

Original Research Article

Effect of furosemide combined with continuous renal replacement therapy on cardiorenal function and inflammatory response in patients with chronic renal and heart failure after hemodialysis

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Abstract

Purpose: To determine the effect of furosemide combined with continuous renal replacement therapy (CRRT) on cardiorenal function and inflammatory response in patients with chronic renal failure (CRF) and heart failure after hemodialysis.

Methods: 130 patients with both CRF and heart failure, who underwent hemodialysis at the Second Hospital Affiliated to Hainan Medical College, China, from October 2020 to October 2022 were recruited as study subjects. They were randomly divided into two groups, with control group administered the Continuous Renal Replacement Therapy (CRRT) while study group received furosemide in addition. The study assessed the clinical outcomes, cardiorenal function and inflammatory factors before and after treatment. Additionally, adverse reactions during treatment were documented for both groups.

Results: Study group exhibited a significantly higher ($p < 0.001$) total response rate compared to control group. Post-treatment, both groups displayed significant increases ($p < 0.05$) in left ventricular ejection fraction, cardiac output and stroke volume, with study group showing significantly superior results ($p < 0.05$). Furthermore, post-treatment, both groups experienced significant reductions ($p < 0.05$) in serum creatinine, blood urea nitrogen, and 24-hour urinary protein levels, with study group displaying significantly lower levels ($p < 0.05$). Additionally, the interleukin-6, interleukin-1 β and tumor necrosis factor- α levels decreased significantly in both groups post-treatment, with study group exhibiting significantly lower levels ($p < 0.05$). There was no significant difference in adverse reaction incidence between the two groups.

Conclusion: Furosemide combined with CRRT significantly improves cardiorenal function and reduces inflammatory response in patients with CRF and heart failure after hemodialysis. Future research could optimize dosage and administration protocols, explore long-term effects and assess applicability in diverse patient populations.

Keywords: Chronic renal failure, Heart failure, Furosemide, CRRT

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INTRODUCTION

Chronic renal failure (CRF) is a prevalent clinical condition characterized by the gradual and persistent deterioration of kidney function, stemming from diverse factors. Some contributing factors include hypertension, diabetes mellitus, glomerulonephritis, and polycystic kidney disease. The prevalence of CRF varies significantly based on geographic location and population. In China, the incidence is estimated to be 31.3 %, and it leads to rapid kidney atrophy and deterioration of kidney function, with main clinical manifestations including acid-base imbalance, anemia, electrolyte disturbances and retention of metabolic waste products [1]. Congestive heart failure is a common complication in patients with CRF and is triggered by factors such as metabolic acidosis, refractory hypertension and dialysis-related factors. Studies have shown that the incidence of congestive heart failure in patients with CRF undergoing hemodialysis is up to 40 % and cardiovascular disease-related deaths account for approximately 50 % of cases [2,3]. In CRF patients with concurrent heart failure, the decreased cardiac output leads to further kidney damage, while the retention of sodium and water caused by CRF exacerbates the heart failure, resulting in a vicious cycle [4]. Clinical intervention for such patients often involves continuous renal replacement therapy (CRRT). Continuous Renal Replacement Therapy (CRRT) is a continuous and gradual blood purification process used for managing acute or severe chronic kidney conditions by removing waste products and excess fluids [4]. This therapy eliminates retained fluids and metabolic waste products from the body, improves the internal environment, and reduces the load on the heart and kidneys [5]. Furosemide, a diuretic, is a fundamental medication for treating heart failure. It functions by increasing the excretion of water and sodium and dilating blood vessels, thus rapidly alleviating clinical symptoms in patients [6]. This study therefore investigates the impact of furosemide combined with CRRT on cardiorenal function and inflammatory response in patients with CRF and congestive heart failure undergoing hemodialysis.

METHODS

General information

A total of 130 patients with chronic renal failure (CRF) and congestive heart failure who underwent hemodialysis at the Second Affiliated Hospital of Hainan Medical University, in China, from October 2020 to October 2022 were selected. They were randomly divided into a

study group (65 cases) and a control group (65 cases) using a random number table method [6]. The hospital ethics committee approved the research protocol (approval no. 20200718) and patients and their families provided informed consent.

Inclusion criteria

Patients who satisfied the following criteria were recruited to the study: Patients meeting the diagnostic criteria for CRF and heart failure according to the American Kidney Foundation [7] and "Diagnosis and Treatment Guidelines for Chronic Heart Failure" [8]; Patients with normal language communication abilities and undergoing regular hemodialysis treatment in the Second Affiliated Hospital of Hainan Medical University hospital; aged 18 years or older; and patients who are eligible for continuous renal replacement therapy (CRRT).

Exclusion criteria

The following categories of patients were excluded from the study: Patients with congenital heart disease and liver disease; Patients with organic lesions of other important internal organs such as lungs, liver, and heart; Patients allergic to the medications used in this study.

Treatments

Control group patients received standard heart failure treatment and continuous renal replacement therapy (CRRT). They were administered Levosimendan at a dose of 2 micrograms per kilogram via intravenous drip, once a day. The blood flow rate ranged from 150 to 200 mL/min, the replacement fluid flow rate was set at 2 - 4 L/hour and the treatment duration was 8 - 10 hours per day [7]. Heparin was used for anticoagulation. The treatment was done for 7 days. Study group received in addition to control group's treatment, slow intravenous drip of Furosemide (40 mg per vial, National Drug Approval No. H20051479, Hunan Wuzhou Tong Pharmaceutical Co., Ltd.) at a rate of 10 - 20 mg/hour. The daily dose, typically determined per body weight, was administered at 100 mg and the treatment was continued for 7 days.

Evaluation of parameters/indices

Clinical efficacy

After 7 days of treatment, a therapeutic efficacy assessment was conducted in the two groups [9] as follows: Significant improvement – an increase of 2 or more levels in the heart

functional classification, significant alleviation of symptoms of heart failure and improvement in renal function; Effective – an increase of 1 level in the heart functional classification, some improvement in symptoms of heart failure and mild improvement in renal function; Ineffective – no significant changes observed in heart and renal functions. The total effective rate (TER) is calculated as the sum of the significant improvement rate (SIR) and the effective rate (ER) as depicted in Eq 1.

$$\text{TER} = \text{SIR} + \text{ER} \dots\dots\dots (1)$$

According to the New York Heart Association (NYHA) functional classification [10] in the United States, Class I patients experience no limitation in their daily activities. Class II patients experience slight limitations in daily activities, with palpitation, shortness of breath, or angina occurring after physical exertion. Class III patients on the other hand experience noticeable limitations in daily activities, with slight exertion leading to shortness of breath, fatigue, or palpitation.

Cardiac function indicators

The levels of the patient's cardiac function indicators were assessed before and after 7 days of treatment. The General Electric Vivid7 color Doppler ultrasound system was used to measure the left ventricular ejection fraction (LVEF), cardiac output (CO), and stroke volume (SV) of patients. Each indicator was determined three times and the average value was calculated [10].

Renal function indicators

To evaluate the patient's renal function, the indicators were assessed before and 7 days after the commencement of treatment. A 3 mL fasting venous blood sample was collected in the morning, centrifuged and the supernatant extracted. A fully automated biochemical analyzer (Model: Aptio; Siemens AG, Germany) was used to assay serum creatinine (Scr) and blood urea nitrogen (BUN) levels. In addition, 5 mL urine sample was collected from patients for a 24-hour urinary protein quantification using immunoturbidimetric assay [10].

Inflammatory factor levels

Before and after 7 days of treatment, the serum inflammatory factor levels of the patients were determined. Fasting venous blood samples (5 mL) were collected from patients and the supernatant was obtained after centrifugation. A fully automated biochemical analyzer was used

to determine interleukin-6 (IL-6), IL-1 β , and tumor necrosis factor- α (TNF- α) levels in the patients. The experiments were conducted with strict adherence to the manufacturer's instructions [7].

Adverse reactions

Occurrences of adverse reactions during the treatment, such as cardiogenic shock, multi-organ failure, vomiting, fatigue, hypotension, and headache, were recorded.

Statistical analysis

Statistic Package for Social Science (SPSS) 21.0 software (IBM, Armonk, NY, USA) was employed to analyze the experimental data. Normally distributed quantitative data were expressed as mean \pm standard deviation (SD) and the differences between groups were compared using the independent two-sample *t*-test. Non-normally distributed data were expressed as M (P25, P75) and intergroup differences were assessed using the non-parametric Mann-Whitney U test. Count data were presented as percentages (%) and intergroup differences were compared using the χ^2 test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Baseline data

In study group, there were 39 males and 26 females, with an age range of 40 to 75 years (mean age: 60.67 ± 5.32 years) and a disease duration range of 1 to 3 years (mean disease duration: 1.57 ± 0.34 years). In control group, there were 35 males and 30 females, with an age range of 45 to 74 years (mean age: 61.70 ± 6.29 years) and a disease duration range of 1 to 3 years (mean disease duration: 1.88 ± 0.53 years). Baseline data between the two groups showed no significant differences ($p > 0.05$).

Clinical efficacy

As shown in Table 1, the total effective rate in study group was 89.23 %, significantly higher than control group's rate of 75.38 % ($p < 0.05$).

Cardiac function indicators

There were no significant differences in pre-treatment cardiac function levels between the two groups ($p > 0.05$). However, after treatment, both groups exhibited significant increases in LVEF, CO and SV ($p < 0.05$). Furthermore, the post-treatment LVEF, CO and SV levels in study

group were significantly higher than those in control group ($p < 0.05$) (Table 2).

Renal function indicators

There were no significant differences in the 24-hour urinary protein, Scr and BUN levels before treatment between the two groups ($p > 0.05$). After treatment, however, both groups experienced significant decreases in Scr, BUN and 24-hour urinary protein ($p < 0.05$). Additionally, the post-treatment levels of Scr, BUN and 24-hour urinary protein in study group

were significantly lower than those in control group ($p < 0.05$) as shown in Table 3.

Inflammatory factors

There were no significant differences in serum inflammatory factor levels between the study and control groups before treatment ($p > 0.05$). After treatment, both groups showed significant reductions in IL-6, IL-1 β , and TNF- α levels ($p < 0.05$). Moreover, the post-treatment levels of IL-6, IL-1 β , and TNF- α in study group were significantly lower than those in control group ($p < 0.05$). This is shown in Table 4.

Table 1: Treatment effect

Group	Significant improvement	Effective	Ineffective	Overall efficacy rate
Study	39(60.00)	19(29.23)	7(10.77)	89.23
Control	24(36.92)	25(38.46)	16(24.62)	75.38
χ^2				4.279
P -value				0.039

Table 2: Cardiac function indicators

Group	LVEF (%)		CO (L/min)		SV (mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	36.59 \pm 7.09	44.28 \pm 6.39 ^a	3.17 \pm 0.95	4.34 \pm 1.02 ^a	32.02 \pm 6.31	38.44 \pm 8.28 ^a
Study	35.47 \pm 7.13	47.14 \pm 6.05 ^{a,b}	3.32 \pm 0.94	4.91 \pm 1.38 ^{a,b}	30.05 \pm 7.48	42.07 \pm 8.24 ^{a,b}
T	0.898	2.620	0.905	2.678	1.623	2.505
P -value	0.371	0.010	0.367	0.008	0.107	0.014

Note: ^a $P < 0.05$ vs. the same group before treatment, ^b $p < 0.05$ vs. control group after treatment

Table 3: Renal function indicators

Group	Scr (μ mol/L)		BUN (mmol/L)		24-hour Urinary Protein (g/24 h)	
	Before treatment	After Treatment	Before treatment	After treatment	Before treatment	After treatment
Control	243.34 \pm 24.12	199.52 \pm 22.66*	29.59 \pm 7.09	17.28 \pm 5.39*	2.52 \pm 0.61	2.04 \pm 0.58*
Study	241.72 \pm 23.75	186.38 \pm 22.59 ^{*,a}	30.47 \pm 7.13	14.14 \pm 4.05 ^{*,a}	2.65 \pm 0.68	1.77 \pm 0.44 ^{*,a}
T	0.386	3.311	0.706	3.755	1.147	2.990
P -value	0.700	0.001	0.482	<0.001	0.253	0.003

Note: * $P < 0.05$ vs. the same group before treatment; ^a $p < 0.05$ vs. control group after treatment

Table 4: Comparison of serum inflammatory factor levels

Group	IL-6 (ng/L)		IL-1 β (ng/L)		TNF- α (ng/L)	
	Before treatment	After treatment	Before treatment	After Treatment	Before treatment	After treatment
Control	39.46 \pm 10.18	34.43 \pm 7.22*	42.89 \pm 10.56	37.25 \pm 8.77*	54.89 \pm 6.56	40.25 \pm 8.77*
Study	37.50 \pm 10.57	30.71 \pm 7.16 ^{*,a}	42.87 \pm 9.55	33.67 \pm 8.34 ^{*,a}	55.87 \pm 7.55	35.67 \pm 8.34 ^{*,a}
T	1.077	2.950	0.113	2.385	0.790	3.051
P -value	0.284	0.004	0.991	0.019	0.431	0.003

Note: * $P < 0.05$ vs. the same group before treatment; ^a $p < 0.05$ vs. control group after treatment (n = 65)

Adverse reactions

In control group, there were 5 cases of headache, 3 cases of vomiting and 2 cases of multi-organ failure, with an incidence rate of 15.38 %. On the other hand, there were 5 cases of headache, 2 cases of vomiting and 1 case of catheter embolism, with an incidence rate of 12.31 % in study group. There was no significant difference between the two groups ($\chi^2 = 0.258$, $p = 0.612$).

DISCUSSION

Chronic renal failure (CRF) is a kidney impairment caused by chronic kidney disease and one of its common complications is heart failure, a complex syndrome resulting from inadequate cardiac output, leading to inadequate tissue organ perfusion, pulmonary congestion and systemic congestion [11]. The occurrence of heart failure in patients with CRF leads to fluid retention, causing peripheral edema, pulmonary congestion, reduced exercise tolerance and a further diminished urine output, thereby exacerbating renal function decline [12]. Continuous Renal Replacement Therapy (CRRT) effectively removes retained fluids and toxins from patients' bodies in a continuous and gradual manner. It reduces cardiac preload, improves pulmonary and systemic congestion, corrects acidosis and electrolyte imbalances and alleviates the burden on the kidneys [13]. Studies have indicated that combining CRRT with furosemide treatment for CRF patients with concomitant heart failure further alleviates cardiac load, improves hemodynamics and electrolyte levels, shortens intensive care center (ICU) stays and accelerates patient recovery when compared to CRRT alone [14]. The results of this study demonstrate that the treatment strategy of combining CRRT with furosemide is superior in efficacy to sole CRRT treatment for patients with CRF and concurrent heart failure. The improvement in cardiac function indicators, renal function indicators and levels of inflammatory factors were significantly more pronounced in the combined treatment group compared to the sole CRRT group.

Furosemide is a clinically preferred potent loop diuretic, primarily acting by inhibiting the reabsorption of sodium ions in the thick ascending limb of the renal tubule. This mechanism reduces oxygen consumption, lessens ischemic injury, increases the excretion of water, sodium, potassium, chloride and other electrolytes, mitigates the damage caused by fluid and sodium retention, improves renal perfusion and reduces cellular apoptosis [15,16]. Studies by Jeon and co-workers showed that furosemide alleviates acute kidney injury,

ameliorates oliguria, accelerates the recovery of renal function and decreases the need for renal replacement therapy [17]. The results of this study demonstrate that post-treatment levels of Scr, BUN and 24-hour urinary protein in study group were significantly lower than those in control group. Serum creatinine (Scr), BUN and 24-hour urinary protein are commonly used indicators reflecting residual renal function in patients. A previous study indicated that elevated Scr and BUN are significant risk factors for mortality in maintenance hemodialysis patients and reducing their levels decreases the risk of death and extends patient survival [18]. Although the appropriate dosing of furosemide remains debated in the academic community, a substantial body of literature has confirmed that low-dose continuous administration maintains stable blood-drug concentrations, aiding the regulation of hourly urine output and the stability of blood volume [19,20]. The retention of metabolic byproducts and anemia in patients with CRF lead to increased respiration and heart rate, and elevated myocardial oxygen consumption, resulting in myocardial cell hypoxia, thus impairing cardiac contraction and relaxation function [21]. The results of this study demonstrate that post-treatment levels of LVEF, CO and SV in study group were significantly higher than those in control group. This indicates that the addition of furosemide significantly promoted vasodilation, stabilized hemodynamics, improved cardiac function and alleviated myocardial damage. Patients undergoing CRRT may experience a chronic non-infectious immune-inflammatory response, known as a microinflammatory state. This often manifests as abnormal elevation of pro-inflammatory factors such as TNF- α and IL-6, leading to phenomena like anemia and malnutrition. This microinflammatory state is considered a significant foundation for various chronic complications in hemodialysis patients [22]. The results of this study indicate that post-treatment levels of IL-6, IL-1 β , and TNF- α were significantly decreased in study group, indicating that the combination of furosemide and CRRT has a positive impact on improving the microinflammatory state within the patients' bodies.

Limitations of this study

However, due to the small sample size and the lack of long-term follow-up results in this study, there are certain limitations. Therefore, further research is needed for validation. Firstly, critical details regarding the furosemide treatment, including dosage, route of administration and treatment duration for both groups, were not

specified, hindering a thorough understanding of the therapeutic protocol. Additionally, the implementation of CRRT was not adequately described, lacking information on specific procedures and techniques employed during therapy sessions. The study's limited external validity is another concern, as it was conducted at a single hospital in China, potentially limiting the generalizability of the findings to broader demographic groups. The absence of specific information on adverse reactions and the unclear method of patient randomization raise questions about the study's transparency and potential bias. Moreover, the study's relatively short duration (7 days) may limit insights into the long-term effects of the interventions. Further, a more comprehensive set of parameters and detailed demographic information would contribute to a more robust analysis. Addressing these limitations in future research is essential to enhance the reliability and applicability of the study's conclusions.

CONCLUSION

The combined treatment of furosemide and Continuous Renal Replacement Therapy (CRRT) in hemodialysis patients with chronic renal failure and concurrent congestive heart failure significantly improves cardiac and renal functions, alleviates inflammatory reactions and exhibits favorable clinical efficacy. Future research could optimize dosage and administration protocols, explore long-term effects and assess applicability in diverse patient populations, paving the way for enhanced management of these complex conditions.

DECLARATIONS

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None provided.

Ethical approval

None provided.

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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