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The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCC* as 1.1; IF without journal self cites: 1.1; 5-year IF: 1.3; Journal Citation Indicator: 0.26; Ranking: 133 among 167 journals in medicine, general and internal; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Si Zhao*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lai Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Salim Surani, Jerzy Tadeusz Chudek, George Kontogorgos, Maurizio Serati

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

January 6, 2024

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Retrospective Study

Efficacy and safety of Nafamostat mesylate in patients with end-stage renal failure

Kun Liu, Zhen-Hua Li

Specialty type: Medicine, research and experimental**Provenance and peer review:** Unsolicited article; Externally peer reviewed.**Peer-review model:** Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0**P-Reviewer:** Naguib HE, Canada**Received:** November 10, 2023**Peer-review started:** November 10, 2023**First decision:** November 22, 2023**Revised:** December 5, 2023**Accepted:** December 18, 2023**Article in press:** December 18, 2023**Published online:** January 6, 2024**Kun Liu**, Department of Critical Care Medicine, The Third People's Hospital Of Hubei Province, Wuhan 430030, Hubei Province, China**Zhen-Hua Li**, Department of Critical Care Medicine, General Hospital of The Yangtze River Shipping, Wuhan Brain Hospital, Wuhan 430015, Hubei Province, China**Corresponding author:** Zhen-Hua Li, MM, Chief Doctor, Department of Critical Care Medicine, General Hospital of The Yangtze River Shipping, Wuhan Brain Hospital, No. 5 Huiji Road, Wuhan 430015, Hubei Province, China. zhenh0911@163.com**Abstract****BACKGROUND**

Recent studies on dialysis anticoagulation therapy in patients with renal failure have shown that Nafamostat mesylate, a broad-spectrum potent serine protease inhibitor, has strong anticoagulation and anti-fiber activity.

AIM

To evaluate the efficacy and safety of Nafamostat mesylate in patients with end-stage renal failure.

METHODS

Seventy-five patients with end-stage renal failure who received hemodialysis at our hospital between January 2020 and August 2021 were selected and divided into the observation group (Nafamostat mesylate for injection, $n = 33$) and control group (heparin sodium injection, $n = 32$). General patient data, indicators of clinical efficacy, dialyzer hemocoagulation parameters, coagulation function indices, and hemoglobin concentration and platelet count before and after treatment, and the occurrence of adverse reactions after treatment were compared between the two groups.

RESULTS

The two groups showed no significant differences in general patient data ($P > 0.05$). The post-treatment effectiveness rate in the control group was lower than that in the observation group ($P < 0.05$). The two groups showed no significant difference in the number of patients in grade I ($P > 0.05$), while the number of patients in grade 0 was lower in the control group, and the number of patients in grades II and III was higher in the control group ($P < 0.05$). The post-treatment prothrombin time, activated partial thromboplastin time, thrombin time, and

international normalized ratio values in the control group were higher than those in the observation group, while the fibrinogen level in the control group was lower than that in the observation group ($P < 0.05$). The two groups showed no significant difference in the platelet count and hemoglobin level before and after treatment ($P > 0.05$). The total number of post-treatment adverse reactions in the observation group was lower than that in the control group ($P < 0.05$).

CONCLUSION

Treatment of patients showing end-stage renal failure with Nafamostat mesylate can significantly improve therapeutic efficacy and has high safety and clinical value.

Key Words: End-stage renal failure; Nafamostat mesylate; Effectiveness; Safety study; Chronic kidney diseases

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Core Tip: End-stage renal disease refers to the terminal stage of the progression of various chronic kidney diseases, such as chronic nephritis, nephrotic syndrome, and tubulointerstitial disease. We aimed to evaluate the efficacy and safety of Nafamostat mesylate in patients with end-stage renal failure. Treatment of patients showing end-stage renal failure with Nafamostat mesylate can significantly improve therapeutic efficacy and has high safety and clinical value.

Citation: Liu K, Li ZH. Efficacy and safety of Nafamostat mesylate in patients with end-stage renal failure. *World J Clin Cases* 2024; 12(1): 68-75

URL: <https://www.wjgnet.com/2307-8960/full/v12/i1/68.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v12.i1.68>

INTRODUCTION

End-stage renal disease (ESRD) refers to the terminal stage of the progression of various chronic kidney diseases, such as chronic nephritis, nephrotic syndrome, and tubulointerstitial disease[1]. However, the early clinical stages of end-stage renal failure do not show any obvious symptoms. With the progression of the disease, limb edema, fatigue, gastrointestinal bleeding, and other symptoms gradually appear, and patients may show more serious symptoms and even life-threatening conditions such as consciousness disorders and cardiac arrest[2]. At present, the disease is incurable, and continuous renal replacement therapy is mainly used to prolong patient survival. However, filter coagulation during dialysis treatment can cause adverse events such as treatment interruption, additional blood loss, and inadequate dialysis, which affects the clinical treatment efficacy and increases equipment costs, highlighting the importance of appropriate anticoagulant therapy[3,4]. Anticoagulant therapy offers the advantage of maintaining extracorporeal circuit patency and reducing the rate of complications. Proteases are enzymes that hydrolyze the amide bonds of polypeptides and protein peptide units, and are involved in the pathogenesis of various diseases, including pancreatitis with trypsin and kinin-releasing enzymes, thrombin and plasmin-mediated disseminated intravascular coagulation syndrome, and autoimmune diseases mediated by the complement system[5]. Recent studies on dialysis anticoagulation therapy in patients with renal failure have shown that Nafamostat mesylate, a broad-spectrum potent serine protease inhibitor, has strong anticoagulation and anti-fiber activity, but Nafamostat mesylate has a short history of use in Linchuan, China, and the relevant literature is limited[6]. We discuss the efficacy and safety of Nafamostat mesylate in patients with end-stage renal failure.

MATERIALS AND METHODS

General information

A total of 75 patients with ESRD undergoing hemodialysis between January 2020 and August 2021 were selected and divided into the observation group (Nafamostat mesylate injection, $n = 33$) and control group (heparin sodium injection, $n = 32$). The observation group consisted of 17 male and 16 female patients aged 50-81 yr (mean age, 66.98 ± 6.45 yr), including 10 patients with chronic nephritis, 9 with nephrotic syndrome, 5 with tubulointerstitial disease, and 9 with other diseases. In contrast, the control group consisted of 18 male 14 female patients aged 52-82 yr (mean age, 67.13 ± 6.13), including 11 patients with chronic nephritis, 7 with nephrotic syndrome, 4 with tubulointerstitial disease, and 10 with other diseases. Comparison of the relevant baseline characteristics in the two groups did not show any significant differences ($P > 0.05$).

The inclusion criteria were as follows: (1) Availability of complete clinical data; (2) Meeting the relevant diagnostic criteria for end-stage renal failure diagnosis[7]; and (3) The patients were informed about the study, and informed consent was obtained from the patients and their families.

Exclusion criteria: (1) Could not participate in the entire research process; (2) Showed coinfection and other systemic diseases or organic lesions; (3) Had hematological diseases; or (4) Lack of consciousness and mental illness.

Dialysis protocol

All patients underwent treatment with a Prismaflex hemodialysis machine (Golden Baxter, Sweden) in the continuous venovenous blood-filtration mode.

Anticoagulation method

The steps involved in the anticoagulation protocol are listed below.

Pipeline pre-charge: After 0.9% sodium chloride injection, the observation group received naphthylstat (Nafamostat mesylate 20 mg, from Jiangsu Durui Pharmaceutical Co., LTD., H20203509) in 500 mL of 0.9% sodium chloride solution, while the control group received 500 mL of a solution containing 20 mg heparin sodium (Hebei Kaiwei Pharmaceutical Co., LTD., H20153264) in a pre-filled dialysis line and dialyzer.

During hemodialysis, the observation group followed the routine dosage of subjects (all subjects received intravenous injection of 60-80 IU/kg low molecular weight heparin sodium or an intravenous first dose of ordinary heparin 0.3-0.5 mg/kg before treatment followed by continuous infusion at 5-10 mg/h. The supplementation was stopped 1 h before the end of treatment with individual adjustments), with nafamostat 20 mg/h to 50 mg/h, continuous infusion from the arterial end of the CPB pipeline to the end of dialysis, the control group gave the first dose of heparin sodium 0.3-0.5mg/kg, at a dose of 5 mg/h to 10 mg/h, continuous infusion, additional heparin sodium was stopped 1 h before the end of hemodialysis treatment[8,9].

Sample collection

Cubital venous blood (6 mL) was collected in the morning, placed in a vacuum centrifuge tube, shaken till it mixed well, and centrifuged at 3000 r/min for 10 min. After obtaining the serum from the upper layer, (Changsha Chuxiang Biotechnology Co., Ltd.) fibrinogen (FIB) was detected by immunoturbidimetry; prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and the international normalized ratio (INR) were measured by coagulation analyses; and the hemoglobin (HGB) concentration and platelet (PLT) count were determined using a fully automated blood analyzer. All tests were conducted by professional examiners in strict accordance with the instructions.

Observational indicators

Comparing the two groups of general data: These include gender (male/female), age, cause of disease (chronic nephritis, nephrotic syndrome, tubulointerstitial disease and others), *etc.*

Comparison of clinical efficacy: Clinical efficacy was categorized as described below. Significant: the filter shows no coagulation, coagulation function indices remain unchanged, and the patient shows no spontaneous bleeding or other clinical symptoms.

Effective: the filter shows no coagulation, the coagulation function indices decrease slightly, and the patient shows no clinical complications.

Ineffective: the filter shows coagulation, no coagulation function index, and the patient shows clinical complications.

The total efficacy rate was calculated as follows: total efficacy rate = (effective + significant)/100% of total cases[10].

Comparison of coagulation status of the two groups: The detailed evaluation criteria for this comparison are listed below.

Grade 0: no coagulation or several pieces of coagulation fibers.

Grade I: less than 10% fibrous coagulation or bundled fibrous coagulation.

Grade II: less than 50% fibrous coagulation or severe coagulation.

Grade III: more than 50% fibrous coagulation, significantly increased venous pressure, or cases requiring dialyzer replacement[11].

Comparison of coagulation function indices: The PT, APTT, TT, INR, and FIB level were compared between the two groups. The normal ranges of PT, APTT, TT, INR, and FIB level were 11-15 s, 25-37 s, 16-18 s, 0.8-1.5 s, and 2-4 g/L, respectively[12].

Comparison of hematological parameters: The HGB level and PLT count were compared before and after the treatment in the two groups. The normal HGB level is 110-150 g/L, while the normal PLT count is $100-300 \times 10^9/L$ [13].

Comparison of post-treatment adverse reactions: The occurrence of adverse reactions, including skin rash, nausea, dizziness, palpitations, diarrhea, fever, chest tightness, and dyspnea, was compared between the groups.

Statistical analysis

Statistical analyses were performed using SPSS 18.0. Measurement data were expressed as mean \pm SD and compared using the *t*-test, while count data were expressed as *n* (%) and compared using the χ^2 test; all data were considered statistically significant at *P* < 0.05.

RESULTS

General information

A comparison of the general data between the two groups showed no statistically significant differences ($P > 0.05$; Table 1).

Table 1 General characteristics of the two groups

Group	Number of patients	Sex		Cause of disease		Age
		Male	Female	Chronic nephritis, nephrotic syndrome, renal tubulointerstitial disease	Others	
Observation group	33	17 (51.51)	16 (48.48)	24 (72.72)		66.98 ± 6.45
Control group	32	18 (56.25)	14 (43.75)	22 (68.75)		67.13 ± 6.13
χ^2/t	-	0.146		0.124		0.096
<i>P</i> value	-	0.701		0.724		0.923

Data are presented as mean ± SD or *n* (%).

Clinical efficacy

The total response rate in the control group was lower than that in the observation group ($P < 0.05$; Table 2).

Blood coagulation status of the dialyzer

After treatment, the proportion of grade I cases did not differ significantly between the two groups ($P > 0.05$). However, the control group showed a lower proportion of grade 0 cases and a higher proportion of grade II and III cases than the observation group ($P < 0.05$; Table 3).

Blood coagulation indices

Before treatment, the PT, APTT, TT, INR, and FIB level did not differ significantly between the groups ($P > 0.05$). However, the post-treatment PT, APTT, TT, INR, and FIB level were significantly lower in the control group ($P < 0.05$; Table 4).

Hematological indices

The two groups showed no significant difference in the PLT count and HGB level ($P > 0.05$; Table 5).

Adverse reactions

The total number of adverse reactions in the observation group was lower than that in the control group ($P < 0.05$; Table 6).

DISCUSSION

Blood-filtration treatment in patients with ESRD is associated with the risk of bleeding when anticoagulants such as common heparin and low molecular weight heparin are used. However, treatment without anticoagulant drugs can result in serious coagulation episodes, inadequate dialysis, and other complications[14].

Some studies from China have reported that anticoagulant treatment with heparin sodium injection can avoid coagulation of the filter in blood-filtration treatment, but heparin sodium injections can cause clinical symptoms such as spontaneous bleeding and fever, impeding the curative effects[15]. In this regard, studies in other countries using nafamostat injection for patients undergoing blood filtration showed that the drug has a rapid onset, short half-life, fast metabolism, and favorable anticoagulant effects, and that its effectiveness is better than that of ordinary anticoagulant drugs[16]. Consistent with these findings, our results showed that the total response rate in the control group was lower than that in the observation group ($P < 0.05$), indicating that the clinical efficacy of Nafamostat mesylate was better. Moreover, foreign studies have reported that the anticoagulant activity of Nafamostat mesylate is more than two times that of ordinary anticoagulant drugs, and because of its short half-life, it can improve the life of the filter[17]. Our results showed that while the two groups did not differ in the proportion of grade I cases ($P > 0.05$), the control group showed a lower proportion of grade 0 cases and a higher proportion of grade II and III cases than the observation group ($P < 0.05$), which was consistent with the findings of the previous studies and indirectly confirmed that the anticoagulant effects of Nafamostat mesylate are better than those of heparin sodium. This may be attributed to the delayed onset of the effects of heparin sodium and its long half-life, which cannot guarantee the life of the filter, potentially causing filter coagulation

Table 2 Response rates in the two groups

Group	Number of patients	Significant	Effective	Ineffective	Total efficacy rate
Observation group	33	22 (66.66)	9 (27.27)	2 (6.06)	31 (93.93)
Control group	32	7 (21.87)	15 (46.87)	10 (31.25)	22 (68.75)
χ^2	-	-	-	-	6.847
<i>P</i> value	-	-	-	-	0.008

Data are presented as *n* (%).

Table 3 Coagulation status in the two groups

Group	Number of patients	Grade 0	Grade I	Grade II	Grade III
Observation group	33	20 (60.60)	5 (15.15)	6 (18.18)	2 (6.06)
Control group	32	5 (15.62)	2 (6.06)	14 (43.75)	11 (34.37)
χ^2	-	13.887	1.339	0.498	8.140
<i>P</i> value	-	< 0.001	0.247	0.025	0.004

Data are presented as *n* (%).

Table 4 Coagulation indices in the two groups

Group	PT (s)		APTT (s)		TT (s)		INR (s)		FIB (g/L)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group (<i>n</i> = 33)	16.25 ± 0.26	12.35 ± 0.56 ^b	40.12 ± 0.13	36.65 ± 0.23 ^b	21.48 ± 0.89	17.56 ± 0.48 ^b	2.31 ± 0.13	0.94 ± 0.05 ^b	6.17 ± 0.19	5.26 ± 0.11 ^b
Control group (<i>n</i> = 32)	16.29 ± 0.33	15.48 ± 0.48 ^b	40.17 ± 0.19	39.48 ± 0.24 ^b	21.15 ± 0.78	20.03 ± 0.26 ^b	2.32 ± 0.19	2.01 ± 0.12 ^b	6.13 ± 0.56	3.26 ± 0.56 ^b
<i>t</i>	0.543	24.160	1.241	48.544	1.587	25.680	0.248	47.181	0.388	20.124
<i>P</i> value	0.588	< 0.001	0.219	< 0.001	0.117	< 0.001	0.804	< 0.001	0.699	< 0.001

^b*P* < 0.001 in comparison with the pre-treatment value. Data are presented as mean ± SD. PT: Prothrombin time; APTT: Activated partial thromboplastin time; TT: Thrombin time; INR: International normalized ratio; FIB: Fibrinogen.

Table 5 Hemoglobin level and platelet count in the two treatment groups

Group	Number of patients	PLT count (× 10 ⁹ /L)		HGB level (g/L)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	33	41.23 ± 2.08	41.45 ± 2.56	96.58 ± 1.23	96.88 ± 1.11
Control group	32	41.45 ± 1.98	41.88 ± 2.43	96.45 ± 1.08	96.78 ± 1.37
<i>t</i>	-	0.436	0.694	0.452	0.323
<i>P</i> value	-	0.664	0.490	0.652	0.747

Data are presented as mean ± SD. PLT: Platelet; HGB: Hemoglobin.

Table 6 Adverse reactions after treatment in the two groups

Group	Number of patients	Autogenous hemorrhage	Rash	Fever	Untoward effect
Observation group	33	1 (3.03)	0 (0.00)	0 (0.00)	1 (3.03)
Control group	32	6 (18.75)	0 (0.00)	1 (3.12)	7 (21.87)
χ^2	-	-	-	-	5.345
<i>P</i> value	-	-	-	-	0.027

Data are presented as *n* (%).

[18].

The results of this study showed that despite the absence of significant pre-treatment differences in the PT, APTT, TT, INR, and FIB level between the two groups ($P > 0.05$), the control group showed higher PT, APTT, TT and INR values and a lower FIB level than the observation group post-treatment ($P < 0.05$). In contrast, the PLT count and HGB levels did not differ significantly between the two groups ($P > 0.05$). These findings together demonstrate that while Nafamostat mesylate improved coagulation levels in patients better than heparin sodium, it had no obvious effect on the PLT count and HGB level, indicating a favorable safety profile. The PLT count and HGB level are often reduced by common heparin anticoagulant therapy, leading to the occurrence of severe anemia. In contrast, Nafamostat mesylate mainly inhibits various enzymes in the coagulation process to show good anticoagulation effects; thus, it only affects coagulation function and does not show obvious effects on the PLT count and HGB levels of the patients[19,20]. Moreover, a 3-yr retrospective study conducted abroad confirmed that naphlimostat can guarantee sufficient filter life without causing serious bleeding, fever, and other complications; thus, the study concluded that Nafamostat mesylate minimizes the risk of coagulation and is safe and effective, making it less risky than heparin sodium anticoagulant therapy[19]. The results of this study showed that the total number of adverse reactions in the observation group was lower than that in the control group ($P < 0.05$), which was consistent with the findings of the retrospective study and indicated that Nafamostat mesylate reduced the incidence of adverse reactions and had higher safety. However, the study still has some limitations. First, the findings may be biased due to the small sample size. Future studies could employ larger RCT trials to reduce bias and increase study reliability. Meanwhile, the long-term efficacy of patients should be evaluated and the treatment efficacy of different patient groups should be considered.

CONCLUSION

In conclusion, treatment with Nafamostat mesylate in patients with ESRD showed significantly improved treatment efficacy with high safety and high clinical potential.

ARTICLE HIGHLIGHTS

Research background

Recent studies on anticoagulation on dialysis in patients with renal failure suggest, Nafamostat mesylate, a broad-spectrum highly potent serine protease inhibitor with potent anticoagulation and antifibrous activity, with a significant anticoagulant effect.

Research motivation

In the early clinical stage of terminal renal failure, there are no obvious symptoms. With the progression of the disease, limb edema, fatigue, gastrointestinal bleeding and other symptoms gradually appear, and more serious and even consciousness disorders and cardiac arrest, seriously endangering the life of the patient.

Research objectives

Efficacy and safety of Nafamostat mesylate in patients with end-stage renal failure.

Research methods

It was divided into observation group and control group. The clinical efficacy indicators of the two groups were compared.

Research results

While the number of patients in grade 0 was lower in the control group, and the number of patients in grades II and III was higher in the control group ($P < 0.05$). The post-treatment prothrombin time, activated partial thromboplastin time, thrombin time, and international normalized ratio values in the control group were higher than those in the observation

group.

Research conclusions

The use of Nafamostat mesylate in patients with end-stage renal failure can significantly improve the treatment effect and have high safety and clinical value.

Research perspectives

We discuss the efficacy and safety of Nafamostat mesylate in patients with end-stage renal failure.

FOOTNOTES

Co-first authors: Kun Liu and Zhen-Hua Li

Author contributions: Liu K and Li ZH designed the research; Liu K contributed new reagents/analytic tools; Liu K and Li ZH analyzed the data; Liu K and Li ZH wrote the paper. Liu K and Li Z has co-first authors are threefold. First, Liu K and Li ZH designed and conceptualized the study. Second, Liu K and Li ZH participated in discussion development and provided expert guidance. Third, Liu K and Li ZH put in the same effort throughout the study, and in summary, we believe that Li ZH can be tagged as co-first author in our manuscript.

Institutional review board statement: This study protocol was approved by the General Hospital of The Yangtze River Shipping, Wuhan Brain Hospital, and all the families have voluntarily participated in the study and have signed informed consent forms.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declared no conflict of interest existing in this paper.

Data sharing statement: Data generated from this investigation are available upon reasonable request from the corresponding author.

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S-Editor: Gao CC

L-Editor: A

P-Editor: Zhao S

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