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<td>Author(s)</td>
<td>Takazono, Takahiro; Nakamura, Shigeki; Imamura, Yoshifumi; Yoshioka, Sumako; Miyazaki, Taiga; Izumikawa, Koichi; Sawai, Toyomitsu; Matsuo, Nobuko; Yanagihara, Katsunori; Suyama, Naofumi; Kohno, Shigeru</td>
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<tr>
<td>Citation</td>
<td>Journal of Infection and Chemotherapy, 20(8), pp.484-488; 2014</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2014-08</td>
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<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/10069/35338">http://hdl.handle.net/10069/35338</a></td>
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<td>Rights</td>
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A retrospective comparative study of recombinant human thrombomodulin and gabexate mesilate in sepsis-induced disseminated intravascular coagulation patients

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Abstract

The novel biological agent recombinant human thrombomodulin (rhTM) has been used clinically in Japan to treat disseminated intravascular coagulation (DIC) since 2008. Previous studies have shown the efficacy of rhTM versus heparin therapy or non-rhTM therapy. We retrospectively evaluated and compared the efficacies of rhTM and gabexate mesilate (GM) in patients diagnosed with sepsis-induced DIC. From September 2010 to October 2012, patients with sepsis-induced DIC who were treated with rhTM (n = 13) or GM (n = 10) at Nagasaki Municipal Hospital were extracted. Patients receiving other anticoagulants in combination were excluded. Clinical information, laboratory data, Sequential Organ Failure Assessment (SOFA) scores, and DIC scores were obtained from the medical records. Mortality at days 7 and 30 after DIC diagnosis and changes in laboratory data and SOFA scores from days 1–7 were evaluated. The groups’ clinical characteristics did not differ, except for the relatively higher C-reactive protein (CRP) levels in the rhTM group (P = 0.0508). The survival rates of the rhTM and GM groups on days 7 and 30 were 92.3%, 69.2% and 80%, 70%, respectively, both group indicated similar mortality. However, on day 7, the platelet counts, SOFA scores, and CRP levels significantly improved in the rhTM group; the platelet counts and SOFA scores did not improve significantly in the GM group. The
platelet counts of the rhTM group significantly improved compared to the GM group ($P=0.004$). Recombinant human thrombomodulin might be more effective for sepsis-induced DIC than GM.

**Key words:** recombinant human thrombomodulin, gabexate mesilate, disseminated intravascular coagulation, sepsis, retrospective study
Introduction

Disseminated intravascular coagulation (DIC) is a serious complication in critically ill patients with infectious diseases and is associated with high mortality. DIC consequent to infectious disease is caused by excessive coagulation activity that generates intravascular fibrin, leading to small vessel thrombosis and eventually multiple organ failures [1, 2]. Treatment of the underlying disease is the cornerstone of DIC management. Although several anticoagulant therapies such as antithrombin, heparin, gabexate mesilate (GM), nafamostat mesilate (NM), and activated protein C have been developed, the efficacies of these anticoagulant therapies in sepsis-induced DIC patients remain controversial worldwide [3-5]. The guidelines for DIC in Britain, Italy, and Japan have recently been published, and there are some apparent discrepancies in the recommendations for anticoagulant therapies among these guidelines [3-5].

GM is a serine proteinase inhibitor that exerts an inhibitory effect on the clotting activity of thrombin and inhibits the hydrolytic reactions of thrombin and factor Xa with synthetic substrates [6]; this agent was initially approved to treat pancreatitis and was later approved to treat DIC by the Japanese Ministry Health and Welfare (JMHW). GM has been evaluated in several studies, but has not been shown to induce significant differences in mortality or DIC score improvements [6, 7]. However, GM remains
frequently used in patients with DIC in Japan, as it does not induce bleeding.

The novel biological agent recombinant human soluble thrombomodulin (rhTM) was approved in 2008 and has been used clinically in Japan to treat DIC. In a phase III randomized controlled trial in Japan, rhTM showed significant improvements with respect to DIC, but not mortality, when compared with heparin [8]. Yamakawa et al. demonstrated the effects of rhTM on improvements in mortality and organ dysfunction, compared with control groups (treated without rhTM) in historical studies [9-11]. In these studies, either a heparin or treatment without rhTM group was assigned as the control group. No reports have directly compared the efficacy of rhTM for DIC with those of serine proteinase inhibitors such as GM or NM. Therefore, we retrospectively evaluated and compared the efficacies of rhTM and GM in patients diagnosed with sepsis-induced DIC.

Patients and methods

Patients and study design

From among all patients admitted to the Nagasaki Municipal Hospital between September 2010 and October 2012, those who developed DIC and were treated with rhTM or GM were extracted. From them, the patients whose main cause of DIC was
considered as non-infectious disease, were excluded. Patients who died within 48 hours from initiation of DIC treatment were also excluded, because anticoagulant therapies didn’t seem to contribute their outcomes. Those patients with complicated fatal or life-threatening bleeding (intracranial, gastrointestinal, or pulmonary bleeding) at diagnosis and those who received other anticoagulants in combination were excluded.

In this study, we applied the Japanese Association for Acute Medicine (JAAM) criteria to diagnose DIC [12], and sepsis was defined as the presence of infection together with systemic inflammatory response syndrome [13].

This study was approved by the institutional review board and ethical committee of Nagasaki municipal hospital. The board waived the need for informed consent for a retrospective study such as this study.

**Data collection and evaluation**

Clinical information including the patients’ ages, sexes, medical histories, underlying diseases, infection sites, positive blood culture rates, antibiotic usage, laboratory data, the presence of acute kidney injury (AKI) [14] or septic shock or acute respiratory distress syndrome (ARDS), Sequential Organ Failure Assessment (SOFA) scores, and DIC scores (JAAM and JMHW) were obtained from the patients’ medical records. The presence or absence of platelet concentrate usage, steroid usage, surgical intervention,
polymyxin B hemoperfusion (PMX), continuous hemodiafiltration (CHDF) were also investigated.

Mortality at days 7 and 30 after the DIC diagnosis (day 1), serial changes in platelet counts and SOFA scores from day 1-7, the change of C-reactive protein (CRP) levels on day 1 and 7 were evaluated.

**Statistical analysis**

Data are expressed as group means ± standard deviations. Categorical and continuous variables were analyzed with the chi-square test or Fisher's exact test and Student’s $t$-test, respectively. A univariate analysis of the time to mortality was compared with a log-rank test. A P-value of <0.05 was considered statistically significant. The comparisons of platelet counts and SOFA scores between groups over time were analyzed by repeated measures analysis of variance (ANOVA) adjusted for the baseline values as a covariate and by post hoc Bonferroni test.

**Results**

The patient flow diagram is shown in Figure 1. Patients whose main cause of DIC was considered as non-infectious diseases such as advanced malignancy, acute interstitial
pneumonia and severe pancreatitis, were excluded. One case with severe gastrointestinal bleeding, two cases received other anticoagulants in combination, were also excluded. Two patients who died within 48 hours from initiation of DIC treatment (GM) were excluded. Anticoagulant therapy was chosen on the basis of each attending doctor’s decision.

Thirteen patients who were treated with rhTM and 10 who were treated with GM met our study inclusion criteria. Treatment with rhTM or GM was initiated within 24 hours from the DIC diagnosis in all cases, and the average administration durations of rhTM and GM were 6.08 and 7.3 days, respectively. The rhTM doses ranged from 130–360 U/kg, and GM was administered at a dosage of 30 mg/kg, according to the manufacturer’s drug information. The rhTM dose was reduced to 130 U/kg in patients with AKI. No side effects such as life-threatening bleeding were observed in either group.

The diagnostic, underlying disease, DIC score (JAAM), SOFA score, and laboratory data for the rhTM and GM groups are summarized in Tables 1 and 2, respectively. In the rhTM group (n = 13), the infections were in the lung (4 cases; 30.7%), abdomen (6 cases; 46.1%), and urinary tract (3 cases; 23.1%). In the GM group (n = 10), the infections were in the lung (3 cases; 30%), abdomen (3 cases; 30%), and urinary tract (3
cases; 30%), and 1 infection was catheter-related (10%). There was no significant difference between the groups. In the abdominal infection cases, 5 of 6 patients were peritonitis in the rhTM group, whereas 3 of 3 patients were acute cholangitis in the GM group. As mortality rates were low in these patients, this difference didn’t seem to affect the total survival rates. A comparison of the clinical characteristics of the rhTM and GM groups on DIC diagnosis is shown in Table 3. The patient age, sex, platelet counts, DIC scores (JMHW, JAAM), SOFA scores, the presence of septic shock, AKI, ARDS, surgical intervention, use of platelet concentrate, corticosteroid, PMX, positive blood culture rates, and solid tumor rates did not significantly differ between the groups. However, CRP and procalcitonin levels tended to indicate higher in the rhTM group than in the GM group respectively, although these difference was not significant ($P = 0.0508, 0.1429$, respectively). Although CHDF was not performed in both groups, PMX was performed in one patient of GM treated group. Nafamostat mesilate was used during PMX treatment in this case. Most bacterial infection-related cases were initially treated with meropenem, and some were switched to narrow-spectrum antibiotics specific for the causative pathogens.

The survival curves of the rhTM and GM groups are shown in Figure 2. The survival rates of the rhTM group on days 7 and 30 were 92.3% and 69.2%, respectively, and
those of the GM group were 80.0% and 70.0%, respectively. The survival rates of the both group were similar results (day 7, \( P = 0.406 \); day 30, \( P = 0.972 \)).

Figure 3 shows the serial changes in the platelet counts and SOFA scores of each groups from day 1 to 7. In the rhTM group, the platelet counts and SOFA scores significantly improved by day 7 (\( P=0.0041 \), 0.0101, respectively). Whereas, those of the GM group didn’t improve significantly by day 7 (\( P=0.1514 \), 0.0696, respectively)

Furthermore, the platelet counts of the rhTM group significantly improved compared to the GM group (\( P=0.004 \)). And we also evaluated the change of CRP levels on day 1 and day 7 for the patients in each group that survived up to day 7 after the DIC diagnosis, that of both groups significantly improved (Figure 4).

Discussion

The results of this study provided evidence that rhTM might have a beneficial effect on sepsis-induced DIC, compared with that of GM. Several previous retrospective studies have reported that rhTM treatment yielded improved survival rates, compared with those in the control group without rhTM [9, 11, 15]. Although in this study the mortality of rhTM was similar to that of the GM group. Three reasons for this finding were considered: first, the numbers of patients were small. Second, the rhTM group had the
possibility to develop more severe infections, as the CRP levels in the rhTM group were higher compared to those in the GM group (Table 3). Third, our study included elderly patients, in contrast to previous studies, as well as some patients with advanced cancers; these differences in the population might have affected the patients’ prognoses.

In a phase III randomized control study of hematological malignancy patients and sepsis-induced DIC patients, the rhTM-treated group exhibited significantly higher DIC resolution rates than did the heparin-treated group [8]. Another 2 retrospective studies of sepsis-induced DIC reported similar results [11, 15]. In our study, the platelet counts had significantly improved by day 7 in the rhTM group, whereas a similar response was not observed in the GM group. This result indicates the superiority of rhTM versus GM with respect to DIC resolution, although we could not calculate the DIC scores on day 7 due to the absence of data. Thrombomodulin has been reported to promote anti-inflammatory effects by suppressing the inflammatory responses induced by high-mobility group-B1 protein [16] or lipopolysaccharides [17]. In our study, rhTM was shown to have improved the SOFA scores and CRP levels on day 7. On the other hand, in the GM group, CRP levels significantly decreased, but SOFA scores didn’t.

In the present study, we evaluated and compared the clinical efficacies of rhTM and GM for the treatment of sepsis-induced DIC. To the best of our knowledge, this is the
first report to compare these agents in DIC patients. However, our study has several limitations, given its retrospective nature, single institution sample, and small sample size. In this study, rhTM promoted the early recovery of platelet counts when compared with GM, and therefore we expect that rhTM will contribute to the improved prognosis of sepsis-induced DIC. Additional multicenter, prospective, randomized controlled trials will be necessary to confirm the effects of rhTM for sepsis-induced DIC.

Conflict of interest

None declared.
References


**Figure legends**

**Figure 1.** Patient flow diagram.

rhTM, recombinant human thrombomodulin; GM, gabexate mesilate

**Figure 2.** Survival curves for the rhTM and GM groups.

The solid line indicates patients in the rhTM group, and the dotted line indicates patients in the GM group. The survival rates of the rhTM group (day 7, 92.3%; day 30, 69.2%) were higher than those of the GM group (day 7, 80%; day 30, 70%). The survival rates of the both group didn’t differ. (day 7, $P = 0.406$; day 30, $P = 0.972$).

rhTM, recombinant human thrombomodulin; GM, gabexate mesilate

**Figure 3.** Serial changes in the platelet counts and SOFA scores.

In the rhTM group, the platelet counts and SOFA scores significantly improved on day 7 ($P=0.0041$, 0.0101, respectively). Those of the GM group didn’t significantly improve by day 7 ($P=0.1514$, 0.0696, respectively). The platelet counts of the rhTM group significantly improved compared to the GM group ($P=0.004$)

rhTM, recombinant human thrombomodulin; GM, gabexate mesilate; SOFA, Sequential Organ Failure Assessment
**Figure 4.** Change of CRP levels

CRP levels in both groups significantly improved after 7 days from diagnosis of DIC.

rhTM, recombinant human thrombomodulin; GM, gabexate mesilate
Figure 1

Excluded cases

• Interstitial pneumonia (n=3)
• Use of antithrombin concentrate (n=1)

rhTM treated sepsis induced DIC (n=14)  
GM treated sepsis induced DIC (n=14)

Excluded cases

• Malignancy (n=3)
• Interstitial pneumonia (n=2)
• Severe pancreatitis (n=1)

• Gastrointestinal bleeding (n=1)
• Use of heparin (n=1)
• Acute death within 48 hours from initiation of DIC treatment (n=2)

rhTM treated group (n=13)  
GM treated group (n=10)
Figure 2

- rhTM (n=13)
- GM (n=10)
Figure 3

Platelet

- rhTM
- GM

SOFA score

- rhTM
- GM

※ $P < 0.05$ compared to GM
† $P < 0.05$ compared to day 1
Figure 4

- rhTM treated group
- GM treated group

※ P < 0.05
### Table 1.
Clinical information of recombinant human thrombomodulin (rhTM)-treated cases with DIC diagnoses. JAAM, Japanese Association for Acute Medicine; SOFA, Sequential Organ Failure Assessment
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Underlying disease</th>
<th>Age</th>
<th>DIC score (JAAM)</th>
<th>SOFA score</th>
<th>Platelet (× 10⁴/mm³)</th>
<th>CRP (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>Cerebral infarction sequelae</td>
<td>85</td>
<td>8</td>
<td>5</td>
<td>9.6</td>
<td>17.4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Hepatocellular carcinoma</td>
<td>84</td>
<td>4</td>
<td>10</td>
<td>0.6</td>
<td>14.5</td>
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<tr>
<td>Acute cholangitis</td>
<td>Gallbladder cancer</td>
<td>79</td>
<td>4</td>
<td>6</td>
<td>4.2</td>
<td>22.4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Cervical cancer</td>
<td>63</td>
<td>4</td>
<td>8</td>
<td>0.2</td>
<td>14.2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Ileus</td>
<td>85</td>
<td>5</td>
<td>7</td>
<td>10.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Catheter related infection</td>
<td>Diabete mellitus</td>
<td>89</td>
<td>5</td>
<td>11</td>
<td>10.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Acute cholangitis</td>
<td>Pancreas cancer</td>
<td>79</td>
<td>8</td>
<td>11</td>
<td>3.6</td>
<td>11.4</td>
</tr>
<tr>
<td>Acute cholangitis</td>
<td>Ovary cancer</td>
<td>68</td>
<td>6</td>
<td>6</td>
<td>0.8</td>
<td>26.5</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>Advanced gastric cancer</td>
<td>75</td>
<td>7</td>
<td>8</td>
<td>4.5</td>
<td>11.8</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Disuse syndrome</td>
<td>86</td>
<td>4</td>
<td>9</td>
<td>1.5</td>
<td>16.5</td>
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Table 2.
Clinical information of gabexate mesilate (GM)-treated cases with DIC diagnoses.
JAAM, Japanese Association for Acute Medicine; SOFA, Sequential Organ Failure Assessment
<table>
<thead>
<tr>
<th></th>
<th>rTM (n=13)</th>
<th>FOY (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>80 (±7.3)</td>
<td>79.3 (±8.42)</td>
<td>0.7797</td>
</tr>
<tr>
<td>Sex male/female</td>
<td>7/6</td>
<td>5/5</td>
<td>1.000</td>
</tr>
<tr>
<td>Platelet (× 10⁴/mm³)</td>
<td>6.18 (±2.55)</td>
<td>4.88 (±4.64)</td>
<td>0.2035</td>
</tr>
<tr>
<td>PT (INR)</td>
<td>1.52 (±0.55)</td>
<td>1.7 (±0.98)</td>
<td>0.7562</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>23.0 (±9.86)</td>
<td>14.4 (±6.96)</td>
<td>0.0508</td>
</tr>
<tr>
<td>Procalcitonin (mg/ml)</td>
<td>43.2 (5 cases)</td>
<td>17.2 (3 cases)</td>
<td>0.1429</td>
</tr>
<tr>
<td>DIC score (JMHW)</td>
<td>5.9 (±1.8)</td>
<td>6.2 (±1.14)</td>
<td>0.6784</td>
</tr>
<tr>
<td>DIC score (JAAM)</td>
<td>5.8 (±1.4)</td>
<td>5.5 (±1.65)</td>
<td>0.419</td>
</tr>
<tr>
<td>SOFA score</td>
<td>8.5 (±2.6)</td>
<td>8.1 (±2.13)</td>
<td>0.6846</td>
</tr>
<tr>
<td>Septic shock</td>
<td>8/13</td>
<td>5/10</td>
<td>0.6850</td>
</tr>
<tr>
<td>AKI</td>
<td>5/13</td>
<td>3/10</td>
<td>1.000</td>
</tr>
<tr>
<td>ARDS</td>
<td>3/13</td>
<td>0/10</td>
<td>0.2292</td>
</tr>
<tr>
<td>Sites of infection</td>
<td>4/6/3/0</td>
<td>3/3/3/1</td>
<td>N.S.</td>
</tr>
<tr>
<td>(lung/abdomen/urinary tract/catheter)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>3/13</td>
<td>5/10</td>
<td>0.2213</td>
</tr>
<tr>
<td>Solid tumor patients</td>
<td>5/13</td>
<td>6/10</td>
<td>0.4136</td>
</tr>
<tr>
<td>Use of platelet concentrate</td>
<td>4/13</td>
<td>4/10</td>
<td>0.6850</td>
</tr>
<tr>
<td>Use of steroid</td>
<td>0/13</td>
<td>2/10</td>
<td>0.1779</td>
</tr>
<tr>
<td>PMX</td>
<td>0/13</td>
<td>1/10</td>
<td>0.4348</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>5/13</td>
<td>2/10</td>
<td>0.4050</td>
</tr>
<tr>
<td>Mortality rate on day 7 (%)</td>
<td>7.7</td>
<td>20</td>
<td>0.406</td>
</tr>
<tr>
<td>Mortality rate on day 30 (%)</td>
<td>30.8</td>
<td>30</td>
<td>0.972</td>
</tr>
</tbody>
</table>

**Table 3.** Comparison of the clinical characteristics of the rhTM and GM groups with DIC diagnoses. rhTM, recombinant human thrombomodulin; GM, gabexate mesilate; JMHW, Japanese Ministry of Health and Welfare; JAAM, Japanese Association for Acute Medicine; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome.