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ARTICLE

Impact of Nafamostat Mesylate Combined with Continuous Renal Replacement Therapy on Clinical Outcomes, Immune Function, and Oxidative Stress Markers in Patients with Sepsis-Associated Acute Kidney Injury

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Abstract

Aims/Background Sepsis is a prevalent critical condition associated with acute kidney injury (AKI). Nafamostat mesylate (NM), a serine protease inhibitor, has anticoagulant and anti-inflammatory properties. This study aimed to investigate the effects of NM combined with continuous renal replacement therapy (CRRT) on clinical efficacy, immune function, and oxidative stress markers in patients with sepsis-associated acute kidney injury (SA-AKI).

Methods A total of 98 patients diagnosed with SA-AKI and treated at The People's Hospital of Pingyang between January 2022 and January 2024 were included. Patients were divided into two groups based on their treatment regimen: a CRRT group (n = 48) and a NM+CRRT group (n = 50). Clinical outcomes, including length of stay in the intensive care unit (ICU) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, were analyzed. Changes in clinical efficacy, immune function, renal function, and oxidative stress markers were assessed before and after treatment. Adverse reactions were also compared between the groups.

Results The total effective rate in the NM+CRRT group was significantly higher than in the CRRT group ($p < 0.05$). Patients in the NM+CRRT group had significantly shorter ICU stays and lower APACHE II scores compared to those in the CRRT group ($p < 0.05$). Baseline levels of renal function markers, serum creatinine (SCr), and blood urea nitrogen (BUN) were similar between the groups ($p > 0.05$). SCr and BUN levels improved significantly in the two groups post-treatment, with significant reductions observed in the NM+CRRT group ($p < 0.05$). Immune function markers, immunoglobulin G (IgG), and immunoglobulin A (IgA) showed no significant differences between groups at baseline ($p > 0.05$), but were significantly higher in the NM+CRRT group after treatment ($p < 0.05$). Oxidative stress markers, glutathione peroxidase (GSH-Px), and malondialdehyde (MDA) also showed no significant baseline differences ($p > 0.05$). After treatment, MDA levels decreased, and GSH-Px levels improved in the two groups, with more significant improvements in the NM+CRRT group. The incidence of adverse reactions was 26.00% in the NM+CRRT group and 16.67% in the CRRT group, with no statistically significant difference ($p > 0.05$).

Conclusion NM combined with CRRT significantly enhances clinical efficacy, immune function, and renal function in patients with SA-AKI and reduces oxidative stress. The therapy demonstrates an acceptable safety profile and is suitable for clinical application.

Key words: nafamostat mesylate; continuous renal replacement therapy; sepsis-associated acute kidney injury; treatment outcome; immunity; oxidative stress

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Introduction

Sepsis, a life-threatening condition characterized by organ dysfunction resulting from a dysregulated host response to infection, leads to a heavy global healthcare and economic burden (Manrique-Caballero et al, 2021; White et al, 2023). Among the organs affected, the kidneys are often among the first to sustain damage during sepsis. Previous studies have identified sepsis as a primary trigger for acute kidney injury (AKI) in critically ill patients, with AKI further predisposing patients to an increased risk of infection or recurrent sepsis (Hu et al, 2022; Zarbock et al, 2023).

The incidence of AKI in septic patients has been reported as 54%, according to earlier investigations; similarly, a multicenter retrospective cohort study conducted across hospitals in China estimated the incidence of AKI in septic patients at 47.1% (Kalantari and Rosner, 2021; Kuwabara et al, 2022). Sepsis-associated acute kidney injury (SA-AKI) is a prevalent complication in critically ill patients, typically occurring within 24 hours after admission to the intensive care unit (ICU) (White et al, 2023). SA-AKI elevates the mortality rate of hospitalized patients and increases the likelihood of chronic kidney disease (CKD), significantly compromising patient survival and quality of life (Garcia et al, 2023).

Continuous renal replacement therapy (CRRT) is the standard clinical approach for managing SA-AKI and aids in restoring kidney function by enhancing the removal of toxins and excess fluid from the body (Karkar and Ronco, 2020). However, effective anticoagulation is crucial for the success of CRRT. While heparin and regional citrate are commonly used anticoagulants, these agents carry a bleeding risk of 4%–25% (Legrand and Tolwani, 2021; Roe et al, 2022). Developing strategies to enhance anticoagulation safety and optimize CRRT outcomes remains a key focus of current research.

Nafamostat mesylate (NM) is a synthetic serine protease inhibitor approved for the treatment of pancreatitis and disseminated intravascular coagulation (DIC) (Takahashi et al, 2021; Yamada and Asakura, 2022). In a study by Kamijo et al (2020), NM demonstrated a favorable safety profile as an anticoagulant and significantly reduced in-hospital and ICU mortality in septic patients undergoing blood purification compared to conventional therapies. Despite these promising findings, limited data are available on the use of NM combined with CRRT for the treatment of SA-AKI patients.

This study retrospectively analyzed the clinical data of 98 patients with SA-AKI to evaluate the efficacy of NM-assisted CRRT. Notably, the study aimed to assess the impact of the combined therapy on the clinical outcomes, immune function, and oxidative stress markers in this patient population.

Methods

General Information

The medical records of 98 patients with SA-AKI treated at the People's Hospital of Pingyang between January 2022 and January 2024 were analyzed retrospectively. Inclusion criteria: ① All patients met the diagnostic criteria for sepsis as

outlined in the Chinese Guidelines for the Treatment of Severe Sepsis/Septic Shock (Chinese Society of Critical Care Medicine, 2015). The diagnosis of SA-AKI was based on serum creatinine level >176.8 μmol/L (2.0 mg/dL) or urine output <0.5 mL/kg/h for more than 12 hours; ② Acute Physiology and Chronic Health Evaluation II (APACHE II) score >12 points (Tekin et al, 2024); ③ Complete clinical data available. Exclusion criteria: ① Presence of dysfunction in other vital organs (e.g., heart failure, liver failure, severe gastrointestinal dysfunction, acute respiratory distress syndrome) or malignancies; ② History of kidney transplantation; ③ Immunotherapy within the previous 3 months. This study was approved by the Ethics Committee of the People's Hospital of Pingyang (Approval No. LW-2024-51). Informed consent was obtained from all patients, and the study was conducted following the principles outlined in the Declaration of Helsinki.

Treatment Methods

Patients in the CRRT group received routine CRRT therapy, nutritional support, and anti-infection treatment. Catheters were placed in the femoral or internal jugular vein to establish effective vascular access. Continuous veno-venous hemofiltration was performed with blood flow rates of 200–220 mL/min and replacement fluid flow rates of 3000–4000 mL/h. Heparin was administered as an anticoagulant (5–15 U/kg/h). Patient conditions were closely monitored during CRRT, and in cases of bleeding tendencies, the flow was reduced or the treatment halted. Filters were replaced every 12 hours, with treatment conducted for at least 12 hours daily.

Patients in the NM+CRRT group received NM in addition to standard CRRT therapy. Before CRRT initiation, blood tubing and filters were prefilled with 1000 mL saline containing 5000 U heparin and subsequently flushed with 1000 mL saline. Patients were administered an initial NM dose of 0.4 mg/kg before cardiopulmonary bypass, followed by a continuous infusion of NM at 0.4 mg/kg/h during treatment (Liu et al, 2024a).

Observation Indicators

Efficacy evaluation: Efficacy was categorized as significantly effective, effective, or invalid. For the significantly effective, clinical signs and symptoms were significantly improved after treatment, and serum creatinine (SCr) levels returned to near-normal values. The effective group was characterized by improved clinical signs and symptoms, with reduced SCr levels by more than 5%. The invalid group encompassed patients who showed no improvement or worsening of the clinical signs and symptoms, with SCr reduction of less than 5% or an increase in SCr levels (Choi et al, 2015).

Clinical indicators: The duration of ICU stay, and APACHE II scores (Tekin et al, 2024) were compared between the two groups. The APACHE II score comprises the following components: (1) The acute physiological score (APS) includes 12 physiological indicators. The first 11 are based on common clinical parameters, scored from 0 (normal) to 4 based on the degree of deviation from normal. The 12th indicator is the Glasgow Coma Scale (GCS), where APS includes 15 minus the

actual GCS score. (2) The age is based on five age groups: <44 years: 0 points, 45–54 years: 2 points, 55–64 years: 3 points, 65–74 years: 5 points, and >75 years: 6 points. (3) The chronic health score (CHS) with 2 points for non-surgical or elective surgery conditions, 5 points for inoperable or emergency surgical conditions, and 0 points if none of the above conditions apply.

The highest theoretical APACHE II score was 71, with higher scores indicating greater disease severity, poorer prognosis, and higher mortality risk. Scoring was performed by an experienced physician.

Laboratory indicators: Fasting venous blood samples were collected from patients before and after treatment to assess immune function by measuring the levels of immunoglobulin G (IgG) and immunoglobulin A (IgA) by rate scattering immunoturbidimetry using automatic biochemical analyzer (Olympus AU600, Olympus Corporation, Tokyo, Japan). Renal function was assessed by measuring the SCr and blood urea nitrogen (BUN) levels using an automatic biochemical analyzer (LABOSPECT 006, HITACHI, Tokyo, Japan). Additionally, the levels of oxidative stress markers, glutathione peroxidase (GSH-Px) and malondialdehyde (MDA), in serum were detected using a double antibody sandwich enzyme-linked immunosorbent assay (ELISA) kits (GSH-Px: cat. BC0025; MDA: cat. BC1195; Solarbio, Beijing, China). Optical density (OD) was measured at 450 nm, and concentrations were calculated based on standard curves. Changes in oxidative stress markers were compared between the two groups.

Occurrences of adverse reactions, including bleeding, hyperkalemia, gastrointestinal symptoms, and thrombocytopenia, were recorded and compared between the groups.

Statistical Methods

All experimental data were analyzed using SPSS 20.0 software (IBM, Armonk, NY, USA). Continuous variables, such as Age, MDA, and GSH-Px levels, were expressed as mean ± standard deviation ($\bar{x} \pm s$). The normality of data distribution was verified using the Shapiro-Wilk test. Independent sample *t*-test was used to compare differences between groups. A paired sample *t*-test was used to compare intra-groups before and after treatment. Categorical variables, such as gender, efficacy, and adverse event rates, were expressed as percentages (%) and analyzed using the chi-square (χ^2). Statistical significance was defined as a two-sided *p*-value < 0.05.

Results

Baseline Characteristics

The CRRT group consisted of 48 patients, including 25 males and 23 females, with a mean age of 51.19 ± 6.41 years and an average APACHE II score of 28.02 ± 3.08. The NM+CRRT group included 50 patients, comprising 28 males and 22 females, with a mean age of 50.88 ± 8.17 years and an average APACHE II score of 27.84 ± 3.60. Baseline data were comparable between the two groups ($p > 0.05$). Details are presented in Table 1.

Table 1. Baseline characteristics of the two groups [n (%) ($\bar{x} \pm s$)].

Group	n	Age (years)	Gender		APACHE II score (points)
			Male	Female	
CRRT group	48	51.19 ± 6.41	25 (52.08)	23 (47.92)	28.02 ± 3.08
NM+CRRT group	50	50.88 ± 8.17	28 (56.00)	22 (44.00)	27.84 ± 3.60
χ^2/t		0.208	0.151		0.265
p-value		0.835	0.697		0.791

APACHE II, Acute Physiology and Chronic Health Evaluation II; CRRT, continuous renal replacement therapy; NM, nafamostat mesylate.

Table 2. Comparison of efficacy between the two groups [n (%)].

Group	n	Significant effect (n, %)	Effective (n, %)	Invalid (n, %)	Total effective (n, %)
CRRT group	48	16 (33.33)	20 (41.67)	12 (25.00)	36 (75.00)
NM+CRRT group	50	19 (38.00)	27 (54.00)	4 (8.00)	46 (92.00)
χ^2					5.181
p-value					0.023

CRRT, continuous renal replacement therapy; NM, nafamostat mesylate.

Comparison of Efficacy between the Two Groups

The total effective rate in the NM+CRRT group was 92.00%, significantly higher than the 75.00% observed in the CRRT group ($p < 0.05$). Details are shown in Table 2.

Comparison of Clinical Treatment Indices between the Two Groups

The APACHE II scoring system was used to assess disease severity comprehensively. The duration of ICU stay and APACHE II score in the NM+CRRT group were significantly lower than those in the CRRT group ($p < 0.05$). Data are summarized in Table 3.

Table 3. Comparison of clinical treatment indices between the two groups ($\bar{x} \pm s$).

Group	n	ICU time (days)	APACHE II score (points)
CRRT group	48	17.77 ± 2.68	17.48 ± 3.29
NM+CRRT group	50	15.42 ± 3.25	14.02 ± 2.39
t-value		3.897	5.974
p-value		<0.001	<0.001

ICU, intensive care unit; CRRT, continuous renal replacement therapy; NM, nafamostat mesylate; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Table 4. Comparison of renal function indices between the two groups ($\bar{x} \pm s$).

Group	n	SCr (μmol/L)				BUN (mmol/L)			
		Before treatment	After treatment	*t*-value	*p*-value	Before treatment	After treatment	*t*-value	*p*-value
CRRT group	48	201.64 ± 36.19	107.64 ± 15.28	16.578	<0.001	15.24 ± 3.02	12.08 ± 2.37	5.703	<0.001
NM+CRRT group	50	200.97 ± 38.20	87.31 ± 12.69	19.966	<0.001	15.30 ± 4.06	8.59 ± 1.85	10.634	<0.001
t-value		0.089	7.177			0.083	8.145		
p-value		0.929	<0.001			0.934	<0.001		

SCr, serum creatinine; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; NM, nafamostat mesylate.

Table 5. Comparison of immune function indices between the two groups ($\bar{x} \pm s$).

Group	n	IgG (g/L)				IgA (g/L)			
		Before treatment	After treatment	*t*-value	*p*-value	Before treatment	After treatment	*t*-value	*p*-value
CRRT group	48	8.15 ± 1.26	10.52 ± 2.64	5.613	<0.001	1.04 ± 0.12	1.85 ± 0.34	15.564	<0.001
NM+CRRT group	50	8.23 ± 1.84	12.36 ± 3.04	8.218	<0.001	1.06 ± 0.13	2.48 ± 0.36	26.233	<0.001
t-value		0.250	3.194			0.791	8.899		
p-value		0.803	0.002			0.431	<0.001		

IgG, immunoglobulin G; IgA, immunoglobulin A; CRRT, continuous renal replacement therapy; NM, nafamostat mesylate.

Table 6. Comparison of oxidative stress markers between the two groups ($\bar{x} \pm s$).

Group	n	MDA (nmol/mL)				GSH-Px (U/L)			
		Before treatment	After treatment	*t*-value	*p*-value	Before treatment	After treatment	*t*-value	*p*-value
CRRT group	48	9.86 ± 2.43	6.89 ± 1.54	8.386	<0.001	143.26 ± 38.45	126.72 ± 28.50	2.394	0.018
NM+CRRT group	50	9.70 ± 2.68	5.71 ± 1.26	9.527	<0.001	145.05 ± 40.39	112.52 ± 27.33	4.717	<0.001
t-value		0.310	4.159			0.225	2.518		
p-value		0.757	<0.001			0.823	0.013		

MDA, malondialdehyde; GSH-Px, glutathione peroxidase; CRRT, continuous renal replacement therapy; NM, nafamostat mesylate.

Table 7. Comparison of adverse reactions and complications between the two groups [n (%)].

Group	n	Bleeding (n, %)	Hyperkalemia (n, %)	Digestive symptoms (n, %)	Thrombocytopenia (n, %)	Total occurrence (n, %)
CRRT group	48	3 (6.25)	0 (0.00)	2 (4.17)	3 (6.25)	8 (16.67)
NM+CRRT group	50	2 (4.00)	2 (4.00)	5 (10.00)	4 (8.00)	13 (26.00)
χ^2						1.267
p-value						0.260

CRRT, continuous renal replacement therapy; NM, nafamostat mesylate.

Comparison of Renal Function Indices between the Two Groups

SCr and BUN are critical indicators of renal function. Post-treatment, both groups demonstrated significant reductions in SCr and BUN levels ($p < 0.05$). The NM+CRRT group exhibited significantly lower SCr and BUN levels compared to the CRRT group ($p < 0.05$). Detailed results are shown in Table 4.

Comparison of Immune Function Indices between the Two Groups

Immunoglobulin levels indicate immune function strength. Post-treatment, the two groups showed significant improvements in IgG and IgA levels ($p < 0.05$). Notably, the NM+CRRT group exhibited significantly higher IgG and IgA levels compared to the CRRT group ($p < 0.05$). Data are presented in Table 5.

Comparison of Oxidative Stress Markers between the Two Groups

MDA and GSH-Px are key biomarkers for oxidative stress and antioxidant capacity. Post-treatment, the two groups exhibited significant reductions in MDA and GSH-Px levels ($p < 0.05$). The NM+CRRT group achieved significantly lower MDA and GSH-Px levels compared to the CRRT group ($p < 0.05$). Results are shown in Table 6.

Comparison of Adverse Reactions between the Two Groups

The total incidence of adverse reactions was 26.00% in the NM+CRRT group and 16.67% in the CRRT group. However, the differences were not statistically significant ($p > 0.05$). Detailed data are presented in Table 7.

Discussion

At present, CRRT is a widely used treatment for critically ill patients, notably those in the ICU with multiple organ failure (MOF) caused by sepsis, which is pivotal in restoring organ function and improving prognosis in critically ill patients (Li et al, 2022; Liu et al, 2023). However, one of the major challenges in CRRT is managing blood clotting during cardiopulmonary bypass. While systemic heparin anticoagulation is the most commonly used method worldwide, it carries a high risk of bleeding complications (Kameda et al, 2023; Soma et al, 2022). Identifying safer and more effective anticoagulants is crucial to improve CRRT outcomes.

NM is a synthetic serine protease inhibitor with a molecular weight of 539 Da (Zhao et al, 2022). NM exerts anticoagulant effects by inhibiting thrombin and coagulation factors (IIa, Xa, XIIa), platelet activation, the kallikrein-kinin system, and lipopolysaccharide-induced nitric oxide production. It also suppresses complement and platelet activation (Tanaka and Ohmine, 2024; Zhou et al, 2023a). The unique characteristics of NM, including its independence from antithrombin III, rapid degradation by liver carboxylesterase, and short half-life of approximately 8 minutes, make it ideal for extracorporeal circulation with a low risk of hemorrhage (Kotake et al, 2023; Sanfilippo et al, 2022). Despite its approval in China since 2022, clinical studies on NM remain limited, especially for patients undergoing hemodialysis (Narumi et al, 2023).

In this study, the NM+CRRT group demonstrated a significantly higher total effective rate than the CRRT group, along with significantly lower ICU stay durations and APACHE II scores. These findings suggest that NM-assisted CRRT improves the therapeutic efficacy in SA-AKI patients, alleviates symptoms, and shortens ICU stays. NM demonstrates distinct advantages over conventional heparin anticoagulation. Unlike heparin, NM is independent of antithrombin III and directly interacts with the glycoprotein Ib-IIIa complex, effectively inhibiting various factors involved in the coagulation pathway. NM forms conjugate with thrombin to block its activity and inhibits the activation of coagulation factors, including factors XIIa, Xa, plasminogen, kinin, and complement (Qian et al, 2023; Yang et al, 2022). Additionally, NM interferes with platelet aggregation by suppressing arachidonic acid secretion and the activity of phospholipase A2 (Liu et al, 2023). These properties confer significant anticoagulant efficacy to NM, facilitating uninterrupted CRRT sessions, which enhances therapeutic outcomes and accelerates patient recovery. Similar findings were reported by Liu and Li (2024b), who demonstrated that NM effectively improves treatment efficacy in patients with end-stage renal failure while maintaining a high safety profile and clinical value.

CRRT is a well-established therapy for SA-AKI and effectively clears inflammatory factors, improves immune function, restores renal function, alleviates symptoms, and improves survival rates (Wald et al, 2022; Zhou et al, 2023b). In this study, SCr and BUN levels showed significant improvements in the NM+CRRT and CRRT groups, with greater reductions observed in the NM+CRRT group. NM also reduces neutrophil activation and aggregation, modulating immune cell functions (Sun et al, 2021). Moreover, NM also exhibits antioxidant properties that mitigate oxidative stress-induced damage to immune cells by reducing the production of free radicals (Kang et al, 2015).

These effects were corroborated by post-treatment observations. IgG and IgA levels significantly increased in both groups, with the NM+CRRT group achieving higher levels. Similarly, oxidative stress markers, including MDA and GSH-Px, significantly improved, with the NM+CRRT group exhibiting more pronounced reductions. These findings suggest that NM-assisted CRRT enhances renal function, improves immune responses, and reduces oxidative stress in SA-AKI patients. The mechanism underlying the benefits associated with NM may be attributed to its potential to prolong cardiopulmonary bypass duration, thereby enhancing more effective CRRT sessions. This contributes to enhanced renal and immune function, reduced oxidative stress, and, ultimately, symptomatic relief for patients (Lang et al, 2022).

This study evaluated adverse reactions and observed an incidence of 26.00% in the NM+CRRT group and 16.67% in the CRRT group, with no statistically significant difference between the two groups. However, study has reported adverse events such as phlebitis associated with NM use, highlighting the need for close monitoring during treatment to ensure patient safety (Okugawa et al, 2023). Liu et al (2024a) demonstrated that the anticoagulant efficacy and safety of NM are comparable to regional citrate anticoagulation in CRRT, even in patients at high risk of bleeding.

Despite its promising findings, this study has several limitations. First, its retrospective design introduces potential selection bias due to reliance on pre-existing data. Second, the small sample size limits the generalizability of the results and increases the risk of coincidental findings. Furthermore, although no significant bleeding complications were observed, the higher incidence of adverse reactions in the NM+CRRT group may be partially attributed to the short duration of the study and limited sample size. To address these limitations, future research should involve larger, prospective randomized controlled trials to validate the findings and reduce potential biases.

Conclusion

In summary, NM-assisted CRRT therapy significantly improves the therapeutic efficacy of patients with SA-AKI. This combined approach improves immune and renal functions, reduces oxidative stress, and demonstrates a favorable safety profile, making it a viable option for clinical application.

Key Points

- The overall efficacy rate was significantly higher in the nafamostat mesylate (NM)+CRRT group compared to the CRRT group.
- NM combined with CRRT effectively alleviates symptoms and shortens ICU stay duration in SA-AKI patients.
- NM combined with CRRT enhances renal function and strengthens immune responses in SA-AKI patients.
- The incidence of adverse reactions was comparable between the NM+CRRT and CRRT-only groups, indicating similar safety profiles.

Availability of Data and Materials

The data analyzed are available upon request from the corresponding author.

Author Contributions

MAM designed the research study. MAM and ZLC performed the research and analyzed the data. MAM drafted the manuscript. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the People's Hospital of Pingyang (Approval No. LW-2024-51). Informed consent was obtained from all patients, and the study was conducted following the principles outlined in the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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