Impact of Recombinant Human Soluble Thrombomodulin for Disseminated Intravascular Coagulation

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Abstract. *Background: Early treatment of disseminated intravascular coagulation (DIC) can be associated with improved early outcomes. We aimed to evaluate the effectiveness of recombinant human soluble thrombomodulin (rTM) administration in patients with peritonitis-induced DIC. Patients and Methods: We treated 39 patients with DIC or pre-DIC caused by peritonitis at the Department of Surgery and Science, Kyushu University, and related facilities between January and December 2013. Results: Patients surviving to 28 days after DIC treatment had significantly better platelet counts, DIC scores, and sequential organ failure assessment scores at 7 days than did those who died earlier than 28 days. Patients receiving rTM had significantly better overall survival rates at 28 days and the results of multivariate analysis showed that rTM administration for DIC treatment was a prognostic indicator of 28-day survival in patients with peritonitis. Conclusion: rTM administration for the treatment of DIC or pre-DIC complicated by peritonitis had acceptable early outcomes.*

Disseminated intravascular coagulation (DIC) is a clinical entity characterized by the systemic activation of coagulation pathways, which leads to fibrin deposition in microvessels and inflammatory reactions. Consumption of platelets and coagulation factors causes clinical bleeding and, with enhanced fibrinolysis, results in organ failure (1, 2). DIC is associated with high mortality in patients with severe sepsis and the clinical course can be rapid and severe (3). Therefore, both early diagnosis and early treatment are required to improve outcomes.

Peritonitis due to gastrointestinal tract perforation or anastomotic leakage after gastrointestinal surgery is a frequent indication for emergency operation and when complicated by DIC, carries a poor prognosis in severe cases (4). However, there have been few reports focusing on DIC treatment in patients with peritonitis.

The novel biological agent, recombinant human soluble thrombomodulin (rTM) was recently approved and has been used clinically for DIC treatment in Japan. rTM is effective in treating DIC (5, 6). Our aim was to clarify the efficacy of rTM administration in patients with peritonitis-induced DIC.

Patients and Methods

We analyzed the records of 100 patients who were diagnosed with DIC or pre-DIC requiring the same treatment as the patients with DIC at the Department of Surgery and Science, Graduate School of Medical Science, Kyushu University, and 15 related facilities between January and December 2013. This retrospective and multicenter study was approved by the Ethics Committees of each hospital (no.25-318) and followed the guidelines of the Declaration of Helsinki. Informed consent was obtained from all patients for use of the details of their records. Of the 100 patients, we retrospectively analyzed data for 39 patients with peritonitis-induced DIC or pre-DIC.

DIC was evaluated using the diagnostic criteria of the Japanese Association for Acute Medicine (JAAM) DIC scoring system. DIC was diagnosed when the DIC score exceeded four points. Patients with pre-DIC were defined as those having a score of ≤ 3 points, but requiring the same treatment as the patients with DIC. The specific identical treatment for DIC and pre-DIC depended on each facility's protocols, as well as those for treating peritonitis. We administered

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Table I. *Comparison of clinical characteristics of peritonitis in survivors vs. non-survivors 28 days after treatment for disseminated intravascular coagulation (DIC). Values are expressed as number (percentage) or median (range).*

Variable	Survivors (n=28)	Non-survivors (n=11)	*p*-Value
Age (years)	77 (50-98)	69 (50-92)	0.795
Gender (male/female)	15/13	6/5	0.956
Cause of peritonitis			0.187
Perforation	24	7	
Anastomotic leakage	4	4	
GI location (upper/lower)	15/13	6/5	0.956
Platelet count	9.9 (1.2-26.9)	6.9 (0.3-51.6)	0.800
Platelet count at 7 days	11.7 (2.2-50.7)	2.7 (0.6-8.1)	0.004
PT-INR	1.32 (0.87-5.25)	1.38 (1-3.6)	0.248
FDP	11 (5.3-78.4)	20.2 (6.3-29.6)	0.676
D-Dimer	7.2 (1.3-27.8)	6.6 (2.1-16.7)	0.701
DIC score	3 (0-7)	5 (2-6)	0.112
DIC score ≥4	13 (46.4%)	8 (72.7%)	0.171
DIC score at 7 days	3 (0-7)	5 (4-7)	0.001
DIC score ≥4 at 7 days	9 (32.1%)	7 (100%)	0.001
SOFA score	4.5 (1-16)	8 (0-18)	0.063
SOFA score at 7 days	3.5 (0-13)	13 (3-19)	0.017
rTM administration	26 (92.8%)	8 (72.7%)	0.125
AT III administration	12 (42.8%)	4 (36.3%)	0.710
PMX administration	15 (53.5%)	4 (36.3%)	0.480
Protease inhibitor administration	10 (35.7%)	3 (27.2%)	0.719

GI, Gastrointestinal; PT-INR, prothrombin time-international normalized ratio; FDP, fibrin/fibrinogen degradation products; DIC, disseminated intravascular coagulation; SOFA, sequential organ failure assessment; AT III, antithrombin III; PMX, polymyxin B-immobilized fiber.

Table II. *Comparison of the clinical characteristics of peritonitis in patients with or without recombinant human soluble thrombomodulin (rTM) administration. Values are expressed as number (percentage) or median (range).*

Variable	With rTM (n=34)	Without rTM (n=5)	*p*-Value
Age (years)	79(50-98)	68(51-69)	0.018
Gender (male/female)	16/18	5/0	0.050
Cause of peritonitis			0.267
Perforation	28	3	
Anastomotic leakage	6	2	
GI location (upper/lower)	17/17	4/1	0.348
Platelet count at diagnosis	10.1 (0.3-51.6)	7.8 (4.4-19.2)	0.680
Platelet count at 7 days	11.4 (0.6-50.7)	6.0 (0.6-8.1)	0.041
PT-INR	1.33 (0.87-5.25)	1.36 (1.18-1.63)	0.593
FDP	11.6 (5.3-78.4)	7 (6.3-29.6)	0.633
D-Dimer	7.2 (1.4-27.8)	3.5 (1.3-16.7)	0.633
DIC score at diagnosis	4 (0-7)	5 (3-6)	0.573
DIC score ≥4 at diagnosis	18 (52.9%)	3 (60%)	0.767
DIC score at 7 days	3 (0-7)	3.5 (2-5)	0.805
DIC score ≥4 at 7 days	14 (45.1%)	2 (50%)	0.854
SOFA score at diagnosis	5.5 (1-16)	4 (0-16)	0.680
SOFA score at 7 days	4 (0-17)	11 (5-19)	0.036
AT III administration	14 (41.1%)	2 (40.0%)	0.960
PMX administration	18 (52.9%)	1 (20%)	0.341
Protease inhibitor administration	10 (29.4%)	3 (60%)	0.310
7-Day mortality	3 (8.8%)	2 (40%)	0.114

GI, Gastrointestinal; PT-INR, prothrombin time-international normalized ratio; FDP, fibrin/fibrinogen degradation products; DIC, disseminated intravascular coagulation; SOFA, sequential organ failure assessment; AT III, antithrombin III; PMX, polymyxin B-immobilized fiber.

Table III. *Multivariate analysis for overall survival in patients with peritonitis.*

Variable	Hazard ratio	95% CI	*p*-Value
Age (increase *vs.* decrease)	1.05	0.97-1.17	0.218
Sex (female *vs.* male)	1.55	0.24-10.7	0.632
Cause of peritonitis (anastomotic leakage *vs.* perforation)	2.45	0.33-18.2	0.359
GI lesion (lower *vs.* upper)	3.62	0.47-49.5	0.227
Platelet count at diagnosis (decrease *vs.* increase)	1.05	0.98-1.15	0.145
DIC score at diagnosis (increase *vs.* decrease)	1.23	0.71-2.33	0.461
SOFA score at diagnosis (increase *vs.* decrease)	1.13	0.98-1.34	0.070
rTM administration (without *vs.* with)	10.8	1.06-186.2	0.044
AT III administration (without *vs.* with)	1.25	0.20-7.01	0.793
PMX administration (without *vs.* with)	2.75	0.39-25.3	0.306
Protease inhibitor administration (without *vs.* with)	1.50	0.37-7.84	0.575

CI, Confidence interval; GI, gastrointestinal; DIC, disseminated intravascular coagulation; PT-INR, prothrombin time-international normalized ratio; FDP, fibrin/fibrinogen degradation products; DIC, disseminated intravascular coagulation; SOFA, sequential organ failure assessment; AT III, antithrombin III; PMX, polymyxin B-immobilized fiber.

rTM at a dose of 380 U/kg (5). We excluded patients with active life-threatening bleeding resulting in shock and evaluated treatment outcomes according to the overall survival rate at 28 days after initiation of the DIC treatment. We classified patients based on whether they survived to 28 days and whether they received rTM.

Continuous variables without normal distribution were compared using non-parametric tests and categorical variables were compared using Fisher's exact test. The overall survival rate was calculated using the Kaplan–Meier estimator and compared using the log-rank test, and multivariate analysis was performed using the Cox's

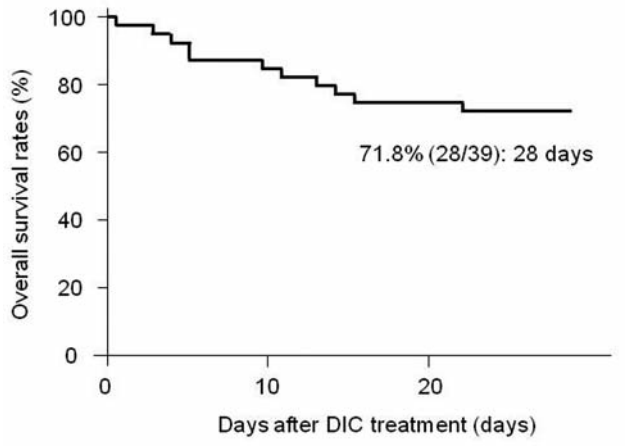

Figure 1. *Overall survival curve after initiation of disseminated intravascular coagulation treatment in patients with peritonitis.*

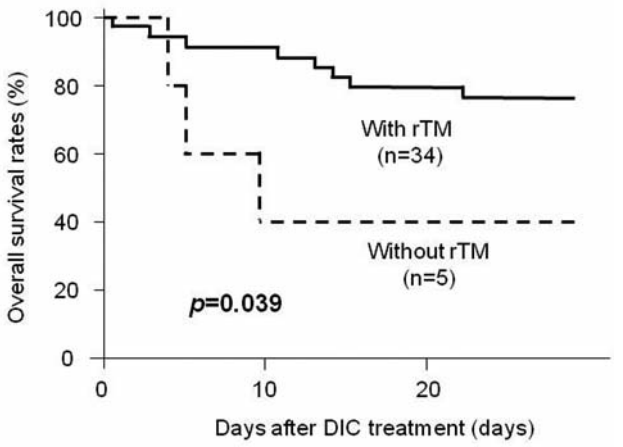

Figure 2. *Comparison of overall survival curves after initiation of treatment for peritonitis-induced disseminated intravascular coagulation(DIC) or pre-DIC comparing patients administered recombinant human soluble thrombomodulin (rTM) versus those without. The survival rate of patients treated with rTM was significantly higher than those not receiving rTM (p=0.039).*

proportional hazards model. Differences were considered significant at $p<0.05$ and all statistical analyses were performed using the JMP software (SAS Institute, NC, USA).

Results

Comparison of the clinical and laboratory data between survivors and non-survivors at 28 days after DIC treatment. As shown in Table I, patients surviving at 28 days after treatment for peritonitis-induced DIC or pre-DIC had significantly better platelet counts, DIC scores, and sequential organ failure assessment (SOFA) scores at 7 days than did the non-survivors. Factors at the initiation of DIC treatment did not differ significantly between the two groups.

Comparisons of the clinical and laboratory data between patients with and without rTM administration for DIC treatment. Patients receiving rTM were significantly older and had better platelet counts and SOFA scores 7 days after treatment for peritonitis-induced DIC or pre-DIC than did patients without rTM and they also tended to have a lower 7-day mortality rate (Table II).

Overall survival in patients with peritonitis. The overall survival rate 28 days after initiation of the DIC treatment in patients with peritonitis was 71.8%, and 28 out of the 39 patients were alive after the 28-day observation period (Figure 1).

Survival curves for patients with *versus* those without rTM administration was significantly better (Figure 2). Multivariate analysis using the Cox's proportional hazards regression model including pretreatment factors identified that rTM administration was an independent prognostic factor (Table III).

Discussion

Our results showed that rTM administration improved the platelet count and SOFA score at 7 days after DIC treatment and carried a better prognosis than no rTM administration for patients with peritonitis-induced DIC or pre-DIC. rTM administration was also an independent predictor of 28-day survival. To our knowledge, ours is the first clinical study of the effect of rTM administration in patients with peritonitis-induced DIC or pre-DIC.

Early treatment for DIC can be associated with improved outcomes. Approximately 43% (16/39) of patients in our study were classified as pre-DIC status; however, the number of patients who fulfilled the JAAM criteria (DIC score ≥4), SOFA score, cause of peritonitis, location, blood data, and initiation of another DIC treatment at baseline status was not significantly different between those treatise with and without rTM administration, despite the small sample size. Therefore, we believe comparisons between the two groups were valid.

TM is a transmembrane glycoprotein expressed predominately on the luminal surface of endothelial cells lining normal blood vessels that are in constant contact with blood under physiological conditions. TM can bind to activated thrombin, disabling its ability to activate platelets and cleave fibrinogen. The TM–thrombin complex also cleaves protein C to activated protein C, which in turn degrades factor Va and factor VIIIa, preventing further thrombin generation. Exposure of endothelial cells to inflammatory cytokines results in down-regulation of TM and increased thrombogenicity, which could

contribute to the development of DIC with concurrent infection (7). In animal studies, rTM administration was effective in the treatment of sepsis. rTM inhibited secretion of cytokines and high-mobility group box 1 protein (8) and the anti-inflammatory action peculiar to these proteins is a reason why rTM is expected to be useful in controlling the inflammatory reaction in peritonitis.

In this study, the SOFA score 7 days after DIC treatment in surviving patients was higher than that of non-surviving patients, and the 7-day SOFA score in patients with rTM administration improved compared with that in patients who did not receive rTM. Yamakawa *et al*. showed that rTM significantly reduced the SOFA score compared to the control group, and 28-day mortality improved significantly (9). Therefore, the 7-day SOFA score might be influenced by the systemic anti-inflammatory action of rTM. These results indicate that rTM may have a protective effect on organ injury complicated by peritonitis-induced DIC or pre-DIC.

Cox regression analysis indicated that 28-day mortality in patients with rTM administration improved significantly compared with that in patients without rTM, although our study sample size was small. It is thought that rTM affects the treatment not only of overt DIC, as diagnosed by the JAAM criteria (DIC score ≥4), but also of pre-DIC (DIC score <3), complicated by peritonitis.

Despite our encouraging results, there are several limitations to our study. The first is a lack of statistical power given the small sample size, especially for patients without rTM administration. The second is the variability in DIC treatment protocols and selection criteria at each institution. These limitations will need to be addressed in future randomized control trials.

In conclusion, we found that rTM had a significant beneficial effect on 28-day mortality in patients with peritonitis-induced DIC or pre-DIC. Moreover, the SOFA score and platelet count 7 days after DIC treatment improved with rTM administration compared with no rTM administration. Further clinical investigations are necessary to evaluate the effect of rTM on the molecular mechanisms of peritonitis-induced DIC.

Conflicts of Interest

The Authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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