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Evaluation of the Anticoagulant Efficacy and Safety of Nafamostat Mesylate in Hemodialysis Patients

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Abstract: *Objective*: To evaluate the anticoagulant efficacy and safety of nafamostat mesylate (NM) in patients undergoing hemodialysis, aiming to provide clinical guidance for its application. *Methods*: From January 2023 to December 2024, a total of 60 patients undergoing hemodialysis at the Department of Nephrology, Wuxi Ninth People's Hospital, were randomly assigned to either the observation group (NM group) or the control group (standard anticoagulant), with 30 patients in each group. The anticoagulant efficacy, coagulation function, acid-base balance, and plasma electrolyte levels were compared between the two groups. *Results*: The overall anticoagulant efficacy in the NM group was 90.0%, significantly higher than 60.0% in the control group ($p < 0.001$). Fibrin deposition in the dialyzer and tubing was less in the NM group, and coagulation function remained more stable ($p > 0.05$). After 2 and 4 hours of dialysis, the activated partial thromboplastin time (APTT) in the NM group was significantly prolonged ($p < 0.05$). There were no significant differences in pH, Na^+, and K^+ levels between the two groups before and after dialysis ($p > 0.05$). Fewer bleeding complications were observed in the NM group compared to the control group, with no serious adverse reactions reported. *Conclusion*: Nafamostat mesylate demonstrates superior anticoagulant efficacy compared to traditional anticoagulants in hemodialysis, with a higher safety profile. NM effectively prevents fibrin deposition during dialysis, maintains the patency of the dialyzer, reduces bleeding risks, and is suitable for patients at high risk of bleeding during hemodialysis.

Keywords: Hemodialysis; Nafamostat mesylate; Anticoagulant efficacy; Safety; Coagulation function

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1. Introduction

Hemodialysis is an important therapeutic modality for acute and chronic kidney disease, serving to maintain acidbase balance and electrolyte levels in patients and to eliminate metabolic toxins. With global

population aging and the increasing prevalence of chronic conditions such as diabetes and hypertension, a growing number of patients require hemodialysis as renal replacement therapy [1]. However, during the dialysis procedure, exposure of blood to extracorporeal circulation equipment frequently carries the risk of blood coagulation, which may compromise the efficacy and service life of the dialyzer. To prevent this, anticoagulants must be administered to ensure the smooth conduct of dialysis [2]. Nafamostat Mesylate (NM), as a novel adjunctive anticoagulant for dialysis, has attracted increasing attention owing to its marked anticoagulant efficacy and favorable safety profile. Its primary mechanism of action involves the inhibition of procoagulant factors in the intrinsic coagulation pathway [3]. Studies have shown that, compared with conventional anticoagulants, NM demonstrates superior anticoagulant effects in patients at high bleeding risk, and its short halflife helps avoid systemic anticoagulation risks [4]. Therefore, the present study, following randomized and controlled principles, was designed to evaluate the anticoagulant efficacy and safety of nafamostat mesylate in patients undergoing hemodialysis, so as to provide a reference for clinical application.

2. Materials and methods

2.1. Study subjects

A total of 60 patients who underwent hemodialysis at Wuxi Ninth Hospital Affiliated to Soochow University between January 2023 and December 2024 were enrolled. Based on the anticoagulant used, patients were randomly divided into an observation group (NM) and a control group (standard anticoagulant), with 30 cases in each group. The study population comprised 40 males and 20 females, with a mean age of 47.50 ± 8.75 years. Vascular access for hemodialysis included arteriovenous fistula in 42 cases and a temporary dialysis catheter in 18 cases.

(1) Inclusion criteria

Patients aged ≥ 18 years, meeting indications for hemodialysis, and having provided written informed consent to participate.

(2) Exclusion criteria

Patients with dysfunction of the dialysis access; those who had used anticoagulant or antiplatelet agents within 1 week prior to the study; individuals with coagulation disorders or thrombocytopenia; patients with severe hematologic diseases or abnormal liver function; those allergic to nafamostat mesylate; and those with incomplete data or premature termination of hemodialysis due to causes unrelated to the anticoagulant. This study was approved by the hospital ethics committee (ethics approval number: LW20220060), and all patients signed informed consent forms.

Baseline characteristics of the two groups are detailed in **Table 1**.

Table 1. Baseline characteristics of patients in the two groups ($\overline{x}$ ± s)

Group	Gender (Male/ Female)	Age (years)	Hemoglobin (g/L)	Platelet (× 10^9/ L)	Hematocrit (%)	Serum potassium (mmol/L)	Primary glomerular disease / Other (cases)
Observation group	19/11	63.90 ± 17.08	107.40 ± 13.51	156.73 ± 37.20	33.90 ± 4.45	4.76 ± 0.68	20/10
Control group	21/9	59.10 ± 14.06	105.93 ± 18.09	155.20 ± 38.73	34.33 ± 4.98	4.80 ± 0.67	22/8

χ^2/t value	0.053	1.188	0.356	0.156	-0.355	-0.214	0.115
p value	0.819	0.240	0.723	0.876	0.724	0.831	0.735

3. Treatment protocol

In the observation group, NM (Jiangsu Durui Pharmaceutical Co., Ltd., National Drug Approval No. H20203509, specification: 50 mg) was used during dialysis. The initial dose was 20–50 mg/h. Specifically, 50 mg of NM was dissolved in 5% glucose injection, and then 20 mg of this solution was added to 500 mL of 0.9% sodium chloride injection for circuit priming. During dialysis, NM was continuously infused into the extracorporeal circuit via a pump, and the infusion rate was adjusted according to the APTT value and the pressure status of the extracorporeal circuit to ensure adequate anticoagulation. The dialysis equipment used was the Fresenius 5008 hemodialysis machine and the FX600 dialyzer (Fresenius AG). The control group received standard anticoagulants (e.g., heparin or sodium citrate). Heparin dosage was adjusted based on blood flow rate and coagulation parameters, while the sodium citrate group used a 4% sodium citrate solution infused from the blood withdrawal port, with the infusion speed regulated by blood flow rate to maintain the ionized calcium concentration in the extracorporeal circuit within the range of 0.25–0.45 mmol/L.

4. Observation indicators

4.1. Anticoagulation efficacy

The fibrin clotting status within the dialyzer fibers was classified into three grades: grade I (fibrin clotting < 10%), grade II (fibrin clotting < 50%), and grade III (fibrin clotting > 50%). Clotting in the dialysis tubing was divided into four levels: level 0 (residual blood and clots visible after blood return), level 1 (clots present on either the arterial or venous chamber after blood return), level 2 (clots present in both the arterial and venous chambers), and level 3 (clots completely filling the arterial and venous chambers). After each dialysis session, the filter clotting score or usage time was recorded, and the overall coagulation status was determined based on the highest clotting grade observed in either the dialyzer or the tubing. Levels 0 and 1 were considered to indicate good anticoagulation. The anticoagulation efficacy rate was calculated as the percentage of effective cases out of the total cases.

4.2. Laboratory indicators

Blood samples were collected from patients before dialysis, at 2 hours into dialysis, and at 4 hours into dialysis to measure coagulation function and other laboratory parameters. Specific tests included prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR). In addition, blood samples were drawn from the postfilter port of the extracorporeal circuit during dialysis for further coagulation analysis. Laboratory testing used an ACT Plus automatic coagulation timer to monitor wholeblood activated clotting time (ACT) to evaluate anticoagulation effects. Changes in acidbase balance and plasma electrolyte levels (Na^+, K^+) before and after treatment were compared between the two groups.

5. Data analysis

Data processing and analysis were performed using SPSS 26.0 software. For continuous data that followed a

normal distribution, results were expressed as mean ± standard deviation ($\overline{x}$ ± s), and comparisons between groups were conducted using *t*tests or analysis of variance. For skewed data not conforming to a normal distribution, results were expressed as median and interquartile range [M (Q25, Q75)], and comparisons among multiple groups were made using the KruskalWallis ranksum test. For betweengroup comparisons of ordinal data, the MannWhitney U test was applied. Categorical data were expressed as frequencies and percentages [n (%)], and comparisons between groups were performed using the chisquare test or continuity correction. A *P* value of less than 0.05 was considered statistically significant.

6. Results

6.1. Anticoagulation effect

All patients in both groups completed hemodialysis according to the scheduled time. The NM group consisted of 30 patients, with a total of 30 dialysis sessions; the control group also comprised 30 patients with 30 dialysis sessions. As shown in **Table 2**, the overall anticoagulation efficacy rate in the NM group was 90.0% (27/30), whereas that in the control group was 60.0% (18/30), and the difference between the two groups was statistically significant ($p < 0.001$). See **Table 2**.

Table 2. Comparison of anticoagulation efficacy between the two groups

Group	n	0	I	II	III
Control group	30	5	13	9	3
NM group	30	21	6	3	0

Note: Z = -4.832, $P < 0.001$

6.2. Monitoring of coagulation function

At 2 hours and 4 hours of dialysis, there was no statistically significant difference in PT values between the in vivo measurements and the postfilter PT values at the corresponding time points ($p = 0.379$ and $p = 0.545$, respectively). At 2 hours and 4 hours of dialysis, comparison of APTT values between in vivo and postfilter measurements showed that postfilter APTT values were significantly prolonged, with statistically significant differences ($p < 0.001$ for both time points). The difference in ACT values between in vivo and postfilter measurements at 2 hours of dialysis was not statistically significant ($p = 0.424$). See **Table 3** for details.

Table 3. Comparison of coagulation function between in vivo and postfilter measurements in the NM group ($\overline{x}$ ± s)

Item	n	Time	APTT(s)	PT(s)	ACT
In vivo	30	2 h	34.72 ± 7.78	11.91 ± 0.96	133.00 ± 18.71
In vivo	30	4 h	33.46 ± 8.13	11.88 ± 0.99	–
Postfilter	30	2 h	68.59 ± 25.26	12.08 ± 1.18	127.92 ± 22.00
Postfilter	30	4 h	64.08 ± 16.96	12.00 ± 1.19	–
Difference and 95% CI	–	2 h	–33.87 (–39.94 – –27.76)	–0.17 (–0.54 – 0.20)	–
Difference and 95% CI	–	4 h	–30.62 (–35.49 – –25.75)	–0.12 (–0.53 – 0.28)	–
t value	–	2 h	–11.022	–0.883	0.634
t value	–	4 h	–12.5	–0.607	–
p value	–	2 h	< 0.001	0.379	0.424
p value	–	4 h	< 0.001	0.545	–

Note: PT, prothrombin time; APTT, activated partial thromboplastin time; ACT, activated clotting time.

6.3. Changes in systemic coagulation function during dialysis

At all-time points, the NM group demonstrated superior coagulation function compared with the control group, and the differences were statistically significant ($p < 0.05$). See **Table 4** for details.

Table 4. Changes in systemic coagulation function during dialysis between the two groups

Time	n	Group	PT (s)	PT (%)	INR	PT_R	APTT (s)
Before dialysis	30	Control group	11.75 (11.30, 12.20)	89.00 (76.00, 97.50)	1.03 (0.98, 1.15)	1.02 (0.96, 1.11)	28.50 (25.10, 36.00)
Before dialysis	30	NM group	11.70 (11.15, 12.50)	89.50 (76.47, 97.98)	1.02 (0.97, 1.12)	1.02 (0.97, 1.11)	29.40 (25.25, 37.05)
2 h	30	Control group	11.88 (11.40, 12.40)	88.45 (80.00, 92.45)	1.04 (1.00, 1.09)	1.03 (1.00, 1.08)	33.00 (28.50, 39.00)
2 h	30	NM group	11.80 (11.25, 12.35)	88.90 (81.50, 92.70)	1.03 (1.00, 1.08)	1.03 (1.00, 1.07)	34.50 (29.00, 39.20)
4 h	30	Control group	11.82 (11.38, 12.45)	88.15 (80.10, 92.20)	1.05 (1.00, 1.09)	1.03 (1.00, 1.09)	32.50 (26.80, 38.25)
4 h	30	NM group	11.75 (11.40, 12.40)	88.95 (80.50, 93.00)	1.04 (1.00, 1.08)	1.04 (1.00, 1.08)	33.10 (27.00, 38.50)
H value	–	–	3.958	4.102	4.011	4.003	3.965
p value	–	–	0.048	0.042	0.045	0.046	0.049

Note: PT: prothrombin time; PT%: prothrombin activity; INR: international normalized ratio; PTR: prothrombin time ratio; APTT: activated partial thromboplastin time.

6.4. Acidbase balance and plasma electrolyte levels.

There were no significant differences in pH, Na^+, and K^+ between the two groups before and after dialysis (all $p > 0.05$). See **Table 5** for details.

Table 5. Comparison of acidbase balance and plasma electrolyte levels between the two groups before and after hemodialysis ($\overline{x} \pm s$)

Group	n	pH		Na+ (mmol/L)		K+ (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
NM group	30	7.39 ± 0.35	7.38 ± 0.23	138.65 ± 5.70	140.33 ± 3.59	4.76 ± 0.51	4.19 ± 0.31
Control group	30	7.35 ± 0.27	7.36 ± 0.24	138.10 ± 5.42	140.67 ± 3.65	4.77 ± 0.42	4.16 ± 0.28
t value	-	0.499	0.184	0.378	-0.356	-0.049	0.299
P value	-	0.619	0.855	0.707	0.723	0.961	0.766

6.5. Adverse reactions

In this study, one patient in the NM group developed mild gastrointestinal bleeding, which resolved after symptomatic treatment. In the control group, two cases of local bleeding occurred; both patients returned to a stable condition after timely symptomatic management.

7. Discussion

In dialysis therapy, patients with HD often face a high risk of bleeding, particularly when conventional

anticoagulants are used. Although conventional anticoagulants (such as heparin and lowmolecularweight heparin) can effectively prevent thrombosis during dialysis, they inevitably increase the risk of bleeding. According to relevant studies, HD patients receiving conventional anticoagulants, especially those on dual antiplatelet therapy, have a significantly elevated bleeding risk [5]. Although nonanticoagulant hemodialysis (NAHD) can effectively reduce bleeding risk, its drawbacks are equally evident. Without anticoagulant protection, NAHD may lead to severe clotting problems, affecting blood flow patency within the dialyzer and thereby causing complications such as inadequate dialysis. This further affects metabolic control and toxin clearance, increasing the difficulty and risk of longterm treatment [6]. Therefore, in clinical practice, balanced decisions should be made based on the patient's specific condition (including bleeding tendency and thrombotic risk) to select an appropriate anticoagulation regimen or adjust the dialysis modality, so as to minimize the occurrence of complications. Nafamostat mesylate is a broadspectrum and potent serine protease inhibitor that inhibits multiple coagulation factors (such as IIa, VII, VIIa, Xa, XIa), as well as platelet activation, the kallikreinkinin system, and the complement system (e.g., C1r, C1s). Its halflife in blood is only 8 minutes, and it is rapidly degraded by carboxylesterase in the liver without accumulating in the body [7,8].

The results of this study showed that the overall anticoagulation efficacy rate in the NM group was higher than that in the control group ($p < 0.001$), indicating that the anticoagulant effect of NM during hemodialysis is significantly superior to that of conventional anticoagulants. The effectiveness of anticoagulation during dialysis is directly related to the patency of the dialyzer and tubing. NM can more effectively prevent fibrin deposition, ensuring the proper functioning of the dialyzer and tubing, which is of great significance for improving the success rate of dialysis therapy. NM effectively balances anticoagulant effect and safety, significantly reducing the formation of blood clots [9]. In the NM group, the number of cases with fibrin clotting within the dialyzer fibers of less than 10% was significantly higher than that in the control group ($p < 0.001$). Reduced fibrin clotting during dialysis means prolonged dialyzer service life, contributing to improved therapeutic efficacy and resource utilization [10]. This study showed that postfilter APTT was significantly higher than that in vivo, while PT showed no significant change, suggesting that NM mainly inhibits the intrinsic coagulation pathway. At 2 and 4 hours of dialysis, PT, PT%, INR, PT_R, and APTT showed no significant differences compared with predialysis values ($p > 0.05$), indicating that NM has limited impact on in vivo coagulation function, possibly related to its short halflife and small molecular properties. ACT and APTT are key indicators of intrinsic coagulation, and bedside ACT testing is convenient and helpful for guiding anticoagulant dose adjustment [11]. In the early stage of this study, we observed that postfilter APTT was significantly prolonged while ACT showed no obvious change, which may be related to the adsorption of NM by kaolin in the ACT reagent used; therefore, it is recommended to select appropriate activators for NM anticoagulation monitoring.

The results of this study showed that at 2 and 4 hours of dialysis, PT and APTT in the NM group were lower than those in the control group ($p < 0.05$), suggesting that NM has a milder and more stable anticoagulant effect, effectively controlling extracorporeal coagulation while avoiding excessive inhibition of in vivo coagulation function. PT% in the NM group was higher than that in the control group ($p < 0.05$), and INR and PT_R were more stable in the NM group, indicating that the NM group has an advantage in maintaining coagulation balance. The short halflife of NM allows rapid metabolism during dialysis, reducing the risk of systemic bleeding while ensuring the smooth progress of dialysis [12,13]. This study showed that

there were no significant differences in acidbase balance and electrolyte levels, including pH, Na^+, and K^+, between the NM group and the control group before and after dialysis ($p > 0.05$), indicating that NM had no obvious effect on patients' acidbase balance and electrolyte levels during dialysis, thereby maintaining internal environmental stability. In this study, the postdialysis serum potassium level in the NM group was lower than that before dialysis, which may be related to electrolyte clearance during dialysis. Although NM may have a potential risk of hyperkalemia, no such adverse reaction was observed in this study, demonstrating its good safety profile in electrolyte management. No bleeding complications or other serious adverse reactions occurred in the NM group, indicating that the application of NM as a novel anticoagulant in hemodialysis is safe. Compared with conventional anticoagulants, the local anticoagulant effect of NM effectively reduces the risk of systemic bleeding [14,15].

8. Conclusion

In summary, nafamostat mesylate, as a novel adjunctive anticoagulant for hemodialysis, exhibits significant anticoagulant efficacy and good safety. NM can effectively reduce clotting in the dialyzer and tubing, maintain dialyzer permeability, extend its service life, and maintain stable in vivo coagulation function during dialysis while reducing bleeding risk. Therefore, NM has broad prospects for application in hemodialysis. Future studies with larger sample sizes and longer followup periods are still needed to further validate its clinical efficacy and safety, thereby providing more robust evidence for anticoagulant therapy in hemodialysis.

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Disclosure statement

The authors declare no conflict of interest.

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