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<th>Pharmacokinetics and pharmacodynamics of recombinant soluble thrombomodulin in disseminated intravascular coagulation patients with renal impairment</th>
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Title:
Pharmacokinetics and pharmacodynamics of recombinant soluble thrombomodulin in disseminated intravascular coagulation patients with renal impairment

Running head:
PK/PD of recombinant thrombomodulin in DIC patients

Authors and institutes:
Mineji Hayakawa  Hiroshi Yamamoto
Taeko Honma  Nobutaka Mukai
Asumi Higashiyama  Masahiro Sugano
Nobuhiko Kubota  Shinji Uegaki
Atsushi Sawamura  Satoshi Gando
Emergency and Critical Care Center, Hokkaido University Hospital

Corresponding author:
Mineji Hayakawa, MD, PhD
Emergency and Critical Care Center, Hokkaido University Hospital,
N14W5 Kita-ku, Sapporo 060-8648 Japan
TEL: +81-11-706-7377  FAX: +81-11-706-7378  E-mail: mineji@dream.com

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ABSTRACT — Recombinant human soluble thrombomodulin (TM-α) was recently developed as an anticoagulant for patients with disseminated intravascular coagulation (DIC). However, the pharmacokinetics and pharmacodynamics of TM-α in DIC patients with severe renal impairment have not yet been elucidated. We investigated the pharmacokinetics and pharmacodynamics of TM-α in DIC patients with severe renal impairment. Eleven DIC patients with the severe renal impairment (creatinine clearance (CL_{cr}) <30 ml/min) and 10 DIC patients without severe renal impairment (CL_{cr} ≥30 ml/min) were included in this study. In all patients, a dose of 380U/kg of TM-α was administered during a 30 min infusion. Blood samples were taken before the start of the first TM-α administration, and at 0.5, 2, 4, 8, and 24 h after the start of administration.

Although the clearance of TM-α in the patients with renal impairment was 80% of that in the patients without renal impairment, none of the pharmacokinetic values were significantly different between the groups. In the pharmacokinetic simulation, however, the trough levels of TM-α increased gradually in the patients with renal impairment.

TM-α: recombinant human soluble thrombomodulin
DIC: disseminated intravascular coagulation
CL_{cr}: creatinine clearance
APACHE: Acute Physiology and Chronic Health Evaluation
SOFA: Sequential Organ Failure Assessment
ELISA: enzyme-linked immunosorbent assay
CRRT: continuous renal replacement therapy
T_{1/2}: elimination half life
C_{max}: maximum concentration
V_{dst}: volume of distribution at steady-state
when the same dose of TM-α was repeatedly administered. After the administration of TM-α, the prothrombinase activities in the patients in both groups were sufficiently inhibited during the observation period. Although the pharmacokinetic values in DIC patients with severe renal impairment were only slightly different from those in DIC patients without severe renal impairment, we need to pay attention to the elevation of the trough levels of TM-α when the same dose of TM-α is repeatedly administered.

**Keywords**

Disseminated intravascular coagulation

Thrombomodulin

Renal dysfunction

Prothrombinase activity

Protein C

Clearance

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INTRODUCTION

Thrombomodulin (TM) is a thrombin receptor on the endothelial cell surface that plays an important role in the regulation of the coagulation system (1). Recently, recombinant human soluble TM (TM-α) was developed as an anticoagulant for patients with disseminated intravascular coagulation (DIC). TM-α represents a new class of anticoagulants, and is composed of the active, extra-cellular domain of TM (2,3). Like the endogenous TM which is observed on the endothelial cells, TM-α binds to thrombin to inactivate coagulation, and the thrombin-TM-α complex activates protein C (2,3). The activated protein C inactivates factors VIIIa and Va, consequently inhibiting thrombin generation (2,3). In Europe and North America, clinical trials of recombinant human TM to treat septic patients with DIC are being conducted (4,5). In Japan, TM-α has been used clinically for the treatment of DIC since May of 2008 (3).

Acute renal dysfunction is a frequent complication in patients with DIC (6).

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Previous reports have indicated that TM-α is excreted mainly by the kidneys in healthy subjects (2,3,7). Although the metabolized form of TM-α with a low molecular weight is also excreted in urine, a large portion of the unchanged form of TM-α is excreted in the urine (3). Therefore, the dose of TM-α required in DIC patients with severe renal impairment was suggested to be decreased to one-third of the normal dose. However, the pharmacokinetics and pharmacodynamics of TM-α in DIC patients with severe renal impairment have not yet been elucidated.

In the present study, we evaluated the pharmacokinetics and pharmacodynamics of TM-α in DIC patients with severe renal impairment. We also investigated the safety and efficacy of TM-α in these patients and then compared them to those without renal impairment.

PATIENTS AND METHODS

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ELISA: enzyme-linked immunosorbent assay
CRRT: continuous renal replacement therapy
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Cmax: maximum concentration
Vdss: volume of distribution at steady-state
The present study was approved by the Institutional Review Board of Hokkaido University Hospital. Written informed consent was obtained from patients or each patient’s family. The present study included patients who were administered TM-α (Ashahi Kasei Pharma Co., Tokyo, Japan) to treat DIC in the intensive care unit. Patients with chronic renal failure requiring hemodialysis were excluded. The diagnosis of DIC was based on the Japanese Association for Acute Medicine DIC diagnosis criteria (8). The severity of illness of the patients was evaluated according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score at the time of administration of TM-α (9). Organ failure was assessed by the Sequential Organ Failure Assessment (SOFA) score at the administration of TM-α (10). Consciousness levels according to the APACHE II and SOFA scores were evaluated before sedation. The systemic inflammatory response syndrome score was assessed according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus

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conference (11) at the time of administration of TM-α. The urine was collected for 24 hours after the administration of TM-α. The creatinine clearance (CL_{cr}) was measured based on the serum and urine creatinine levels and the urine volume for 24 hours. Severe renal impairment was defined as CL_{cr} < 30ml/min according the FDA Guidance for Industry (12). The patients were divided in two groups, those with and without severe renal impairment.

In all patients, a dose of 380U/kg of TM-α was administered during a 30 min intravenous infusion. Blood samples were taken before the start of the first TM-α administration, and at 0.5, 2, 4, 8, and 24 h after the start of the administration. All samples were diluted (9:1 v/v) with 3.8% sodium citrate. The blood samples were promptly centrifuged and plasma was separated. The samples were frozen at −80°C until analysis. Thereafter, a second dose of TM-α adjusted to one-third of the first dose was administered to the patients with severe renal impairment, according to the current treatment protocol.

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The plasma TM-α and soluble TM concentrations were measured by enzyme-linked immunosorbent assay (ELISA) using two types of mouse monoclonal antibodies against TM-α (13). ELISA is able to measure the unchanged form of TM-α, because the results of ELISA correlated with those of a functional assay (14). Tissue factor-induced prothrombinase activity was measured by a slightly modified version of the method described in a previous report (7). Citrated plasma (200 µL) from the patients was incubated with 10 µL of 200 U/mL batroxobin (Pentapharm, Tokyo, Japan) for 10 min. After centrifugation, defibrinated plasma (20 µL) was incubated with 5 µL of a buffer solution containing 12500 times diluted rabbit brain tissue factor, 0.1 mg/mL of phospholipid vesicles, and 60 mmol CaCl₂. After a 10 min incubation, 5 µL of a buffer solution with or without 15 µmol/L prothrombin was added to the reaction mixture. After a 3 min incubation, 500 µL of 1 mmol/L S-2366 chromogenic substrate was added, and after another 1 min incubation, glacial acetic acid (50 µL) was added, and the absorbance was monitored at 405 nm. The prothrombinase activity (amount of

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Cₘₐₓ: maximum concentration
V_dss: volume of distribution at steady-state
thrombin formation) was calculated as the amount of thrombin (measured in μM) generated in 1 min after adding prothrombin minus that after adding the buffer.

The pharmacokinetic parameters of TM-α were analyzed by model-independent methods (non-compartment model) using the Phoenix WinNonlin (Ver. 6.1, Pharsight, CA, USA) software package. Regarding the simulation curves after multiple dosing of 380U/kg of TM-α to patients with and without severe renal impairment, the mean plasma concentrations in each group were analyzed by a 2-compartment model, and the simulation curves were generated with these pharmacokinetic parameters using the above-mentioned software package.

All measurements are expressed as the means ± SD. The SPSS 15.0J statistical software package (SPSS Inc., Chicago, Illinois) was used for all statistical analyses. Comparisons between the two groups were made using either Student’s t-test or the chi square test. A value of $P < 0.05$ was considered to be statistically significant.
RESULTS

Twenty-one DIC patients who were treated with TM-α were included in this study. Eleven patients with a CL_{cr} < 30ml/min were classified into the severe renal impairment group. There were 10 patients without severe renal impairment included for comparison. Table 1 presents the characteristics of the patients. The renal SOFA scores of the patients with severe renal impairment were higher than those of the patients without severe renal impairment. The soluble TM shed from the endothelial cell surface before the administration of TM-α in the DIC patients with severe renal impairment was higher than in the DIC patients without severe renal impairment. Seven patients with severe renal impairment were treated with continuous renal replacement therapy (CRRT) during the study period. The CRRT circuit was set up using a cellulose triacetate hollow fiber 1.1 m^2 hemofilter (UT-110, Nipro, Japan). In the seven
investigated patients, the ultrafiltrate flow was defined as 1.0 l/h, and dialysate flow was infused in a countercurrent at rates of 1.0 l/h. Nafamostat mesilate was used as an anticoagulant for CRRT in all patients.

The plasma concentration of TM-α and prothrombinase activity in DIC patients with and without severe renal impairment are presented in Table 2. After the administration of TM-α, the prothrombinase activities in both groups were sufficiently inhibited during the observation period. No bleeding-related or other adverse events were observed. The mortality rates 28 days after the TM-α administration were 45% (5/11) and 20% (2/10) in the DIC patients with and without severe renal dysfunction, respectively.

The pharmacokinetic parameters of TM-α in the DIC patients are presented in Table 3. In the patients with severe renal impairment, the elimination half life (T_{1/2}) was prolonged to about 1.2 times that of the patients without severe renal impairment. In contrast, the maximum concentration (C_{max}) in the patients with severe renal impairment

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was decreased compared with that in the patients without severe renal impairment, because of volume of distribution at steady-state ($V_{dss}$) was increased in the patients with severe renal impairment. However, none of these changes were statistically significant. In the severe renal impairment group, the pharmacokinetic parameters of TM-α in the patients with and without CRRT are presented in Table 4. There was no substantial difference between the patients with and without CRRT.

Based on the pharmacokinetic data, plasma time-concentration curves of TM-α in patients with and without severe renal impairment were simulated in two-compartment models (Fig. 1). When the same dose of TM-α (380U/kg) was repeatedly administered every 24 hours in the simulation, the trough levels of TM-α gradually increased, reaching 600ng/mL at 120 hours after the first administration.

**DISCUSSION**

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The present study is the first report of the pharmacokinetics and pharmacodynamics of TM-α in DIC patients with severe renal impairment. The pharmacokinetics and pharmacodynamics of TM-α in DIC patients with severe renal impairment were only slightly different from those in DIC patients without severe renal impairment. However, the trough levels of TM-α increased gradually in the patients with severe renal impairment when the same dose (380 U/kg) of TM-α was repeatedly administered in the pharmacokinetic simulation.

Most of the plasma TM-α is excreted by the kidneys (2,3,7). In the healthy volunteers, 40% of the administered dose of TM-α was excreted during the first 24 hours after the administration of TM-α (2,7). Furthermore, Tsuruta et al. indicated that TM-α was excreted in either an unchanged form (40%) or in a metabolized form (55%) in the urine during the first 24 hours in an animal study using a rat model without DIC (3). However, in a rat model with severe renal impairment, the clearance of TM-α was

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not markedly decreased (3). The clearance of TM-α in the non-DIC rat with severe renal impairment was 80% of that in the normal rat (3). Our present study revealed similar results. We showed that the clearance of TM-α in the DIC patients with severe renal impairment was 80% of that in the DIC patients without severe renal impairment.

In the DIC patients with severe renal impairment, the decomposition of TM-α may increase, although the elimination of TM-α decreases.

Previous reports have indicated that albumin (15,16) and antithrombin (17) leak from the capillary vessels into the interstitial space in critically ill patients, because of the increased vascular permeability. The vascular permeability increases in accordance with the increase in disease severity of the patients (15,16). The molecular weight of TM-α (62000 Da) (18) is almost same as albumin (56000 Da) and antithrombin (63000 Da) (15-17). In the present study, the severity of the patients with severe renal impairment was higher than that in patients without severe renal impairment. In the patients with severe renal impairment, the $V_{dss}$ of TM-α was larger.

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than that in the patients without severe renal impairment although the difference was not statistically significant because of the small study population. Therefore, the severity of this condition in patients may affect the $V_{dss}$ and $C_{max}$ of TM-$\alpha$ because of the increased vascular permeability.

Seven patients with severe renal impairment were treated with CRRT during the administration of TM-$\alpha$. The pharmacokinetics of the drugs with a small molecular weight are affected by CRRT because of the additional elimination enforced by the CRRT. The large molecular weight of TM-$\alpha$ (62000), which is larger than that of albumin (56000), suggests that the pharmacokinetics of TM-$\alpha$ are not likely to be affected by CRRT. In the present study, the clearance of TM-$\alpha$ was not significantly different between the patients with and without CRRT, although the number of patients examined was very small. A part of the administered TM-$\alpha$ has been reported to be metabolized to a low molecular fraction (3). The low molecular fraction of TM-$\alpha$ may be eliminated by CRRT, although its molecular weight is still unclear. However, the
pharmacokinetics and pharmacodynamics of TM-α are not related to the elimination of TM-α fragments with a low molecular weight, which does not have any activity.

A phase III study of TM-α in Japan showed that the bleeding-related adverse events of TM-α were markedly lower than those related to heparin in DIC patients (19). Mohri et al. indicated that the concentration of TM-α required for the direct inhibition of thrombin activity was 50 times higher than that for the inhibition of thrombin generation (20). Therefore, the plasma concentration of TM-α does not reach the level to directly inhibit thrombin activity in the clinical setting (19,20). No adverse events were observed in the present study. In the pharmacokinetic simulation when the same dose of TM-α (380U/kg) was repeatedly administered to the two groups, the trough levels of TM-α increased gradually in the patients with severe renal impairment (Figure 1). Although the simulated concentrations of TM-α in the patients with severe renal impairment did not reach levels high enough to directly inhibit thrombin activity, the potential effect of this elevation in the trough levels on bleeding-related adverse effects

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is unclear. Confirmation of the actual pharmacokinetics and safety of repeated
administration of the normal dose of TM-α in DIC patients with severe renal
impairment will be needed.

Thrombomodulin is an endothelial cell membrane protein that plays an important
role in the protein C system (1). In critically ill patients, soluble TM fragments circulate
in the plasma as a result of endothelial cell activation and damage (21). The
concentrations of soluble TM were reported to be around 10 ng/mL in critically ill
patients (21). In the present study, the soluble TM originating from the endothelial cells
before the administration of TM-α in the DIC patients with severe renal impairment was
higher than that in the DIC patients without severe renal impairment. However, the
concentrations of soluble TM were less than 15 ng/mL in the present study, the same as
in the previous studies (21). The measured values of TM-α used for this
pharmacokinetic/pharmacodynamic study included the soluble TM shed from the
endothelial cells. However, the influence of this soluble TM on the measurement of the

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The present study has the same limitations, because the effects of the first administration were investigated, and there were simulated plasma time-concentration curves for TM-α. Furthermore, the number of patients evaluated in the present study was relatively small. Therefore, further large-scale clinical studies will be needed to clarify the appropriate adjustment of TM-α administration based on the patient renal function.

In conclusion, we herein clarified the pharmacokinetics and pharmacodynamics of TM-α in DIC patients with severe renal impairment. The clearance of TM-α in the patients with severe renal impairment was similar to that in the patients without severe renal impairment. However, a pharmacokinetic simulation of multiple administrations demonstrated an elevation of the trough levels of TM-α. Further clinical studies will be

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the newly established diagnostic criteria for critically ill patients: results of a


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T$_{1/2}$: elimination half life
C$_{max}$: maximum concentration
V$_{dss}$: volume of distribution at steady-state


18. Mohri M: ART-123: Recombinant Human Soluble Thrombomodulin


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FIGURE LEGEND

FIG. 1. Plasma time-concentration curve simulations of thrombomodulin (TM)-α in disseminated intravascular coagulation (DIC) patients using the two-compartment models

The time-concentration curves were simulated when the same dose of TM-α (380U/kg) was repeatedly administered to the patients in both groups (with and without severe renal impairment). The closed and open circles represent the actual concentrations of TM-α in the DIC patients with and without severe renal impairment, respectively. The error bars show ± SD. The solid and dotted lines represent the TM-α plasma concentration-time simulation curves for DIC patients with and without severe renal impairment, respectively.

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TABLE 1. Characteristics of the DIC patients

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<th>( \text{CL}_{\text{cr}} &lt; 30\text{ml/min} )</th>
<th>( \text{CL}_{\text{cr}} \geq 30\text{ml/min} )</th>
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<td>11</td>
<td>10</td>
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<tr>
<td>Age (year)</td>
<td>67 ± 14</td>
<td>69 ± 11</td>
<td>NS</td>
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<td>Sex (male / female)</td>
<td>8 / 3</td>
<td>8 / 2</td>
<td>NS</td>
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<tr>
<td>Height (cm)</td>
<td>160 ± 13</td>
<td>162 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.8 ± 11.9</td>
<td>58.0 ± 8.9</td>
<td>NS</td>
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<td>APACHE II score</td>
<td>30 ± 6</td>
<td>25 ± 9</td>
<td>NS</td>
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<td>SIRS score</td>
<td>3.5 ± 0.7</td>
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<td>NS</td>
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<td>DIC score</td>
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<td>Cause of DIC</td>
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<td></td>
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<tr>
<td>Heat stroke</td>
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<td>1</td>
<td>NS</td>
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<td>Pancreatitis</td>
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<td>SOFA score (except CNS)</td>
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<td>Respiration</td>
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<td>Circulation</td>
<td>3.1 ± 1.3</td>
<td>2.4 ± 1.6</td>
<td>NS</td>
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<tr>
<td>Liver</td>
<td>1.5 ± 1.2</td>
<td>0.8 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Renal</td>
<td>2.7 ± 1.0</td>
<td>0.7 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coagulation</td>
<td>2.8 ± 1.0</td>
<td>2.0 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>( \text{CL}_{\text{cr}} ) (ml/min)</td>
<td>10.7 ± 7.7</td>
<td>56.0 ± 16.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRRRT (yes / no)</td>
<td>7 / 4</td>
<td>0 / 10</td>
<td>0.002</td>
</tr>
<tr>
<td>Soluble TM (ng/mL)</td>
<td>9.4 ± 2.7</td>
<td>6.2 ± 2.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Dose of TM-α (U/kg)</td>
<td>379 ± 8</td>
<td>381 ± 8</td>
<td>NS</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation; \( \text{CL}_{\text{cr}} \), creatinine clearance; NS, not significant; APACHE, Acute Physiology and Chronic Health Evaluation; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; CNS, central nervous system; CRRT, continuous renal replacement therapy; TM, thrombomodulin.
TABLE 2. Plasma concentration of TM-α and prothrombinase activity after TM-α administration

<table>
<thead>
<tr>
<th></th>
<th>0 h</th>
<th>0.5 h</th>
<th>2 h</th>
<th>4 h</th>
<th>8 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL\textsubscript{cr} &lt; 30ml/min</td>
<td>0</td>
<td>766 ± 208</td>
<td>660 ± 189</td>
<td>580 ± 193</td>
<td>490 ± 125</td>
<td>310 ± 111</td>
</tr>
<tr>
<td>CL\textsubscript{cr} ≥ 30ml/min</td>
<td>0</td>
<td>879 ± 286</td>
<td>670 ± 203</td>
<td>655 ± 175</td>
<td>518 ± 156</td>
<td>296 ± 164</td>
</tr>
<tr>
<td>Prothrombinase activity (nM thrombin/min)</td>
<td>54.2 ± 25.3</td>
<td>5.0 ± 4.0</td>
<td>4.8 ± 2.9</td>
<td>4.9 ± 3.0</td>
<td>8.4 ± 6.7</td>
<td>11.4 ± 9.7</td>
</tr>
<tr>
<td>CL\textsubscript{cr} &lt; 30ml/min</td>
<td>82.8 ± 54.0</td>
<td>5.6 ± 5.0</td>
<td>5.3 ± 6.0</td>
<td>5.7 ± 4.6</td>
<td>7.1 ± 5.2</td>
<td>9.7 ± 9.4</td>
</tr>
<tr>
<td>CL\textsubscript{cr} ≥ 30ml/min</td>
<td>-</td>
<td>91 ± 6</td>
<td>90 ± 7</td>
<td>89 ± 8</td>
<td>83 ± 11</td>
<td>81 ± 12</td>
</tr>
<tr>
<td>Inhibition rate of prothrombinase activity (%)</td>
<td>93 ± 3</td>
<td>94 ± 3</td>
<td>93 ± 5</td>
<td>91 ± 7</td>
<td>89 ± 7</td>
<td></td>
</tr>
</tbody>
</table>

TM, thrombomodulin; CL\textsubscript{cr}, creatinine clearance.
All values were not statistically significance between two groups.
<table>
<thead>
<tr>
<th></th>
<th>CL&lt;sub&gt;cr&lt;/sub&gt; &lt; 30ml/min</th>
<th>CL&lt;sub&gt;cr&lt;/sub&gt; ≥ 30ml/min</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=11</td>
<td>n=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</strong></td>
<td>24.5 ± 10.8</td>
<td>19.5 ± 13.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</strong></td>
<td>760 ± 194</td>
<td>879 ± 286</td>
<td>NS</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;inf&lt;/sub&gt; (ng/mL·hr)</strong></td>
<td>22945 ± 10626</td>
<td>21350 ± 17720</td>
<td>NS</td>
</tr>
<tr>
<td><strong>V&lt;sub&gt;dss&lt;/sub&gt; (mL/kg)</strong></td>
<td>95.0 ± 21.4</td>
<td>83.4 ± 24.2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CL of TM-α (mL/hr/kg)</strong></td>
<td>3.1 ± 3.1</td>
<td>3.7 ± 1.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

CL<sub>cr</sub>, creatinine clearance; NS, not significant; T<sub>1/2</sub>, elimination half life; C<sub>max</sub>, maximum concentration; AUC<sub>inf</sub>, area under the concentration-time curve; V<sub>dss</sub>, distribution volume in steady-state; CL, clearance.
<table>
<thead>
<tr>
<th></th>
<th>With CRRT</th>
<th>Without CRRT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>22.5 ± 7.9</td>
<td>28.0 ± 15.4</td>
<td>NS</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>767 ± 220</td>
<td>745 ± 167</td>
<td>NS</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt; (ng/mL · hr)</td>
<td>20884 ± 6880</td>
<td>26552 ± 15951</td>
<td>NS</td>
</tr>
<tr>
<td>V&lt;sub&gt;dss&lt;/sub&gt; (mL/kg)</td>
<td>93.5 ± 21.6</td>
<td>97.6 ± 24.0</td>
<td>NS</td>
</tr>
<tr>
<td>CL of TM-α (mL/hr/kg)</td>
<td>3.2 ± 1.2</td>
<td>3.0 ± 1.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

CRRT, continuous renal replacement therapy; NS, not significant; T<sub>1/2</sub>, elimination half life; C<sub>max</sub>, maximum concentration; AUC<sub>inf</sub>, area under the concentration-time curve; V<sub>dss</sub>, distribution volume in steady-state; CL, clearance.