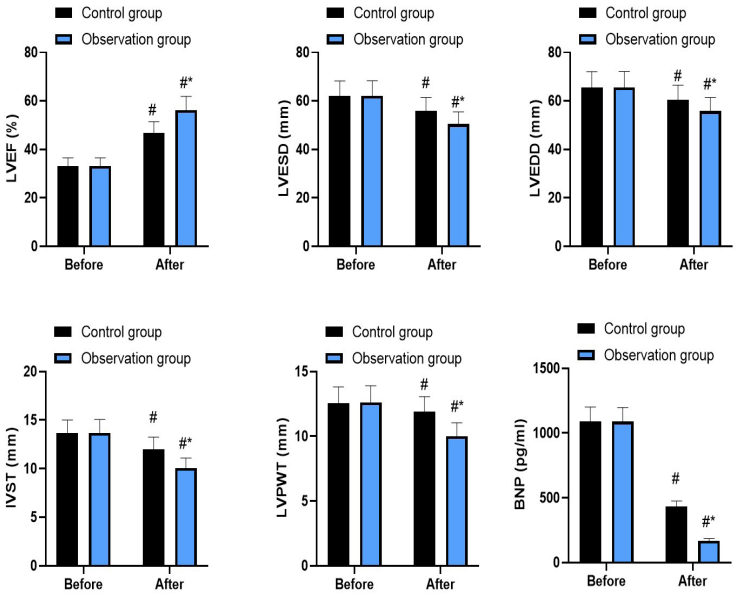

Figure 1 Cardiac function in 2 groups. #P<0.05, vs before intervention, *P<0.05, vs control group

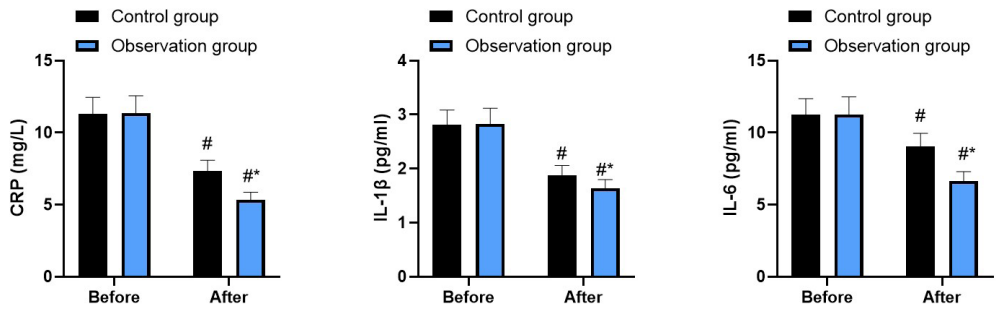

Figure 2 Microinflammatory status in 2 groups. #P<0.05, vs before intervention, *P<0.05, vs control group

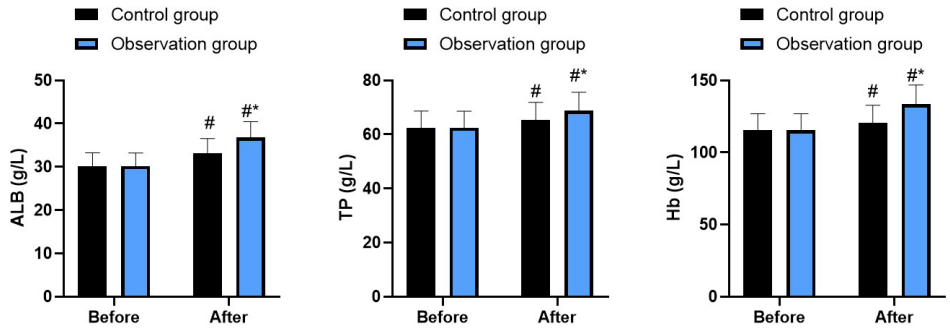

Figure 3 Nutritional status in 2 groups. #P<0.05, vs before intervention, *P<0.05, vs control group

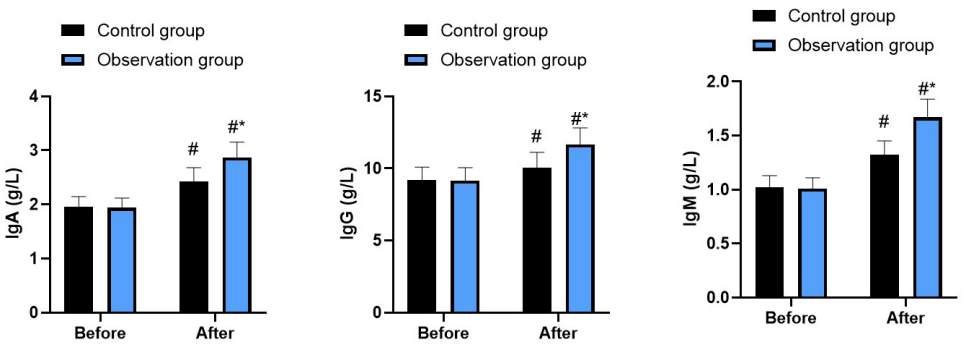

Figure 4 Immune function in 2 groups. #P<0.05, vs before intervention, *P<0.05, vs control group

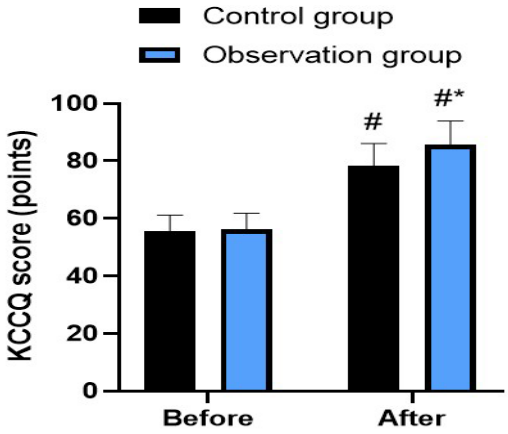

Figure 5 Quality of life in 2 groups. #P<0.05, vs before intervention, *P<0.05, vs control group

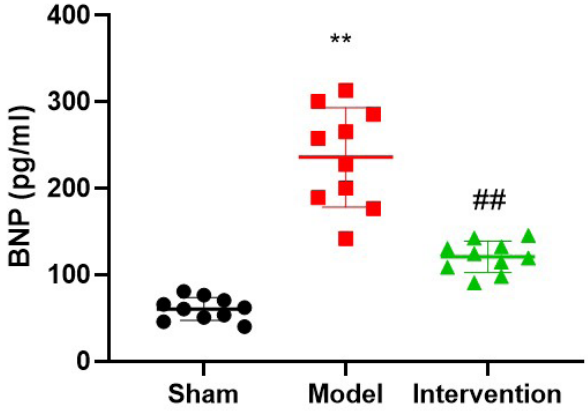

Figure 6 BNP of rats in each group. **P<0.01, vs sham operation group, ##P<0.01, vs model group

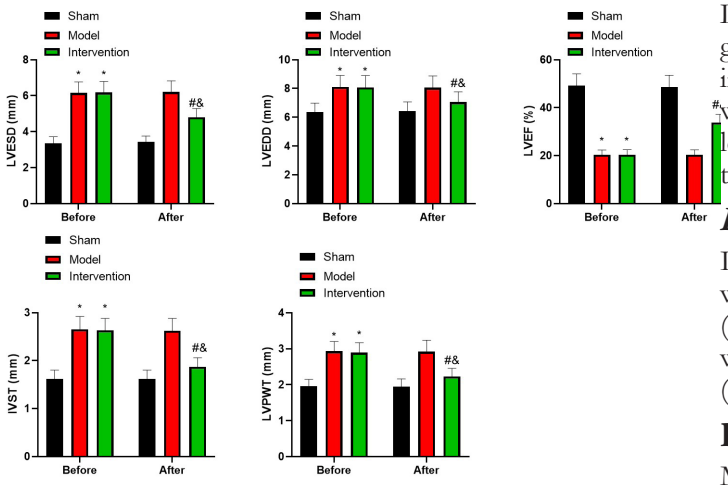

Figure 7 Cardiac color ultrasound parameters of rats in each group. *P<0.05, vs sham operation group, #P<0.01, vs model group, &P<0.01, vs before intervention

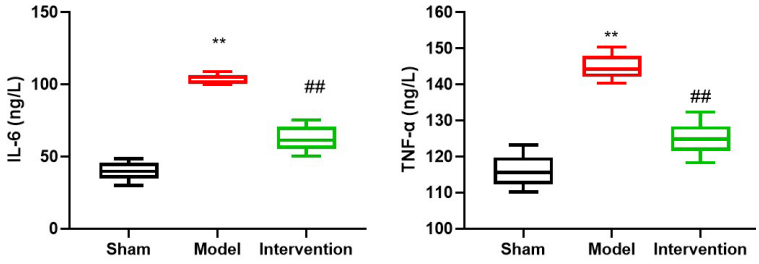

Figure 8 Inflammatory response of rats in each group. **P<0.01, vs sham operation group, ##P<0.01, vs model group

in the incidence of adverse reactions between 2 groups (P>0.05).

Quality of life in 2 groups

No difference was seen in KCCQ score between 2 groups before intervention (P>0.05). Followed by intervention, KCCQ score was elevated in 2 groups, and relative to the control group, KCCQ score in the observation group was elevation (P<0.05, Figure 5).

BNP of rats in each group

In contrast to the sham operation group, BNP level presented elevation in the model group (P<0.01). BNP level was reduced in the intervention group as comparing with the model group, (P<0.01, Figure 6).

Cardiac color ultrasound parameters of rats in each group

In comparison with the sham operation group, LVESD, LVEDD IVST, and LVPWT levels were elevated while LVEF level was declined in the model group and intervention group before intervention (P<0.05). After intervention, LVESD, LVEDD, IVST, LVPWT as well as LVEF in the intervention group were obviously improved as comparing with before intervention (P<0.05). Followed by intervention, compared with the model group, LVESD, LVEDD, IVST, and LVPWT levels presented reduction while LVEF level was increased in the intervention group (P<0.05, Figure 7).

Inflammatory response of rats in each group

In contrast to the sham operation group, IL-6 together with TNF-α levels presented elevation in the model group (P<0.01). In contrast to the model group, IL-6 together with TNF-α levels were reduced in the intervention group (P<0.01, Figure 8).

Discussion

MHD patients have a high incidence of cardiovascular disease[10]. Studies have pointed out that with the decline of renal function in patients, cardiovascular disease may change

from typical atherosclerosis to a structural heart disease, often manifested as HF disease, and MHD patients with HF will increase the risk of death, so drug intervention is very important[11]. At present, ACEI/ARB as well as other drugs is mainly applied in clinical therapy, but the effect is not satisfactory only in clinical practice, which may be because the occurrence of HF is related to multiple mechanisms, while conventional drugs only have a poor effect on improving heart function from a single way[12].

Sacubitril/valsartan is a new angiotensin-receptor neprilysin inhibitors (ARNI)[13]. Many studies have displayed that ARNI can significantly promote the cardiac function of HF patients, as well as promote the survival rate of HF patients[14]. ARNI has a bidirectional regulatory function, which can antagonize angiotensin II receptor and enkephalase at the same time, inhibit the activation of RAAS system, inhibit the hydrolysis of natriuretic peptide, and enhance the activity of the natriuretic peptide system[15]. With the synergistic effect of the above two mechanisms, ARNI can not only inhibit the progression of HF, promote the cardiac function of patients, but also has obvious antihypertensive effect[16]. In addition, because of the high plasma protein binding rate of sacubitril/valsartan, it is not easy to be cleared by dialysis, so it is suitable for MHD patients with HF[17].

Sacubitril is a prodrug that is rapidly converted to its active metabolite LBQ657. Both sacubitril and LBQ657 exhibit high plasma protein binding (approximately 94% for sacubitril and LBQ657, and >98% for valsartan), a large molecular weight (~412 Da for sacubitril, ~435 Da for LBQ657, and ~434 Da for valsartan), and a relatively small volume of distribution. These properties make them unlikely to be efficiently removed by conventional hemodialysis membranes[18]. Clinical pharmacokinetic studies have confirmed that the dialytic clearance of sacubitril, LBQ657, and valsartan is negligible (<5% of the administered dose[19]. Therefore, no supplemental dose is required after hemodialysis sessions, which simplifies the dosing regimen in MHD patients. In our study, the initial dose of sacubitril/valsartan was 50 mg twice daily, which is consistent with the recommended starting dose for patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2), including those on hemodialysis. The gradual up titration scheme—increasing by 50 mg twice daily every 2 weeks—was designed to minimize the risk of symptomatic hypotension and hyperkalemia while allowing patients to reach the target maintenance dose of 200 mg twice daily. This approach was well tolerated in our observation group, and no patient required dose reduction due to adverse effects during the titration period. Key safety concerns for sacubitril/valsartan in MHD patients include hyperkalemia, hypotension, and potential worsening of renal function (though the latter is less relevant in anuric patients). In our study, the incidence of adverse reactions such as hypotension, hyperkalemia, dizziness, and gastrointestinal symptoms did not significantly differ between the observation group and the control group ($P>0.05$). Notably, no patient in the observation group developed severe hyperkalemia (serum potassium ≥6.2 mmol/L) requiring emergency intervention. This favorable safety profile may be attributed to the careful dose titration and routine monitoring of serum electrolytes before each dialysis session. Nevertheless, we emphasize that sacubitril/valsartan should be used with caution in MHD patients with a baseline serum potassium >5.5 mmol/L or systolic blood pressure <110 mmHg. Regular monitoring of blood pressure, serum potassium, and clinical symptoms remains essential during treatment. Taken together, the pharmacokinetic properties of sacubitril/valsartan—specifically its low dialyzability—make it an attractive therapeutic option for MHD patients with HF. Our dosing protocol (starting 50 mg twice daily, titrated every 2 weeks to 200 mg twice daily) appears safe and feasible in this population, as supported by the comparable adverse event rates between groups.

The main cause of HF is the exhaustion of the heart's energy. In comparison with other organs, the heart needs more energy. MHD patients with HF usually possess reduced nutrient intake capacity, poor nutritional status, weight loss, and malnutrition increase the risk of cardiac energy metabolism disorders, promoting the progression of HF[20]. Clinical studies have displayed that enteral nutrition support can meet the nutritional needs of human intestinal mucosa and plays a key role in treating MHD patients with HF[21]. The advantages of enteral nutrition are: (1) in the short term, it can enhance the nutritional status of patients, improve the immunity of patients, lessen the inflammatory response, facilitate the metabolism of inflammatory factors, along with repress myocardial damage[22]; (2) it can improve the negative nitrogen balance and metabolic disorders in patients, block the vicious cycle, delay the development of cardiogenic cachexia, and improve the HF process[23]; (3) it can promote the intestinal function of patients, prevent the over-reproduction of normal intestinal flora, endotoxin displacement, etc., so that the nutritional supply and demand of the body can reach a dynamic balance, provide energy required for myocardial contraction, assist in improving the purpose of myocardial contractility, and thus reduce the difficulty of treatment[24]; (4) enteral nutrition support is better than intravenous nutrition, which does not increase the circulation burden and avoid aggravating the cardiac load[25].

In our study, the results indicated that after intervention, LVEF was elevated while LVESD, LVEDD, IVST, LVPWT and BNP were declined in 2 groups, and relative to the control group, the improvements of these cardiac function indexes were more significant in the observation group. These results suggested that sacubitril/valsartan combined with enteral nutrition support could promote the cardiac function in MHD patients with HF, which was consistent with studies proposed by James L Januzzi Jr et al[26] and Zhao et al.[27], respectively.

MHD patients with HF also generally show microinflammatory states, which are reflected in the imbalance between pro-inflammatory and anti-inflammatory states[28]. The pro-inflammatory indicators, containing CRP, IL-1β as well as IL-6, are elevated due to the inflammatory response caused by kidney inflammation and immune imbalance caused by treatment, and the existence of such inflammatory responses further affects the status of vascular endothelial function, leading to the development of cardiovascular diseases[29]. Therefore, during the treatment of MHD patients with HF, the control of microinflammatory status is also one of the key points of clinical evaluation[30]. In our study, the results indicated that after intervention, IL-1β, IL-6 along with CRP levels were declined in 2 groups, and relative to the control group, IL-1β, IL-6 as well as CRP levels in the observation group presented reduction, suggesting that sacubitril/valsartan and enteral nutrition support could improve the microinflammatory status in MHD patients with HF, which

was in accordance with previous literatures[23,31].

In addition, our study indicated that after intervention, ALB, TP and Hb levels as well as IgA, IgG and IgM levels were elevated in 2 groups, and relative to the control group, the above indexes in the observation group presented elevation. Meanwhile, followed by intervention, KCCQ score was elevated in 2 groups, and relative to the control group, KCCQ score in the observation group was elevation. All these results suggested that sacubitril/valsartan and enteral nutrition support could enhance the nutritional status and immune function as well as improve the quality of life in MHD patients with HF, which was similar to previous literature[32].

Moreover, our study also performed animal experiments to further validate that sacubitril/valsartan combined with enteral nutrition support could improve the cardiac function as well as microinflammatory status in rats with HF, which was in line with previous study[33].

In conclusion, sacubitril/valsartan combined with enteral nutrition support could improve the cardiac function as well as microinflammatory status in MHD patients or rats with HF.

Declarations

Ethics approval and consent to participate

The human study protocol was reviewed and approved by the Ethics Committee of Changzhou Geriatric Hospital Affiliated to Soochow University, Changzhou No. 7 People's Hospital. Written informed consent was obtained from all participants or their legal guardians prior to enrollment. All animal experiments were approved by the institutional animal ethics committee and conducted in accordance with relevant guidelines.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests. Disclosure of potential conflicts has been considered per MMJ instructions.

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Authors' contributions

Xiangying Liu: patient enrollment, data curation, investigation, draft writing.

Qiangyan Hu: methodology, echocardiography and laboratory measurements, data validation.

Chengyi Yang: animal experiment design and execution, data analysis, figure preparation.

Tao Lu (corresponding author): conceptualization, supervision, project administration, critical revision of the manuscript.

All authors read and approved the final manuscript. Author contributions are presented in accordance with MMJ authorship criteria.

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