IJAO
ISSN 0391-3988

Int J Artif Organs 2016; 39(1): 16-21
DOI: 10.5301/ijao.5000465

ORIGINAL ARTICLE

Comparison of nafamostat mesilate and unfractionated heparin as anticoagulants during continuous renal replacement therapy

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ABSTRACT

Purpose: Nafamostat mesilate (NM) can be used as a regional anticoagulant for continuous renal replacement therapy (CRRT). The primary aim of this study was to assess the association of the use of NM with risk of bleeding complications and compare it with the use of unfractionated heparin (UFH).

Methods: We conducted a single-center retrospective observational study. We included adult patients who required CRRT in our intensive care unit from 2011 to 2013. The primary outcome was the risk of bleeding complications during CRRT and the secondary outcome was filter life for the first filter of CRRT.

Results: We included 101 patients (76 with NM, 25 with UFH). Among the 101 patients, use of NM tended to be associated with lower risk of bleeding complications (6.6% vs. 16%; odds ratio, 0.37; p = 0.16). Propensity score matching generated 30 patients with NM and 15 patients with UFH with well-balanced baseline characteristics. Among the propensity score-matched cohorts, use of NM was significantly associated with decreased risk of bleeding complications (3.3% vs. 27%; odds ratio, 0.09; p = 0.04). In multivariate logistic analysis using the inverse probability of treatment weighting for sensitive analysis, the use of NM was independently associated with reduced risk of bleeding complications (p = 0.02). The median filter life was not significantly different for patients with NM and patients with UFH (25.5 hours vs. 30.5 hours, p = 0.16).

Conclusions: In our retrospective analysis, the use of NM as an anticoagulant during CRRT was associated with decreased incidence of bleeding complications compared with the use of UFH.

Keywords: Bleeding complications, Continuous renal replacement therapy, Filter life, Nafamostat mesilate, Unfractionated heparin

Introduction

Acute kidney injury is common in critically ill patients (1). Continuous renal replacement therapy (CRRT) has been commonly used in critically ill patients, especially in those with hemodynamic instability (2). Administration of an anticoagulant during CRRT may be required to reduce the downtime due to filter clotting (3). However, it can expose patients to the risk of bleeding, which may lead to the requirement of additional hemostasis intervention and transfusion (4, 5).

Unfractionated heparin (UFH) is still the most common anticoagulant used worldwide to maintain CRRT, although other anticoagulants including citrate, low molecular weight heparin, prostacyclin and hirudin have been used (6, 7). Nafamostat mesilate (NM) is a synthetic serine protease inhibitor with a short half-life (8 minutes) (8). Thus, NM might be an alternative anticoagulant during CRRT and might be useful for patients with a risk of bleeding (9).

NM was introduced as an alternative anticoagulant for CRRT in 1990, but its use has been mainly limited to Japan (9). In 2005, NM was licensed in Korea and the use of NM in CRRT has been increasing. However, there are few reports on a comparison of NM with UFH in this setting. Therefore, we performed a retrospective observational study to assess the risk (bleeding complications) and benefit (filter life) of NM and compared them with those of UFH.

Accepted: January 15, 2016
Published online: February 9, 2016

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Methods

Study design

We conducted a single-center, retrospective, observational study. The Kobe University Hospital Ethics Committee approved this investigation. The committee waived the need for informed consent for studies involving the use of the database. The main objective of this study was to compare the incidences of bleeding complications during CRRT in patients receiving NM and patients receiving UFH.

Patients

We screened all adult critically ill patients who required CRRT in our intensive care unit (ICU) from January 2011 to December 2013. The size of our ICU is 36 beds and the number of admissions per year is approximately 3,000 patients. We included patients in whom NM or UFH was exclusively used as the anticoagulant for CRRT. Patients who required additional extracorporeal intervention including extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pumping (IABP) were excluded from the study. Patients for whom both NM and UFH were used simultaneously and patients who were administered other anticoagulants including gabexate mesilate and urokinase were also excluded.

Anticoagulation

Specialist intensive care physicians decided whether NM or UFH would be administered as an anticoagulant for CRRT. Both anticoagulants were given prefilter into the CRRT circuit, and the starting doses were 20 mg/h for NM and 400 IU/h for UFH without bolus administration. The goal of anticoagulation was to maintain systemic prefilter activating clotting time (ACT) at approximately 150 seconds. ACT was measured 1 hour after the change of dose and as clinically required.

Data collection

We collected demographic information on age, sex, weight, acute physiology and chronic health evaluation (APACHE) II score, post-surgical admission, reason for ICU admission, the presence of neoplasia, and estimated glomerular filtration rate (GFR) (10), total bilirubin levels and the presence of sepsis (11) at commencement of CRRT. We also collected data for daily hemoglobin levels, serum creatinine levels, and coagulation laboratory measurements; platelet count, prothrombin time-international normalized ratio (PT-INR), and activated partial thromboplastin time (aPTT).

Primary and secondary outcomes

The primary outcome of this study was the incidence of clinically significant bleeding complications during CRRT. Clinically significant bleeding was defined as bleeding that required transfusion of 2 units or more of packed red blood cells or bleeding accompanied by a decrease in hemoglobin level of 2 g/dL or more as previously reported (12). The secondary outcome was filter life for the first filter of CRRT. Time to filter failure was measured from the starting time to the time of filter clotting or elective discontinuation (e.g., computed tomography or surgery).

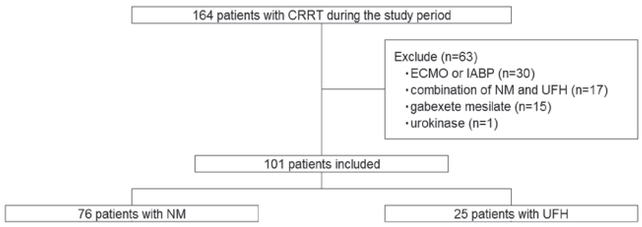

Fig. 1 - Study flow. 164 patients required CRRT and 61 patients who met the exclusion criteria were excluded. Ultimately, 101 patients were included in this study (76 patients with NM, 25 patients with UFH). CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pumping; NM = nafamostat mesilate; UFH = unfractionated heparin.

Statistical analysis

Data are expressed as median (25-75% interquartile range) or n (%). Data in the 2 groups were compared using the Mann-Whitney *U* test or Fisher's exact test. Confounding factors in baseline characteristics were addressed using propensity score analysis. To calculate the propensity score, a logistic regression model was fitted with the administration of NM as a dependent outcome. We used all measured baseline characteristics as covariates for this model: age, sex, weight, post-surgical admission and coagulation function measures (platelet count, PT-INR and aPTT) before commencement of the first CRRT. A previously reported method for selection of possible confounders was used for this propensity score model (13). A 2:1 matching was performed using a caliper of 0.03 of the logit of the propensity score. The baseline characteristics and outcomes of the patients that matched were compared using the Mann-Whitney *U* test or Fisher's exact test.

For sensitive analysis, we further developed a multivariate logistic model using the inverse probability of treatment weighting (IPTW) to estimate the independent association of the use of NM for the risk of bleeding complications in all patients.

We performed filter life analysis using the Kaplan-Meier method and log-rank test. Furthermore, multivariate analysis of filter life was assessed by the Cox proportional hazards model using IPTW and propensity score. A p-value less than 0.05 was defined as statistically significant for all analyses. Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 20.0.

Results

Study flow

During the study period, 164 critically ill patients required CRRT (Fig. 1). We excluded 30 patients who also simultaneously required ECMO (n = 17) or IABP (n = 13). We also excluded 17 patients for whom both NM and UFH were used at the same time and 15 patients for whom gabexate mesilate

TABLE I - Patient demographics

	Before matching			After matching		
	Unfractionated heparin (n = 25)	**Nafamostat mesilate (n = 76)**	**p-value**	**Unfractionated heparin (n = 15)**	**Nafamostat mesilate (n = 30)**	**p-value**
Age (years)	79 (70-83)	76 (67-82)	0.60	80 (66-83)	75 (64-81)	0.22
Sex (Male) (%)	22 (88)	49 (64)	0.05	12 (80)	25 (83)	0.99
Weight (kg)	60 (55-65)	54 (47-62)	0.02	58 (54-64)	54 (47-67)	0.21
APACHE II	18 (14-21)	20 (17-22)	0.1	19 (16-22)	20 (17-21)	0.99
Surgical admission	5 (20)	43 (56.6)	0.002	4 (26.7)	7 (23.3)	0.81
Post-Elective operation (%)	1 (4)	24 (31.6)	0.006	0 (0)	4 (13.3)	0.14
Post-Emergency operation (%)	4 (16)	19 (25)	0.35	4 (26.7)	3 (10)	0.15
Reason for ICU admission (%)			0.65			0.73
Neurological	0 (0)	4 (5.3)		0 (0)	2 (6.7)	
Cardiovascular	18 (72)	47 (61.8)		8 (53.3)	16 (53.3)	
Respiratory	1 (4)	7 (9.2)		1 (6.7)	1 (3.3)	
Gastrointestinal	1 (4)	2 (2.6)		1 (6.7)	4 (13.3)	
Renal	4 (16)	9 (11.8)		4 (26.7)	4 (13.3)	
Others	1 (4)	7 (9.2)		1 (6.7)	3 (10)	
Patients with neoplasia (%)	0 (0)	5 (6.6)	0.19	0 (0)	1 (3.3)	0.47
eGFR at the commencement of CRRT (ml/min/1.73 m^2)	16.3 (10.6-27.4)	16.3 (7.9-25.7)	0.39	17 (10.5-26.4)	17.3 (8.2-30.0)	0.73
Total bilirubin levels at the commencement of CRRT (mg/dL)	1.0 (0.5-1.5)	0.7 (0.4-1.0)	0.12	1.1 (0.5-1.5)	0.8 (0.4-1.5)	0.25
The presence of sepsis at the commencement of CRRT (%)	9 (36)	25 (33)	0.76	5 (33)	12 (40)	0.66
Serum creatinine levels at the commencement of CRRT(mg/dL)	3.4 (2.3-4.8)	3.6 (2.3-6.5)	0.35	3.2 (2.3-5.3)	3.9 (2.0-6.1)	0.73
Hemoglobin levels at the commencement of CRRT (g/dL)	9.6 (8.5-10.2)	9.4 (8.2-10.4)	0.80	9.2 (8.4-9.9)	9.2 (8.0-10.6)	0.93
Coagulation tests before commencement of CRRT						
Plt ($\times 10^4 \mu l$)	17.8 (6.5-20.5)	9.5 (6.2-14.8)	0.04	14.7 (5.8-21.0)	11.3 (7.2-20.1)	0.74
aPTT (sec)	38 (30-48)	31 (28-38)	0.09	42 (33-51)	34 (29-49)	0.17
PT-INR	1.1 (1.1-1.4)	1.1 (1.0-1.3)	0.13	1.2 (1.0-1.5)	1.1 (1.0-1.6)	0.53
Propensity score	0.40 (0.23-0.58)	0.13 (0.06-0.34)	<0.001	0.27 (0.14-0.46)	0.28 (0.15-0.50)	0.83

was used as an anticoagulant. One patient who was administered urokinase prior to CRRT was also excluded. Ultimately, 101 patients were included in this study. The 101 patients included 76 patients for whom NM was used and 25 patients for whom UFH was used. The total number of filters used was 239, of which 173 (72.4%) were used with NM and 66 (27.6%) were used with UFH. There was no difference in the median number of filters used per patient (p = 0.27).

Patient demographics

Table I shows a univariate comparison of the demographics of patients for whom NM and UFH were used. Before matching on propensity score, patients for whom NM was used were significantly more likely to require post-surgical admission (p = 0.002) and platelet count was significantly lower in patients for whom NM was used (p = 0.04). There was no difference between the two groups in age, APACHE II, the reason for ICU admission, the presence of neoplasia, and estimated GFR, total bilirubin level, the presence of sepsis, serum creatinine level, and hemoglobin at the commencement of CRRT. There is also no significant difference in aPTT and PT-INR.

Matching on propensity score yielded 30 patients for whom NM was used and 15 patients for whom UFH was used. The propensity score-matched groups were well balanced for all baseline characteristics including post-surgical admission and coagulation function measures prior to commencement of CRRT.

TABLE II - Doses of anticoagulants for CRRT

	Before matching		After matching	
	Unfractionated heparin (n = 25)	**Nafamostat mesilate (n = 76)**	**Unfractionated heparin (n = 15)**	**Nafamostat mesilate (n = 30)**
Dose at commencement of CRRT	400 (400-625)IU/h	20 (20-20)mg/h	400 (400-550)IU/h	20 (20-20)mg/h
Time-weighted average dose during CRRT	500 (400-688.8)IU/h	20 (18.4-24.4)mg/h	450 (333-515)IU/h	20 (19.4-23.2)mg/h

Data are expressed as median (25-75% interquartile range). CRRT = continuous renal replacement therapy; IU/h = international unit per hour; mg/h = mg per hour.

TABLE III - Association of anticoagulant with incidence of significant bleeding during CRRT

	Unfractionated heparin	**Nafamostat mesilate**	**Unadjusted or adjusted odds ratio [95% CI]**	**p-value**
All patients (n = 101)				
Univariate comparisons	4/25 (16%)	5/76 (6.6%)	Unadjusted OR; 0.37 [0.09-1.50]	0.16
Multivariate logistic analysis using IPTW			Adjusted OR; 0.16 [0.04-0.75]	0.02
Propensity score-matched cohort (n = 45)	4/15 (27%)	1/30 (3.3%)	Unadjusted OR; 0.09 [0.01-0.94]	0.04

CRRT = continuous renal replacement therapy; CI = confidential interval; OR = odds ratio; IPTW = inverse probability of treatment weighting.

The doses of anticoagulants during CRRT are shown in Table II. The median dose of NM at the commencement of CRRT was 20 mg/h, and the time-weighted average dose of NM during CRRT was 20 mg/h. The median dose of UFH at the commencement of CRRT was 400 IU/h, and the time-weighted average dose of UFH during CRRT was 450 IU/h.

Risk of bleeding complications

Table III shows unadjusted and adjusted associations of the use of NM with risk of bleeding complications. Among the 101 patients, use of NM tended to be associated with a lower risk of bleeding (6.6% vs. 16%; odds ratio, 0.37; p = 0.16), but the association was not statistically significant. Among the propensity score-matched cohorts, use of NM was significantly associated with a decreased risk of bleeding (3.3% vs. 27%; odds ratio, 0.09; p = 0.04). For sensitive analysis, we performed multivariate logistic analysis using IPTW as independent factors. In these analyses, the use of NM showed a significant independent association with lower risk of bleeding complications (p = 0.02).

Filter life

Figure 2 shows the median of first filter life for patients in whom each anticoagulant was used. The filter life was not significantly different between patients with NM and patients with UFH (before matching: 25.5 hours vs. 30.5 hours, p = 0.12; after matching: 25.5 hours vs. 30.5 hours, p = 0.16). In multivariate analysis by the Cox proportional hazards model using IPTW as independent factors, the use of NM did not show a significant independent association with filter life (p = 0.54) (Tab. IV).

Discussion

Key findings

In our retrospective analysis of critically ill patients who required CRRT, we found that the use of NM as an anticoagulant during CRRT was significantly associated with decreased risk of bleeding complications compared with the use of UFH, although the filter life with UFH and that with NM were comparable.

Relationship with previous findings

The incidence of bleeding complications during CRRT using UFH as an anticoagulant was previously reported to be as high as 22.7% (12). Citrate is a well-known alternative anticoagulant for CRRT, and there was a significant reduction in the incidence of bleeding complications when citrate was used (risk ratio, 0.24; p = 0.02) (14). However, citrate may have side effects such as hypocalcemia and metabolic alkalosis (15). Additionally, most of the citrate anticoagulation methods require calcium administration to maintain systemic serum ionized calcium concentration in an appropriate range. This may increase the work load of physicians and nurses to measure ionized calcium concentration and adjust the dose of calcium administration.

NM is rapidly eliminated from the blood with a half-life of only 8 minutes. In this regard, NM administration would not need an antidote. Thus, NM may be useful as a regional anticoagulant for CRRT. Two studies have shown that there was no significant difference in the frequency of red blood cell transfusion between patients with NM and those without an

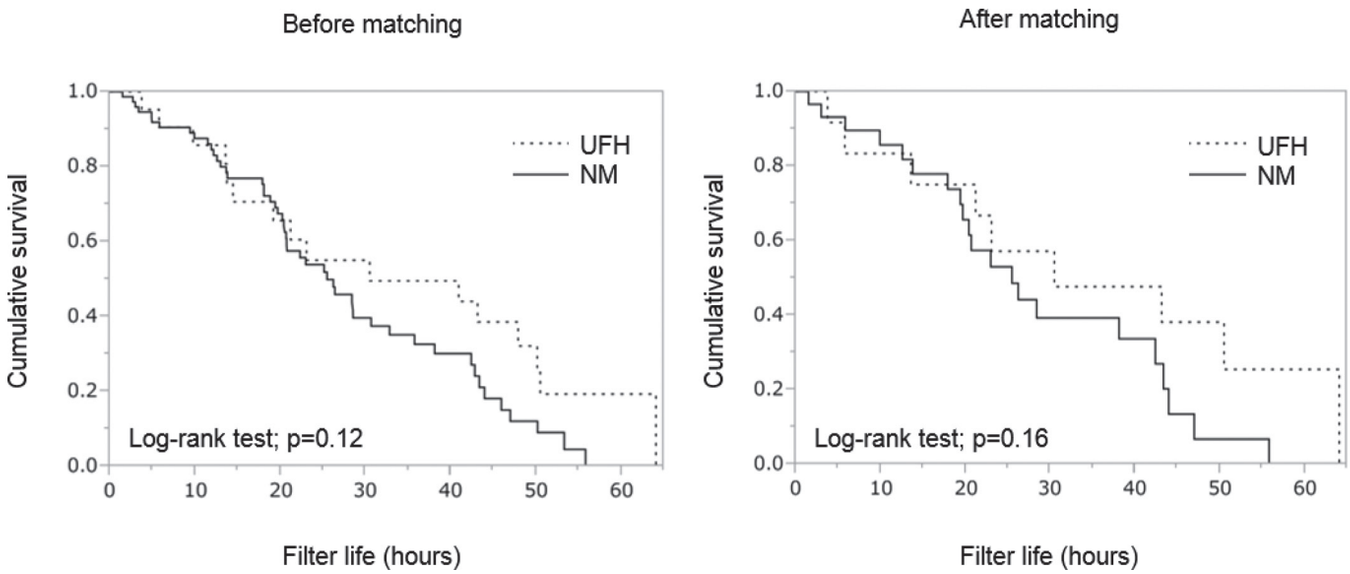

Fig. 2 - Comparisons of first filter life between nafamostat mesilate and unfractionated heparin. The filter life was not significantly different between patients with NM and patients with UFH. NM = nafamostat mesilate; UFH = unfractionated heparin.

TABLE IV - Association of anticoagulant with filter life

	Unfractionated heparin	Nafamostat mesilate	p-value
All patients (n = 101)			
Univariate comparisons	30.5 hours (14.5-50.5)	25.5 hours (18.0-42.8)	0.12
Multivariate logistic analysis using IPTW			0.54
Propensity score-matched cohort (n = 45)	30.5 hours (17.4-64.1)	25.5 hours (17.9-43.4)	0.16

Data are expressed as median (25-75% interquartile range). IPTW = inverse probability of treatment weighting.

anticoagulant during CRRT (9, 16). However, there has been only 1 study in which the incidences of bleeding in patients with NM and in patients with UFH were compared.

Hwang et al reported the results of a retrospective observational study in critically ill patients who required CRRT. They compared data for 25 patients with CRRT using NM with 56 patients using UFH (17). The mean doses of NM and UFH were 16.5 mg/h and 307.9 IU/h, respectively. They used the same definition of bleeding complications as that in our study, and they reported that the incidence of bleeding complications in patients in whom NM was used was not significantly different from that in patients in whom UFH was used (2% vs. 0.9%, per filter, p = 0.71).

Since there have been no other studies in which NM and UFH as anticoagulants for CRRT were compared, it might be worth comparing the results of Hwang's study with the results of our study. There are several possible reasons for the difference in results. First, the doses of the anticoagulants used in our study were different from those used in Hwang's study. Second, we determined the incidence of bleeding complications per patient, whereas Hwang et al reported the incidence of bleeding complications per filter. Third, the case mix of patients including the proportion of post-surgical patients and patients with coagulopathy may be different in the 2 studies. Finally, since the main aim of Hwang's study was to compare the filter life using NM and that using UFH, they did not adjust possible confounders between the 2 cohorts. Thus, the differences in doses of anticoagulants, calculation of the incidence of bleeding complications and possible confounding factors including case mix may have caused the difference in results of the 2 studies.

To clarify whether our cohort using UFH was appropriate as a control cohort, it might be better to compare our patients with those in a prior study. The incidence of bleeding complications using UFH during CRRT was reported to be 22.7%. This is not significantly different from our results (crude: 16%, p = 0.83; propensity score-matched cohort: 27%, p = 0.51). In this regard, our cohort using UFH is similar to those in prior studies and may thus be appropriate as a control group.

Strengths and limitations

In this study, confounding factors in patients' characteristics were addressed using propensity score analysis, and for

sensitive analysis, we further developed a multivariate logistic model using IPTW to estimate the independent association of the use of NM with the risk of bleeding complications in all patients. It should be noted that this is the first study to assess the independent association of using NM during CRRT compared with that using UFH.

However, there were several limitations in our study. First, it was a retrospective study in nature and was thus potentially subject to systematic error and bias. Second, the study was conducted in 1 center and the results were not statistically powered enough to be generalized. Third, we could not obtain information on the CRRT technique, type of filter, flow of dialysate/replacement fluid, site of catheter insertion, and catheter patency and functioning (18), which all have a potential to influence the filter life of CRRT. Although the main aim of this study was to assess the association of the choice of anticoagulant with the risk of bleeding, these data are relevant to this issue. Furthermore, there were few patients whose antithrombin III activity was measured before commencement of CRRT, which would influence the effect of UFH, the risk of bleeding, and the filter patency (19). Thus, future prospective studies should obtain these data to assess the impact of the type of anticoagulant on the filter patency. Finally, our study showed the association but not the causal link.

Implications for practice

Our study might provide useful information for considering the impact of bleeding complications on patient care. Our findings suggest that the use of NM is at least safe with regard to the risk of bleeding complications. Additionally, it can be hypothesized on the basis of the results that using NM during CRRT would lower the incidence of bleeding complications compared with that in the case of using UFH. However, considering the limitations of an observational study with propensity score analysis, especially regarding the presence of unknown confounders, further study is necessary to refute or confirm the results of our study.

In conclusion, our retrospective analysis showed that the use of NM as an anticoagulant for CRRT is associated with a decreased incidence of bleeding complications compared with that when using UFH. Filter life for patients with NM is comparable to that for patients with UFH.

Disclosures

Financial support: No grants or funding have been received for this study.
Conflict of interest: None of the authors has financial interest related to this study to disclose.

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