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Association between Intra-Circuit Activated Clotting Time and Incidence of Bleeding Complications during Continuous Renal Replacement Therapy using Nafamostat Mesilate: a Retrospective Pilot Observational Study

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It has been proposed that anticoagulant activity during continuous renal replacement therapy with nafamostat mesilate can be monitored by using intra-circuit activated clotting time. However, it is still unclear whether activated clotting time would be useful for this purpose. We conducted a retrospective study and included 76 patients who required continuous renal replacement therapy using nafamostat mesilate. We obtained information for pre- and post-filter activated clotting times and bleeding complications. We calculated time-weighted average activated clotting time. We divided the patients into three activated clotting time groups (low, middle, high) according to the tertiles of pre- and post-filter activated clotting times.

Regarding post-filter time-weighted average activated clotting time, the incidence of bleeding complications in the high activated clotting time group was significantly higher than those in the low and middle activated clotting time groups (p=0.04). The incidences of bleeding complications were not significantly different among the three groups according to pre-filter time-weighted average activated clotting time (p=0.35). In sensitive analysis, the duration on continuous renal replacement therapy without bleeding complications was significantly longer for filters with post-tw ACT<262 than for those with post-tw ACT≧262 (p=0.03). This result suggested that post-filter time-weighted average activated clotting time might be a good predictor of bleeding complications during continuous renal replacement therapy with nafamostat mesilate. Further study is required to refute or confirm our findings.

INTRODUCTION

Acute kidney injury is common in critically ill patients (4). Continuous renal replacement therapy (CRRT) is commonly used in critically ill patients, especially in those with hemodynamic instability (13). Administration of an anticoagulant during CRRT may be required to reduce the downtime due to filter clotting (11). However, it can expose patients to the risk of bleeding, which may lead to the requirement of additional hemostasis intervention and transfusion (6, 8). In this regard, monitoring of anticoagulant activity during CRRT would be important to avoid bleeding complications and frequent filter clotting.

Nafamostat mesilate (NM) is a synthetic serine protease inhibitor with a short half-life (12). NM might be a useful anticoagulant during CRRT, especially for patients with a high risk of bleeding. There has been a report on monitoring of intra-circuit activated clotting time (ACT) during CRRT using NM (1). However, it is still unclear whether intra-circuit ACT is useful for monitoring intra-circuit anticoagulant activity of NM. Accordingly, we conducted a study to assess the association between intra-circuit ACT and incidence of bleeding complications.

MATERIALS AND METHODS

Study design

This study was 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 a database.

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Patients and data collection

We screened all adult critically ill patients who required CRRT in our intensive care unit (ICU) from January 2011 to December 2013. We included patients in whom NM 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. We also excluded patients who were administered other anticoagulants including unfractionated heparin and gabexate mesilate.

We collected demographic information on age, sex, weight, acute physiology and chronic health evaluation (APACHE) II score, post-surgical admission, reason for ICU admission, presence of neoplasia, estimated glomerular filtration rate (eGFR) (7), total bilirubin level, patients with total bilirubin levels ≧2 mg/dl (14), presence of sepsis (10) and presence of disseminated intravascular coagulation (DIC) related to sepsis (3) at commencement of CRRT. We also collected data for daily hemoglobin levels, serum creatinine levels, and coagulation laboratory measurements including platelet count, prothrombin time-international normalized ratio (PT-INR), and activated partial thromboplastin time (aPTT).

Administration of NM and measurements of intra-circuit ACT

NM was administered at pre-filter into the CRRT circuit. The initial dose was 20 mg/hour without bolus administration, and the dose of NM was adjusted to maintain pre-filter ACT at 150 seconds.

ACT was measured 1 hour after commencement of CRRT and as clinically required at both pre-filter and post-filter simultaneously. ACT was measured using the HEMOCHRON Response Coagulation Monitoring Instrument (ITC, USA). We obtained all ACT values during the first filter and then calculated the time-weighted average from all ACT values at both pre-filter (pre-tw ACT) and post-filter (post-tw ACT). All measured ACT values and their corresponding sampling times were taken into account for its calculations. The tw ACT was calculated with the assumption of a linear trend between individual measurements and giving a time value to such measurements.

Primary and secondary outcomes

The primary outcome of this study was the incidence of clinically significant bleeding complications for the first filter of CRRT. Based on a previous report, 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 (15). The secondary outcome was filter life for the first CRRT. Time to filter failure was defined as from the starting time to the time of filter clotting.

Statistical analysis

Data are expressed as means (standard deviation, SD) or n (%). Before analysis, patients were divided into three ACT groups (low, middle, high) according to the tertile of ACT values: separation using an ordered distribution of ACT indices each containing a third of the patients. Comparison among groups was done by using one-way ANOVA and Fisher's exact test. For sensitive analysis of bleeding complications, we further obtained information on all of the filters used in the study cohort, filter life, presence and absence of bleeding complications, and duration from commencement of CRRT to bleeding complications. Then we further separated filters according to the possible threshold of ACT values, and we used the log-rank test to compare the durations on CRRT without bleeding complications for the separated filters.

Filter life estimates were compared using the log-rank test. Filter life analysis was also carried out using a Cox proportional hazards model with platelet count, PT-INR, aPTT, APACHE II score and post-surgical admission as independent factors. We analyzed the risk ratio of filter clotting in which the reference was the middle ACT group. A p-value less than 0.05 was defined as statistically significant. Statistical analyses were performed using SPSS 20.0.

RESULTS

Study flow

During the study period, 122 critically ill patients required CRRT (Fig. 1). We excluded 17 patients who required ECMO (n=8) or IABP (n=9). We also excluded 29 patients who were administered other anticoagulants such as unfractionated heparin (n=16) and gabexate mesilate (n=13). Finally, 76 patients (76 filters) were included in this study. There was no missing value except for pre-aPTT in two patients.

Patient demographics

The mean age of the 76 patients was 73 years, and the mean APACHE II score was 20. There were 43 patients (57%) with post-surgical admission. The mean dose of NM at commencement of CRRT was 20±4

mg/hour, and the time-weighted average dose of NM during the first CRRT was 20±6 mg/hour. Mean pre-tw ACT and mean post-tw ACT were 149±27 and 246±56 seconds, respectively. Tables I and II show univariate comparisons of patient demographics among the three ACT groups of pre-tw ACT and post-tw ACT. Patient demographics, except for age (in post-tw ACT) and the presence of septic DIC (in pre-tw ACT), were not significantly different among the three groups stratified by tertiles of pre- and post-tw ACT.

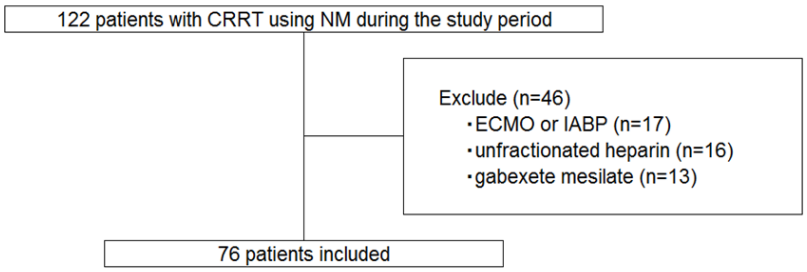

Figure 1. Study flow of patient selection.
During the study period, 122 critically ill patients required CRRT. Forty-six patients were excluded and finally 76 patients were included in this study.
CRRT: continuous renal replacement therapy, NM: nafamostat mesilate, ECMO: extracorporeal membrane oxygenation, IABP: intra-aortic balloon pumping

Table I. Comparison of patient demographics in the three groups of pre-tw ACT.

	Total cohort (n=76)	Low tw ACT (Pre-filter) (n=25)	Middle tw ACT (Pre-filter) (n=25)	High tw ACT (Pre-filter) (n=26)	p-value*
pre-tw ACT (range)	(80-243)	(80-135)	(136-153)	(157-243)	
pre-tw ACT (mean)	149±27	126±12	143±6	177±25	<0.001
Age (years)	73±13	75±14	71±14	73±11	0.66
Male (%)	49 (64)	12 (48)	17 (68)	20 (77)	0.09
Weight (kg)	56±14	55±10	57±15	55±16	0.84
APACHE II score	20±5	19±3	19±5	21±6	0.16
Sepsis (%)	25 (33)	5 (20)	9 (36)	11 (42)	0.22
Septic DIC (%)	14 (18)	0 (0)	5 (20)	9 (35)	0.01
Neoplasia (%)	5 (7)	2 (8)	1 (4)	2 (8)	0.82
Surgical admission (%)	43 (57)	19 (76)	13 (52)	12 (46)	0.07
Elective operation	24 (32)	12 (63)	7 (28)	6 (23)	0.75
Emergency operation	19 (25)	7 (37)	6 (24)	6 (23)	0.75
Reason for ICU admission (%)					0.33
Neurological	4 (5)	0 (0)	1 (4)	3 (12)	
Cardiac	46 (61)	17 (68)	17 (68)	12 (46)	
Respiratory	3 (4)	0 (0)	1 (4)	2 (8)	
Gastrointestinal	6 (8)	2 (8)	0 (0)	4 (15)	
Renal	9 (12)	3 (12)	4 (16)	2 (8)	
Others	8 (11)	3 (12)	2 (8)	3 (12)	
Laboratory test before commencement of CRRT					
eGFR (ml/min/1.73m^2)	20.9±19.5	21.9±24.7	22.5±19.7	18.3±13.3	0.71
Total bilirubin (mg/dl)	1.5±2.8	1.6±2.9	1.0±0.9	1.9±3.7	0.45
Total bilirubin≧2mg/dl (%)	10 (13)	2 (8)	2 (8)	6 (23)	0.18
Hemoglobin (g/dl)	9.4±1.7	9.6±1.4	9.5±2.0	9.0±1.8	0.36
Serum creatinine (mg/dl)	4.4±2.6	4.0±2.1	4.4±2.8	4.8±2.8	0.56
Coagulation test before commencement of CRRT					
Platelet count (×10^4/μL)	11.4±8.1	9.9±4.8	11.8±6.2	12.4±11.7	0.53
PT-INR	1.4±0.9	1.0±0.1	1.4±1.0	1.6±1.1	0.06
aPTT (sec)	36±15	32±7	36±17	41±17	0.08

*p-value for comparisons among the 3 groups (low, middle and high). Data are expressed as means (standard deviation, SD) or n (%).
tw: time-weighted, ACT: activated clotting time, APACHE: acute physiology and chronic health evaluation, DIC: disseminated intravascular coagulation, ICU: intensive care unit, eGFR: estimated glomerular filtration rate, CRRT: continuous renal replacement therapy, PT-INR: prothrombin time-international normalized ratio, aPTT: activated partial thromboplastin time

Table II. Comparison of patient demographics in the three groups of post-tw ACT.

	Total cohort (n=76)	Low tw ACT (Post-filter) (n=25)	Middle tw ACT (Post-filter) (n=25)	High tw ACT (Post-filter) (n=26)	p-value*
post-tw ACT (range)	(157-457)	(157-219)	(220-260)	(262-457)	
post-tw ACT (mean)	246±56	196±20	237±11	305±52	<0.001
Age (years)	73±13	76±9	70±16	76±10	0.01
Male (%)	49 (64)	16 (64)	16 (64)	17 (65)	0.99
Weight (kg)	56±14	55±9	56±16	56±16	0.99
APACHE II score	20±5	20±5	18±4	21±5	0.13
Sepsis (%)	25 (33)	5 (20)	8 (32)	12 (46)	0.14
Septic DIC (%)	14 (18)	3 (12)	3 (12)	8 (31)	0.14
Neoplasia (%)	5 (7)	1 (4)	1 (4)	3 (12)	0.45
Surgical admission (%)	43 (57)	18 (72)	13 (52)	13 (50)	0.22
Elective operation	24 (32)	12 (48)	5 (20)	8 (31)	0.27
Emergency operation	19 (25)	6 (24)	8 (32)	5 (19)	0.27
Reason for ICU admission (%)					0.19
Neurological	4 (5)	1 (4)	1 (4)	2 (8)	
Cardiac	46 (61)	20 (80)	14 (56)	12 (46)	
Respiratory	3 (4)	0 (0)	0 (0)	3 (12)	
Gastrointestinal	6 (8)	1 (4)	2 (8)	3 (12)	
Renal	9 (12)	2 (8)	3 (12)	4 (15)	
Others	8 (11)	1 (4)	5 (20)	2 (8)	
Laboratory test before commencement of CRRT					
eGFR (ml/min/1.73m^2)	20.9±19.5	22.8±17.7	18.8±24.3	21.0±16.4	0.77
Total bilirubin (mg/dl)	1.5±2.8	1.3±2.1	1.2±2.2	2.0±3.7	0.58
Total bilirubin≧2mg/dl (%)	10 (13)	2 (8)	2 (8)	6 (23)	0.18
Hemoglobin (g/dl)	9.4±1.7	9.3±1.6	9.6±1.9	9.2±1.7	0.66
Serum creatinine (mg/dl)	4.4±2.6	3.9±2.5	5.0±2.6	4.3±2.6	0.32
Coagulation test before commencement of CRRT					
Platelet count (×10^4/μL)	11.4±8.1	10.1±4.2	12.7±6.7	11.3±11.6	0.52
PT-INR	1.4±0.9	1.2±0.4	1.6±1.1	1.4±0.9	0.27
aPTT (sec)	36±15	31±6	36±18	41±16	0.06

*p-value for comparisons among the 3 groups (low, middle and high). Data are expressed as means (standard deviation, SD) or n (%).

tw: time-weighted, ACT: activated clotting time, APACHE: acute physiology and chronic health evaluation, DIC: disseminated intravascular coagulation, ICU: intensive care unit, eGFR: estimated glomerular filtration rate, CRRT: continuous renal replacement therapy, PT-INR: prothrombin time-international normalized ratio, aPTT: activated partial thromboplastin time

Dose of Nafamostat mesilate

Table III shows a comparison of time-weighted doses of NM during CRRT in the three groups of post-tw ACT. There was no significant difference in time-weighted doses of NM between the three ACT groups of post-tw ACT (p=0.40).

Table III. Comparison of time-weighted doses of NM during CRRT in the three groups of post-tw ACT.

	Low (n=25)	Middle (n=25)	High (n=26)	p-value
Time-weighted dose of NM during CRRT	21.4±5.6	20.7±6.2	19.1±5.4	0.40

*p-value for comparison among the 3 groups (low, middle and high). Data are expressed as means (standard deviation, SD).
tw: time-weighted, NM: nafamostat mesilate, CRRT: continuous renal replacement therapy, ACT: activated clotting time

Incidence of bleeding complications

Bleeding complications occurred in 3 (4%) of the 76 patients during the first CRRT using NM. The sites of bleeding were the gastrointestinal tract, abdominal cavity, and the wound of tracheotomy, respectively. None of the patients with bleeding complications received anti-platelets, warfarin, or direct oral anticoagulants. In pre-tw ACT, the incidence of bleeding complications was not significantly different between the 3 ACT groups (low: 0, middle: 2, high: 1, p=0.35). In post-tw ACT, the incidence of bleeding complications in patients with high ACT

was 12% (3/26), which was significantly higher than the incidence of 0% in those with low ACT and middle ACT (p=0.04).

Since the above analysis was statistically weak due to the limited filters obtained, we further performed sensitive analysis using all filters to refute or confirm our results. Accordingly, we obtained information of consequence 173 filters used in the study cohort. There were 5 patients with bleeding complications during the whole duration on CRRT (3 patients with bleeding complications at the first filter, one patient at the second filter and one patient at the fourth filter). Among these filters, post-tw ACT was 251±62 on average. Since the possible threshold of post-tw ACT was 262 seconds, we further separated these filters according to the 262 seconds of post-tw ACT (61 filters with ≧262 seconds of post-tw ACT and 112 filters with <262 seconds). We used the Kaplan-Meier method and log-rank test for analysis of bleeding complications between post-tw ACT≧262 and <262 seconds. We found that the duration on CRRT without bleeding complications was significantly longer for filters with post-tw ACT<262 seconds than for those with post-tw ACT≧262 seconds (p=0.03) (Fig. 2).

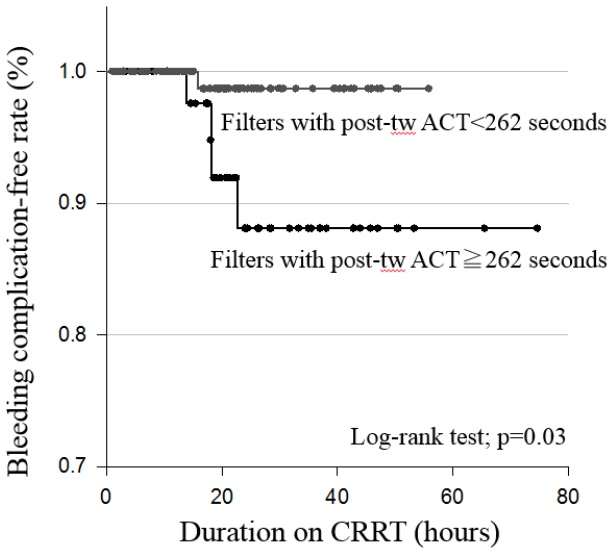

Figure 2. Comparison of the durations on CRRT without bleeding complications for filters with post-tw ACT≧262 seconds and post-tw ACT<262 seconds.

The duration on CRRT without bleeding complications was significantly longer for filters with post-tw ACT<262 seconds than for those with post-tw ACT≧262 seconds (p=0.03).

tw: time-weighted, ACT: activated clotting time, CRRT: continuous renal replacement therapy

Filter patency

Clotting occurred in 50 (66%) of the 76 filters during the first CRRT using NM. The other 26 filters were ceased without clotting and thus treated as censoring. Filter life was not significantly associated with either pre-tw ACT or post-tw ACT by univariate analysis and multivariate analysis (Table IV).

Table IV. Comparison of filter life

		Low (n=25)	Middle (n=25)	High (n=26)	p-value
Pre-tw ACT	Estimated filter life (hours)*	20.2±13.3	23.5±12.3	22.4±16.1	0.83
	Cox proportional hazards model (risk ratio)	1.3 (p=0.47)	(reference)	1.6 (p=0.25)	-
Post-tw ACT	Estimated filter life (hours)*	18.0±11.8	24.4±14.5	23.5±14.8	0.25
	Cox proportional hazards model (risk ratio)	1.5 (p=0.29)	(reference)	0.6 (p=0.23)	-

***** Comparison of estimated filter life (hours) was performed using the log-rank test.

tw: time-weighted, ACT: activated clotting time

DISCUSSION

Key findings

Our pilot retrospective analysis of critically ill patients who required CRRT using NM showed that the incidence of bleeding complications in patients with high post-tw ACT was significantly higher than the incidences in patients with low and middle post-tw ACT. There was no significant association between intra-circuit ACT and filter life. Although this is a hypothesis-generating observational study, the results of the study were novel and thus require further discussion.

Comparison with previous studies

NM is an inhibitor of serine protease and is rapidly eliminated from the blood (12). In this regard, NM can be used as a regional anticoagulant during CRRT (9). Thus, NM can be used safely for patients with a high risk of bleeding complications as an anticoagulant for CRRT. Monitoring of anticoagulant activity during CRRT using NM would be important to avoid preventable bleeding complications and frequent filter clotting. Baek et al. reported that the dose of NM should be adjusted according to intra-circuit ACT (1). However, it is unfortunate that they did not assess the association between intra-circuit ACT and bleeding complications or filter life during CRRT. Therefore, our study might be the first study in which their associations during CRRT using NM were assessed.

Implications

The biological half-life of NM is approximately 8 minutes (12). NM administered into the CRRT circuit is rapidly metabolized by esterase in the liver and blood to a metabolite with extremely vulnerable active. Thus, the concentration of NM is lower at pre-filter than at post-filter. A previous study showed that there is a relationship between the concentration of NM and ACT (5). According to that study, ACT values remained unchanged until the blood concentration of NM reached about 540 ng/ml. When the blood concentration of NM exceed 540 ng/ml, ACT values continued to increase at a rapid pace. Thus, there is not a linear trend between ACT values and blood concentration of NM, especially at lower concentrations. When NM was administered at 40 mg/hour, the blood concentration of NM measured at pre-filter was reported to be 300 ng/ml (16). Since the dose of NM in our patients was 20 mg/hour on average, it can be assumed that the NM concentration at pre-filter was too low to monitor anticoagulant activity using ACT. Thus, pre-filter ACT may not be optimal for monitoring anticoagulant activity during CRRT using NM, and ACT values measured at pre-filter were not associated with the incidence of bleeding and filter life in this study.

On the other hand, our study revealed that higher post-filter ACT was associated with higher incidence of bleeding complications. When NM was administered at 16 mg/hour, the blood concentration of NM measured at post-filter was reported to be 2880 ng/ml (16). Therefore, it can be assumed that the NM concentration at post-filter was sufficiently high to monitor anticoagulant activity using ACT. This might explain our findings and suggests that ACT values measured at post-filter may be useful for monitoring anticoagulant activity during CRRT using NM.

With respect to filter life, there was no significant linear association between post-filter ACT and risk of filter clotting (Table IV). One reason why ACT was not significantly associated with filter life was the lack of power for analysis. Additionally, there might be hidden confounders that had not been observed in our study. Since the main aim of our study was to determine the association between bleeding complications and ACT values, further study with a large cohort is required to refute or confirm the association between post-filter ACT and risk of filter clotting.

Strengths and limitations

Our study might be first study in which the association between intra-circuit ACT and incidence of bleeding complications during CRRT using NM was assessed. 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 one center and the results were not statistically powered sufficiently to be generalized. Third, this was a preliminary hypothesis-generating observational study with a limited number of patients. Thus, it is possible that our results are biased with an alpha type error. Thus, a future study should be conducted to refute or confirm our results. Fourth, we conducted this study both in surgical and non-surgical patients. A future study should be conducted in a much larger cohort with subgroup analysis in surgical and non-surgical patients separately. Finally, we could not obtain information on the CRRT technique, type of filter, flow of dialysate/replacement fluid, and site of catheter insertion, which all have the potential to influence the outcome of this study (2).

In conclusion, this hypothesis-generating observation study showed that post-tw ACT might have a potential to be a good predictor of the incidence of bleeding complications in patients receiving NM during CRRT. Future studies should be conducted to refute or confirm our results.

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