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ORIGINAL ARTICLE

Nafamostat mesilate for anticoagulation in continuous renal replacement therapy

Seun Deuk Hwang, Yu Kyung Hyun, Sung Jin Moon, Sang Choel Lee, Soo Young Yoon

Division of Nephrology, Department of Internal Medicine, College of Medicine, Kwandong University, Goyang - Korea

ABSTRACT

Purpose: *During continuous renal replacement therapy (CRRT), anticoagulation of the extracorporeal circuit is required. The aim of this study was to assess the efficacy and safety of nafamostat mesilate, a serine protease inhibitor, compared with heparin.*

Methods: *We retrospectively studied 222 patients treated with CRRT in the intensive care unit (ICU). Clinical and filter-related data were extracted.*

Results: *We reviewed the medical records of the patients treated with CRRT. Initial anticoagulation methods were 56 heparin and 25 nafamostat mesilate; 10 patients received infused heparin systemically, and 131 patients were treated without anticoagulation. Total number of filters used was 1,236. Median filter lifespan with nafamostat mesilate was significantly greater than heparin (24.3 vs. 17.5 hours, p<0.001) and Kaplan-Meier survival plots revealed the longer survival of the circuits using nafamostat mesilate than heparin or without anticoagulation. In Cox proportional hazard models, nafamostat mesilate predicted longer filter survival. Although nafamostat mesilate induced activated partial thromboplastin time prolongation in 11 circuits (5.4%), bleeding episodes were not increased.*

Conclusions: *Nafamostat mesilate anticoagulation was associated with prolonged filter survival compared with heparin. These data suggest that nafamostat mesilate is a good choice for anticoagulant with prolonged filter survival during CRRT in critically ill patients.*

KEY WORDS: *Nafamostat mesilate, Continuous Renal Replacement Therapy, Anticoagulation*

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INTRODUCTION

Acute kidney injury (AKI) develops in up to 36% to 67% of critically ill patients depending on the definition used (1-3), and is associated with a poor prognosis (4). Despite recent advances in the management of critically ill patients, the mortality rate in intensive care unit (ICU) patients with AKI remains high (5, 6). As an effort to reduce this high mortality rate, many physicians offer renal replacement therapy to the patients with AKI in ICUs. Continuous renal replacement therapy (CRRT) is the preferred choice over intermittent hemodialysis (IHD) because it can remove more solutes and does not exaggerate hemodynamic instability (7, 8). One of the main drawbacks with CRRT is the requirement for anticoagulation in order to prevent the blood from clotting. The ideal anticoagulant should provide optimal anti-thrombotic activity with minimal bleeding complications and negligible systemic effects. To this aim, it should have a short half-life, and be easily reversed. Moreover, monitoring methods of the anticoagulant effect should be simple and readily available (9). Until now, unfractionated heparin has been the mainstay of anticoagulation for CRRT (10), especially in Asian countries, including Korea. However, it is associated with a risk of life-threatening hemorrhage and thrombocytopenia (11, 12).

Nafamostat mesilate (6-amidino-2-naphthyl para-guanidinobenzoate) is a synthetic serine protease inhibitor and its biological half-life is approximately 8 minutes (13, 14). Although

use of nafamostat mesilate is increasing, there are few studies reporting the safety and efficacy of this drug (15, 16).
The aim of this study is to characterize the efficacy of nafamostat mesilate anticoagulation compared with heparin or without anticoagulation on filter life span in patients treated with CRRT. We hypothesized that nafamostat mesilate lengthens the life span of filter with minimal side effects.

PATIENTS AND METHODS

Patients

We reviewed the medical records of the patients treated with CRRT in the ICUs of the Kwandong University Myongji Hospital, Goyang, Korea from January 2004 to December 2008. We included patients aged between 20 and 80 years old and excluded the patients who died within the first filter use. We also excluded the patients who ingested paraquat because we provided CRRT to all the patients who ingested paraquat regardless of whether they had AKI or not and they were usually infused with heparin due to absence of coagulopathy. In addition, they were transfused RBCs as antioxidants, which could interfere with the filter survival. We extracted the data including demographics, causes of ICU admission, severity scores at initiation of CRRT including APACHE II and SAPS II, blood urea nitrogen (BUN), creatinine and coagulation profile including platelet count, prothrombin time and activated partial thromboplastin time at CRRT start, anticoagulation methods, and doses of anticoagulants. The study protocol was approved by the institutional review board of Myongji hospital.

CRRT technique

All patients were treated with continuous veno-venous hemodiafiltration using the PRISMA quadruple pump system (Gambro, Lund, Sweden). Veno-venous access was obtained by inserting a double-lumen catheter (Mahurkar Catheter Kit 11.5 FR 13.5-19 cm, Quinton Instrument, Bothell, WA, USA) in a central vein. Either AN69 or HF1000 (Gambro, Lund, Sweden) hollow-fiber hemofilters were used. Commercially-prepared, lactate-free, bicarbonate-buffered fluid (Hemosol; Gambro, Lund, Sweden) was used as dialysate and replacement solution. The replacement fluid and dialysate flow rate were set as 1,000 ml/h in all the patients and ultrafiltration rate was individualized. Replacement fluid was infused in pre-circuit mode. The blood flow was kept at 100 ml/min to 150 ml/min.

Anticoagulation

Patients were divided into four groups based on the anticoagulation method: heparin, nafamostat mesilate, systemic heparinization, and no anticoaluation. In most CRRT cases, we used heparin; however, in patients with obvious or suspicious bleeding, we conducted CRRT without anticoagulation. Since 2007, we have been using nafamostat mesilate in some patients who have bleeding or coagulopathy and are able to pay for this drug. In the heparin group, filters were primed with 2 L of isotonic saline containing 10,000 U/l of heparin, and then 1 U/kg to 20 U/kg per hour of heparin was given. The goal of heparinization was to maintain systemic pre-filter aPTT between 45 and 55 seconds (1.5 × control) as described in a previous report (17). In the nafamostat mesilate group, filters were primed with 2 L of isotonic saline containing 50 mg/l of nafamostat mesilate, and then 10 mg/h to 30 mg/h were given. Patients in the group of systemic heparinization received continuous infusion of heparin intravenously for the purpose of systemic anticoagulation due to acute coronary syndrome or cerebral infarction. All filters were flushed every 1 h to 2 h with 100 mL of isotonic saline.

Outcome measures

Primary outcome was life span of each hemofilter and secondary outcomes included coagulation parameters, side effects of anticoagulants such as hemorrhagic episodes, and survival. A hemorrhagic episode was defined as observation of a site of gross bleeding with decrease in blood pressure or as a patient requiring transfusion or a decrease in hemoglobin level more than 2 g/dl within 24 h as in a previous report by Wu et al (18). We regarded the bleeding episodes which occurred after initiation of each filter as complications of the anticoagulants used for the filter.

Statistical analysis

Data were expressed as mean ± standard deviation. We compared baseline characteristics among patients based on their initial anticoagulation method and then all the variables of each filter according to the anticoagulation method. Continuous data were compared using analysis of variance (ANOVA) test, and categorical data were expressed

as numbers with proportions using Pearson's chi-squared test and Fisher's exact test.

Finally, we performed survival analysis using the Kaplan-Meier survival curve and the Cox proportional hazard model to compare the survival between groups with each anticoagulation method. A two-tailed p value <0.05 defined statistical significance for all analyses. Statistical analyses were conducted using SPSS 19.0 (IBM, Chicago, IL, USA).

RESULTS

A total 334 patients were treated with CRRT during the study period. Among them, we excluded 112 patients because 48 ingested paraquat and 64 did not have available CRRT records. Finally, we reviewed the medical records of the 222 patients treated with CRRT.

Clinical characteristics of the patients

Initial anticoagulation methods were 56 heparin and 25 nafamostat mesilate; 10 patients received infused heparin systemically, and 131 patients were treated without anticoagulation. The total number of filters used was 1,236. The patients in systemic anticoagulation tended to be older than patients in other groups but there was no significant difference. There were no differences in sex, causes of ICU admission, days from ICU admission to CRRT, days on mechanical ventilation, days of inotropic use, APACHE-II, SAPS-II, BUN, creatinine, platelet, and prothrombin time. Activated partial thromboplastin time was longer in the nafamostat mesilate group than in that of other groups (54.9 ± 25.3 in nafamostat mesilate, 50.7 ± 21.2 in without anticoagulation, 41.3 ± 13.4 in heparin, and 45.9 ± 19.4 seconds in systemic heparinization; p = 0.020). Mortality was not different among 4 groups (Tab. I).

TABLE I - CLINICAL CHARACTERISTICS OF THE PATIENTS ACCORDING TO INITIAL ANTICOAGULATION

	Total (n = 222)	No (n = 131)	Heparin (n = 56)	Nafamostat mesilate (n = 25)	Systemic (n = 10)	p-value
Age (years)	67.3 ± 13.9	66.3 ± 15.0	69.5 ± 13.0	65.2 ± 11.0	73.6 ± 10.1	0.21
Male (%)	123 (55.4)	77 (58.8)	25 (44.6)	16 (64.0)	5 (50)	0.25
Cause of ICU admission (%)						0.84
Cardiac	75 (33.8)	45 (34.4)	17 (30.4)	7 (28.0)	6 (60.0)	
Neurological	36 (16.2)	22 (16.8)	7 (12.5)	6 (24.0)	1 (10.0)	
Sepsis	44 (19.8)	22 (16.8)	13 (23.2)	6 (24.0)	3 (30.0)	
Gastrointestinal	25 (11.3)	16 (12.2)	6 (10.7)	3 (12.0)	0	
Renal	16 (7.2)	8 (6.1)	6 (10.7)	2 (8.0)	0	
Respiratory	8 (3.6)	6 (4.8)	2 (3.6)	0	0	
Others	18 (8.1)	12 (9.2)	5 (8.9)	1 (4.0)	0	
Days from ICU admission to CRRT	5.5 ± 6.7	5.4 ± 6.4	5.5 ± 8.1	6.6 ± 6.2	3.8 ± 4.2	0.71
Days on CRRT	6.0 ± 6.6	5.9 ± 6.3	5.9 ± 7.7	7.2 ± 6.3	5.1 ± 3.8	0.77
Days on mechanical ventilation	9.0 ± 18.0	9.2 ± 21.3	8.6 ± 13.0	10.1 ± 10.0	6.2 ± 9.3	0.94
Days of inotropics use	7.5 ± 7.2	7.2 ± 7.2	7.2 ± 9.1	8.9 ± 7.2	8.9 ± 8.5	0.71
APACHE-II	24.9 ± 6.1	24.9 ± 6.1	24.3 ± 5.8	25.6 ± 7.1	26.2 ± 6.2	0.72
SAPS-II	47.2 ± 17.0	48.7 ± 16.5	45.8 ± 17.3	45.5 ± 18.6	40.2 ± 16.9	0.35
BUN (mg/dl)	65.3 ± 57.9	68.1 ± 68.1	60.4 ± 33.2	70.8 ± 52.4	42.7 ± 21.6	0.49
Creatinine (mg/dl)	4.2 ± 3.2	4.3 ± 3.4	4.1 ± 3.1	4.2 ± 2.9	4.1 ± 2.9	0.99
Platelet ($\times 10^3/mm^3$)	167.0 ± 124.0	164.6 ± 139.1	180.0 ± 93.1	136.9 ± 108.4	200.3 ± 95.4	0.42
Prothrombin time (sec)	18.0 ± 15.2	19.5 ± 18.5	14.5 ± 3.8	19.3 ± 13.0	14.2 ± 2.8	0.21
aPTT (sec)	48.7 ± 20.5	50.7 ± 21.2	41.3 ± 13.4	54.9 ± 25.3	45.9 ± 19.4	0.020
Death (%)	133 (59.9)	84 (64.1)	29 (51.8)	15 (60.0)	5 (50.0)	0.41

ICU, intensive care unit; CRRT, continuous renal replacement therapy; APACHE-II, acute physiology and chronic health evaluation; SAPS-II, a new simplified acute physiology score; BUN, blood urea nitrogen, aPTT, activated partial thromboplastin time.

Characteristics of filters by anticoagulation method

Among 1,236 filters, 640 (51.8%) were used without anticoagulation, 341 (27.6%) with heparin, 204 (16.5%) with nafamostat mesilate, and 51 (4.1%) were used in systemic anticoagulation with heparin. Mean dosage was 307.9 ± 36.2 U/h for heparin and 16.5 ± 1.0 mg/h for nafamostat mesilate. The filters used with nafamostat mesilate had lower blood flow rates and less fluid removal than others. Flushing with saline was performed less frequently to the filters with nafamostat mesilate (1.22 ± 0.62 vs. 1.04 ± 0.47 without anticoagulation, 1.05 ± 0.53 with heparin, and 1.00 ± 0.28 with systemic heparinization; p<0.001) (Tab. II).

Clotting variables and life span of the filters

We collected the data of clotting variables at the starting time of each filter. While 30% of the filters without anticoagulation and 20% of the filters with nafamostat mesilate had pre-existing bleeding, mainly in the gastrointestinal tract and the cerebrum respectively, 5.6 % of the filters with heparin and 11.7% of the filters with systemic heparinization had underlying bleeding. Major vascular access sites were the femoral vein and the internal jugular vein, regardless of anticoagulation method. Initial platelet count was lower and prothrombin time was longer in filters without anticoagulation and with nafamostat mesilate than in other groups. Activated partial thromboplastin time was more prolonged in filters with nafamostat mesilate and systemic anticoagulation. The life span of individual filter was longer in the nafamostat mesilate group (24.3 ± 17.8 vs. 16.8 ± 14.5 without anticoagulation, 17.5 ± 15.8 with heparin, and 19.4 ± 16.8 with systemic heparinization; p<0.001) (Tab. III). During the study period, we tried to maintain filter function as long as possible within 72 hours as per manufacturer's instructions. Among 1,236 filters, only 6 were stopped for procedures such as CT scan, EEG, and angiography (3 in filters without anticoagulation, 2 in heparin, and 1 in nafamostat mesilate) and we used all the data of all the filters in analysis including these. Kaplan-Meier survival plots revealed that the survival of the circuits using nafamostat mesilate was longer than with heparin or with no anticoagulation (Fig. 1, p<0.001). In Cox proportional hazard models, low blood flow rate, high fluid removal rate, and high platelet counts predicted filter clotting. Regardless of the coagulation profile or the CRRT prescription, saline flushing without anticoagulation predicted shorter filter survival and nafamostat mesilate predicted longer filter survival compared with heparin (Tab. IV).

Complications of each anticoagulation method

Each anticoagulation method had 0.9% to 2.6% hemorrhagic complications and there was no difference in occurrence of hemorrhagic episodes between anticoagulation methods. The activated partial thromboplastin time was prolonged during the use of anticoagulants in 5.4% of patients with nafamostat mesilate and in 7.8% of systemic anticoagulation showed (Tab. V).

DISCUSSION

This study shows that nafamostat mesilate lengthened the filter life span with similar side effects to heparin or no anticoagulation in CRRT. Unlike heparin, nafamostat

TABLE II - CHARACTERISTICS OF FILTERS BY ANTICOAGULATION USED

	No	Heparin	Nafamostat mesilate	Systemic	p-value
Number of filters (%)	640 (51.8)	341 (27.6)	204 (16.5)	51 (4.1)	
Dose of maintaining anticoagulant	-	307.9 ± 36.2 (U/h)	16.5 ± 1.0 (mg/h)	variable	
Blood flow rate (ml/min)	123.9 ± 17.0	123.2 ± 18.5	115.2 ± 16.4	122.8 ± 15.0	<0.001
Dialysate flow rate (ml/h)	1,000	1,000	1,000	1,000	
Replacement flow rate (ml/h)	1,000	1,000	1,000	1,000	
Fluid removal (ml/h)	210.8 ± 80.3	203.7 ± 81.3	187.5 ± 75.8	215.7 ± 73.3	0.003
Flushing interval (h)	1.04 ± 0.47	1.05 ± 0.53	1.22 ± 0.62	1.00 ± 0.28	<0.001

TABLE III - CLOTTING VARIABLES AT THE STARTING TIME OF EACH FILTER AND FILTER LIFE SPAN

	No (n = 640)	Heparin (n = 341)	Nafamostat mesilate (n = 204)	Systemic (n = 51)	p-value
Underlying bleeding (%)					<0.001
Cerebral	24 (3.8)	3 (0.9)	24 (11.8)	0	
Gastrointestinal	131 (20.5)	14 (4.1)	15 (7.4)	2 (3.9)	
Lung	3 (0.5)	0	1 (0.5)	0	
Others	33 (5.2)	2 (0.6)	2 (1.0)	4 (7.8)	
Access site (%)					0.13
Femoral vein	326 (50.9)	161 (47.2)	108 (52.9)	19 (37.3)	
Internal jugular vein	306 (47.8)	180 (52.8)	96 (47.1)	31 (60.8)	
Permanent catheter	5 (0.8)	0	0	0	
Arteriovenous fistula	3 (0.5)	0	0	1 (2.0)	
Platelet ($\times 10^3/mm^3$)	101.7 ± 85.7	133.4 ± 80.4	98.7 ± 77.6	134.6 ± 78.5	<0.001
Prothrombin time (sec)	21.3 ± 19.1	14.5 ± 10.1	19.3 ± 11.3	14.2 ± 6.6	0.014
aPTT (sec)	56.8 ± 24.6	56.7 ± 28.2	74.0 ± 30.3	66.1 ± 32.3	<0.001
Filter life (hours)	16.8 ± 14.5	17.5 ± 15.8	24.3 ± 17.8	19.4 ± 16.8	<0.001

aPTT, activated partial thromboplastin time.

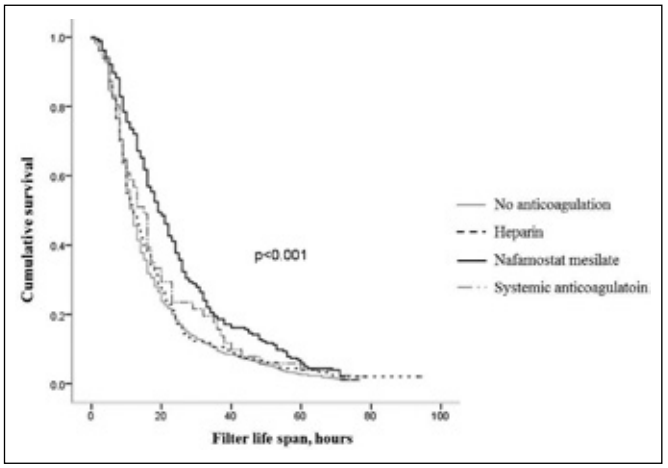

Fig. 1 - *Comparison of CRRT filter life with heparin, systemic anticoagulation, nafamostat mesilate, or no anticoagulation (p<0.001).*

mesilate has potent inhibitory activity with respect to plasmin, thrombin, coagulation factors in the active form (XIIa, Xa), kallikrein, complement factor (C1r, C1s), and trypsin without dependence on anti-thrombin III (19). In addition, nafamostat mesilate has direct inhibitory effects on platelet aggregation via suppression of activated glycoprotein IIb/IIIa expression, which enables it to bind to fibrinogen (20). While heparin has a sustained systemic effect for several hours after withdrawal, nafamostat mesilate is rapidly metabolized in the liver and blood with an eight-minute half-life.

Given that these two characteristics—anti-thrombotic activity and short half-life—are essential for anticoagulation in renal replacement therapy, nafamostat mesilate has been used as an anticoagulant during hemodialysis in patients with bleeding or coagulopathy. In 1988, Pak et al applied nafamostat mesilate to 33 patients who were undergoing hemodialysis and susceptible to bleeding in order to avoid the use of heparin (21). In that study, they found that the concentration and anticoagulant activity of this drug were stable during hemodialysis and its anticoagulant activity decreased immediately after hemodialysis. After this report, lots of studies have been performed using nafamostat mesilate in hemodialysis patients at high risk for bleeding (22-24).

On the other hand, there are few reports about the use of nafamostat mesilate in critically ill patients because this drug was originally made in Japan and is available only in several countries, including Japan and Korea. Recently, Maruyama et al reported a three-year retrospective cohort experience of nafamostat mesilate in CRRT (15). The authors reported 20.8 hours of filter survival with this drug. Subsequently, Baek et al reported that the use of

TABLE IV - COX PROPORTIONAL HAZARD MODELS PREDICTING FILTER CLOTTING

Variable	Coefficient estimate	Hazard ratio	95% Confidence Interval	
Systolic BP	-0.002	0.998	0.995	1.001
Diastolic BP	0.001	1.001	0.995	1.008
Blood flow rate	-0.006	0.994	0.989	0.999
Fluid removal	0.001	1.001	1.000	1.002
Flushing interval	-0.068	0.934	0.800	1.091
Anticoagulation				
Heparin		1		
None	0.260	1.297	1.074	1.567
Nafamostat mesilate	-0.375	0.687	0.537	0.880
Systemic	-0.293	0.746	0.502	1.107
Access site				
Internal jugular vein		1		
Femoral vein	-0.098	0.907	0.781	1.053
Permanent catheter	-0.009	0.991	0.357	2.750
Arteriovenous fistula	-0.189	0.828	0.304	2.255
Platelet	0.003	1.003	1.002	1.004
Prothrombin time	-0.002	0.998	0.994	1.002
aPTT	0.000	1.000	0.997	1.003

aPTT, activated partial thromboplastin time.

TABLE V - FREQUENCIES OF HEMORRHAGIC COMPLICATIONS AND COAGULATION PROFILE ABNORMALITIES OF EACH ANTICOAGULATION METHOD

	No (n = 640)	Heparin (n = 341)	Nafamostat mesilate (n = 204)	Systemic (n = 51)	p-value
Hemorrhage (%)	17 (2.6)	3 (0.9)	4 (2.0)	1 (1.9)	0.71
Cerebral (%)	1 (0.2)	-	-	-	
GI (%)	14 (2.2)	1 (0.3)	3 (1.5)	1 (2.0)	
Lung (%)	1 (0.2)	1 (0.3)	1 (0.5)	-	
Others (%)	1 (0.2)	1 (0.3)	-	-	
Coagulation profile abnormalities (%)	6 (0.9)	10 (3.0)	11 (5.4)	4 (7.8)	<0.001
Thrombocytopenia (%)	2 (0.3)	3 (0.9)	0	0	
aPTT prolongation (%)	4 (0.6)	5 (1.5)	11 (5.4)	4 (7.8)	
Thrombocytopenia and aPTT prolongation (%)	0	2 (0.6)	0	0	

GI, gastrointestinal; aPTT, activated partial thromboplastin time.

nafamostat effectively lengthened the filter survival without an increase in RBC transfusion (16). In their report, the filter lifespan was shorter than that of our study (19.8 h vs. 24.3 h). We think the short hemofilter lifespan might be caused by the low dosage of nafamostat used (10 mg/h). These recent studies evaluated the efficacy and safety of nafamostat mesilate, however, they never compared nafamostat with other anticoagulants.

Usually, in CRRT, we use unfractionated heparin as an anticoagulant. The advantages of heparin use are that it is inexpensive, familiar to physicians, easy to administer, simple to monitor, and reversible with protamine. However, heparin has several side effects such as life-threatening hemorrhage, thrombocytopenia, osteoporosis, hyperlipidemia, aldosterone suppression, and allergic reaction (25, 26). Due to these side effects of heparin, citrate is gaining popularity during CRRT in ICU in Western countries. According to a recent meta-analysis, the efficacy of citrate as an anticoagulant for CRRT was similar to heparin with decreased risk of bleeding (18). The disadvantage of citrate use is that frequent monitoring of electrolytes, ionized calcium, and acid-base status is required, because it has the potential to cause hypernatremia, metabolic alkalosis, and systemic ionized hypocalcemia. In addition, patients with liver failure and lactic acidosis may have difficulty with citrate metabolism and develop citrate toxicity including decreased ionized calcium, decreased total calcium and metabolic acidosis (27, 28). Although there are many reports on the safety of citrate use in CRRT (29, 30), only a few centers use citrate in Korea. We do not use citrate in our hospital, either, so we could not compare nafamostat mesilate with citrate in this study.

CRRT has been performed without anticoagulation as well, often combined with saline flushes of 50 ± 100 mL every 1 to 2 h in patients with bleeding or a disturbed coagulation system (10, 31). In the present study, we saw more prolonged aPTT in patients with no anticoagulation and with nafamostat mesilate than in those with heparin or systemic anticoagulation. Recently, Panphanpho et al reported that the use of saline flush in the pre-filter site of the CRRT circuit did not provide any benefit for circuit clotting prevention in patients at a high-risk of bleeding who required CRRT without anticoagulants (32). In our study, we applied saline flush at 1-hour intervals in almost all patients, so we could compare these three methods: no anticoagulation; heparin; and nafamostat mesilate without interference of saline flushing. Although the interval of saline flushing was slightly longer and blood flow rate was slower in the nafamostat mesilate group than in that of other groups, the filters using nafamostat mesilate had a longer life span than others.

The use of nafamostat mesilate has several limitations. Since nafamostat mesilate was reported to be adsorbed by negatively-charged membranes such as polyacrylonitrile (AN69) (33), we used polyarylethysulfone membrane for nafamostat mesilate. In addition, unfortunately, nafamostat mesilate has no antidote and several side effects (agranulocytosis, hyperkalemia, and anaphylactoid reactions) have been described (34-37). Recently, Maruyama et al reported that aPTT was lengthened during the first 24 hours of nafamostat mesilate use, however, no patients experienced any major bleeding. In the present study, aPTT was prolonged in the nafamostat mesilate group compatible with systemic anticoagulation group. However, nafamostat mesilate did not increase the risk of bleeding. Finally, this drug is still not cheap. It costs approximately US$20 for a 50 mg vial in Korea. Using 16.5 mg/h of nafamostat, US$160 is needed per day. If we use heparin, we may spend no more than US$5 for anticoagulation. However, since we have to pay US$200 for each filter, we can save money through prolongation of filter survival.

This study has two limitations: first, it was a retrospective, single-center study; and second, the filter material used for nafamostat mesilate was different from that used for the other anticoagulants. This could be another reason for the longer filter life for nafamostat. However, there is no report comparing filter survival between AN69 and HF1000. To our knowledge, this is the first study of nafamostat mesilate with comparisons to other anticoagulants, including without the use of any anticoagulation. Therefore, we hope that this study can provide valuable information about this little-known drug.

Since nafamostat mesilate lengthens the filter life span with similar side effects to heparin or no anticoagulation in CRRT, we suggest that this drug can be used safely in patients at a high risk for bleeding.

Conflict of Interest Statement: None to report.

Address for correspondence:
Soo Young Yoon, MD, PhD
697-24, Hwajung-dong
Duckyang-gu, Goyang-si, Gyeonggi-do, Korea
e-mail: diva502@kd.ac.kr

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