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Effectiveness of Soluble Recombinant Human Thrombomodulin in Patients with Severe Acute Pancreatitis Complicated by Disseminated Intravascular Coagulation

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Abstract

Objective: We aimed to evaluate retrospectively the effect of soluble recombinant human thrombomodulin (rTM) on prognosis in patients with severe acute pancreatitis complicated by disseminated intravascular coagulation (DIC).

Methods: Based on Japanese diagnostic criteria of acute pancreatitis and DIC, patients who entered our intensive care unit (ICU) were selected. Comparisons were made between patients treated with rTM (rTM group) and without rTM (control group).

Results: A total of 38 patients were selected, and rTM was administered to 13 patients. Mortality on the 60th day after entering the ICU was significantly lower in the rTM group (15%) as compared with the control group (56%) (p=0.036). Although the platelet count was significantly lower in the rTM group at the start of treatment, the reversal rate from DIC was significantly higher than in the control group (rTM 62%, control 24%, p=0.035). According to logistic regression analysis of therapeutics, only rTM contributed to survival on the 60th day (odds ratio, 12.5; 95% confidence interval, 1.80-160; p=0.009).

Conclusion: In patients with severe acute pancreatitis complicated by DIC, it was suggested that rTM might improve the prognosis of survival, even if the platelet count was markedly reduced.

Keywords: Disseminated intravascular coagulation, mortality, severe acute pancreatitis, thrombomodulin

Introduction

Acute pancreatitis is defined as a condition that can affect other systemic organs due to acute inflammation of the pancreas. In the majority of cases, the epigastric symptoms suddenly appear, and diagnosis is obtained from the pancreatic enzyme elevation and image findings (1, 2). Approximately one-third of acute pancreatitis is diagnosed as severe acute pancreatitis due to the elevation of inflammatory markers and the complication of organ dysfunction (3).

In Japan, a large-scale epidemiological survey has been conducted since the 1980s, and increases in the number of patients and the incidence of severe acute pancreatitis have been reported (1). In severe acute pancreatitis, as a result of a systemic inflammatory reaction, there is a high possibility of multiple organ failure. In the most severe cases, blood coagulation disorder is recognised, and it is reported that, when accompanied by disseminated intravascular coagulation (DIC), it brings the risk of multiple organ dysfunction (4). The acute pancreatitis mortality rate is 2.6%, and that of severe acute pancreatitis is 10.1% (1).

Disseminated intravascular coagulation is considered to be a risk factor for sepsis, and effective DIC treatment is reported to improve the prognosis of patients with sepsis (5). In recent years, the efficacy of soluble recombinant human

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thrombomodulin (rTM) as a DIC therapeutic agent has been reported (5-7). Since DIC is a frequent complication in severe acute pancreatitis, the therapeutic effect of rTM for severe acute pancreatitis was expected. However, no reports verified the effect of rTM on severe acute pancreatitis, and its effect on prognosis was unknown. In this study, therefore, a retrospective study was conducted on the effect of rTM on prognosis in patients with severe acute pancreatitis complicated by DIC.

Methods

This study was conducted after being approved by the ethics committee of the University of Miyazaki (#O-0151). We conducted a retrospective survey using an electronic medical record system for patients who entered the intensive care unit (ICU) of Miyazaki University Hospital during the 8 years from January 1, 2009, to December 31, 2016. Briefly, we selected patients with pancreatitis as the diagnosis on an electronic medical record (CUMNAVI, Core Create System, Miyazaki, Japan) and biological information management system (PrimeGaia, Nihon Kohden, Tokyo, Japan), and those who received treatment for severe acute pancreatitis in the ICU were selected according to details from the medical information.

Severe acute pancreatitis was diagnosed using the Japanese severity scoring system (3). Inspection parameters of the Japanese severity scoring system include base excess, arterial oxygen partial pressure, urea nitrogen, lactate dehydrogenase, platelet count, calcium concentration, C-reactive protein (CRP), systemic inflammatory response syndrome (SIRS) score, age, etc. The diagnosis of severe acute pancreatitis was judged by contrast computed tomography findings or by judgement scores reaching 3 points or more (3). For the first, second and 3rd day in the ICU, Japanese severity scores for acute pancreatitis were calculated.

After the patients to be investigated were determined, basic patient information, the cause of severe acute pancreatitis, various blood test results, image diagnostic information, vital signs after entering the ICU and treatment details were obtained. Patient mortality rates were evaluated on the 28th and 60th day after entering the ICU.

Furthermore, patients diagnosed as having DIC according to the Japanese Association for Acute Medicine criteria (JAAM criteria) and the judgement of the doctor in charge at the time of medical examination were discriminated. Test items of JAAM criteria include the SIRS score, platelet count, prothrombin time-international normalised ratio (PT-INR), fibrin degradation product (FDP) concentration and diagnosis of DIC based on 4 points or more (8). DIC based on the JAAM criteria was judged on the 7th day after entering the ICU. Patients who had a DIC score based on JAAM criteria lower than 3 by the 7th day were judged as reversed, and those whose DIC scores did not decrease by the 7th day, or those who died within 7 days without recovering, were categorised as having irreversible DIC.

The primary endpoint was set as the evaluation of the effect of rTM on the 60th day of life after prognosis of patients with DIC-merged severe acute pancreatitis. The secondary endpoint was set as the evaluation of the effect of rTM on the damage to several organs, including coagulation dysfunction. To evaluate the mortality rate, diagnostic parameters of DIC and the transition of organ failure, a study was conducted comparing those treated with rTM (rTM group) and those treated without rTM (control group). Organ failure was evaluated by calculating the Sequential Organ Failure Assessment (SOFA) score from the 1st to the 7th day in the ICU. Items evaluated in a SOFA score include the ratio of partial pressure arterial oxygen and fraction of inspired oxygen (P/F ratio), platelet count, total bilirubin concentration, haemodynamics, Glasgow coma scale (GCS) and creatinine concentration. Since several therapeutics were administered for the treatment of severe acute pancreatitis and/or DIC, a multiple logistic regression analysis of the therapeutics was conducted.

Statistical analysis

Statistical software (JMP 11, SAS Institute, Cary, NC, USA) was used to calculate the sample size and analyse data. The sample size was calculated based on a comparison of mortality rates between the rTM group and the control group. Forty-six patients were required to have an 80% chance of detecting, as significant at the 5% level, an increase in the primary outcome measure from 40% in the control group to 80% in the rTM group. As for comparisons of the two groups, among the obtained data, a t-test or Mann-Whitney U test was used for continuous variables, and a chi-squared test or Fisher's exact test was used for discrete variables. Data were expressed as the mean±standard deviation (SD). A multivariate logistic regression analysis of protease inhibitors and DIC therapeutics was performed to obtain the independent factors associated with survival on the 60th day. The five variables selected based on clinical experience and the previous knowledge included rTM, gabexate mesylate, nafamostat mesylate, urinastatin and antithrombin III, and they were processed by forced-entry method. The significance level was set at $p<0.05$.

Results

Overview of patients with severe acute pancreatitis

Among the 7769 patients admitted to the ICU during the study period, the details of 200 patients diagnosed with acute pancreatitis were investigated, and 43 subjects who were treated due to severe acute pancreatitis were selected as subjects to be investigated in this study. The 43 patients had an

average age of 59 years (male/female, 29/14). The causes of severe acute pancreatitis were drinking alcohol, 28%; idiopathic, 28%; gallstone, 26%; and endoscopic retrograde cholangiopancreatography, 16%. The Japanese severity score for acute pancreatitis was 4.5±1.8 (mean±SD). In 43 patients with severe acute pancreatitis, the mortality on the 28th and 60th days were 28% and 37%, respectively.

According to the JAAM score, DIC was confirmed in 38 patients (88%) within 3 days of starting ICU treatment. Initial treatments including mechanical ventilation (70%) and continuous haemodiafiltration (70%) were performed after ICU admission, and prophylactic antibiotics (imipenem 40%, meropenem 47%) were administered. Protease inhibitors (gabexate 74% and urinastatin 21%) were administered as a treatment for severe acute pancreatitis and/or DIC, and antithrombin III preparation (51%) and rTM (34%) were used for DIC. rTM was administered at 130 IU/kg/day to 7 patients and 380 IU/kg/day to 6 patients, for 1-6 days. rTM administration was started, on average, 58 hours after the onset of severe acute pancreatitis. Mortality rates at the 28th and 60th days in the 38 patients were 32% and 42%, respectively.

Table 1. Comparisons of demographics and clinical characteristics between the groups

		Control n=25		rTM n=13		p
Age	Mean (SD)	59.7	(18)	56.6	(13)	0.591
Gender						
Male	Number (%)	14	(56)	10	(77)	0.205
Height, cm	Mean (SD)	158	(9)	164	(10)	0.089
Body weight, kg	Mean (SD)	57.6	(14)	59.8	(14)	0.645
Aetiology						
Alcohol	Number (%)	6	(24)	4	(31)	0.709
Gallstone	Number (%)	6	(24)	2	(15)	0.689
Idiopathic	Number (%)	9	(36)	3	(23)	0.486
Iatrogenic	Number (%)	1	(4)	3	(23)	0.392
Other	Number (%)	1	(4)	1	(8)	1.000
Japanese severity score for acute pancreatitis						
Day 1	Mean (SD)	4.6	(2)	5.1	(2)	0.324
Day 2	Mean (SD)	4.9	(2)	4.7	(2)	0.627
Day 3	Mean (SD)	4.4	(2)	4.6	(1)	0.663
Mechanical ventilation	Number (%)	21	(84)	9	(69)	0.289
Continuous haemodiafiltration	Number (%)	20	(79)	10	(77)	0.825
Arterial infusion therapy	Number (%)	3	(12)	2	(15)	0.588
Early fluid resuscitation, mL day^{-1}	Mean (SD)	4079	(1517)	4297	(1800)	0.695
Intravenous use of protease inhibitors						
Gabexate mesilate	Number (%)	21	(84)	6	(46)	0.024*
Nafamostat mesilate	Number (%)	2	(8)	2	(15)	0.482
Urinastatin	Number (%)	5	(20)	1	(8)	0.643
Antithrombin III	Number (%)	10	(40)	10	(77)	0.043*
Use of prophylactic antibiotics						
Meropenem	Number (%)	11	(44)	7	(54)	0.734
Imipenem	Number (%)	9	(36)	5	(38)	0.881
Other	Number (%)	4	(16)	2	(15)	0.973
Days of intensive care unit	Mean (SD)	15	(12)	13	(8)	0.817
Days of hospital stay	Mean (SD)	37	(29)	39	(22)	0.559
Mortality						
28 day	Number (%)	10	(40)	2	(15)	0.158
60 day	Number (%)	14	(56)	2	(15)	0.036*

*p<0.05. Statistically significant p-value determined by chi-squared test. SD: standard deviation

Comparisons of patients with and without rTM treatment

For the 38 patients with severe acute pancreatitis who approved the merger of DIC, comparisons of the patients treated with rTM (rTM group, n=13) and without rTM (control group, n=25) are shown in Table 1. No differences were observed between groups in the patient background, Japanese pancreatitis severity score and the cause of pancreatitis. There was no difference in most treatment details; however, gabexate was significantly used in the control group, and antithrombin III was significantly used in the rTM group. The mortality rate on the 60th day after entering the ICU was significantly higher in the control group (56%) as compared with the rTM group (15%) (Table 1).

When comparing DIC scores based on JAAM criteria, there was no difference in the DIC scores between the groups at the start of treatment. However, significantly lower values were observed in the rTM group on the 6th day with the disease than in the control group (p=0.048) (Figure 1). When comparing various markers as indicators of DIC, in the rTM group, a significantly low platelet count was observed at the beginning of treatment (rTM 82±61×10^3/μL, control 148±104×10^3/μL, p=0.029) (Figure 2). There was no difference between the groups in the FDP, PT-INR and SIRS score. Including those who died within 7 days without recovering from DIC, the proportion of those recovered from DIC was significantly higher in the rTM group than in the control group (Figure 3).

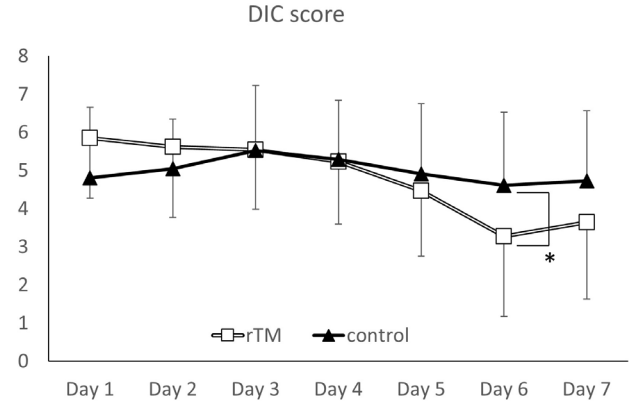

Figure 1. Comparisons and time course change of the DIC score
There were no significant differences in DIC scores at the start of treatment; however, on Day 6, the DIC score of the rTM group significantly improved.
***p<0.05; comparison between groups**

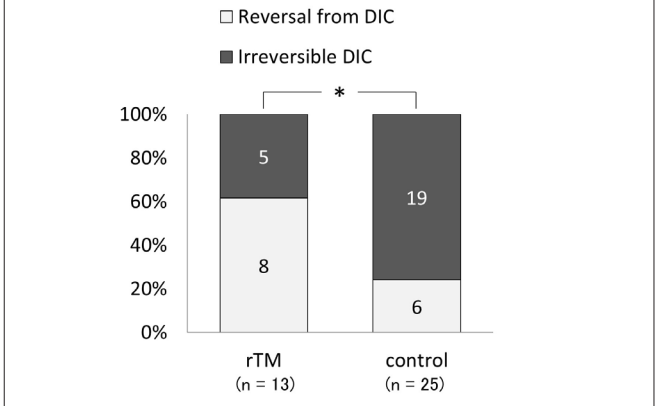

Figure 3. Comparisons of the DIC reversal rate
The DIC reversal rate (percentage of patients with a DIC score of 3 or less) on Day 7 was significantly higher in the rTM group (rTM 61.5%, control 24.0%, *p=0.035). Of the 24 subjects who did not recover from DIC (irreversible DIC), five died within 7 days, one was in the rTM group and four were control group. The 60-day mortality of patients who were judged as the irreversible DIC was 58%.

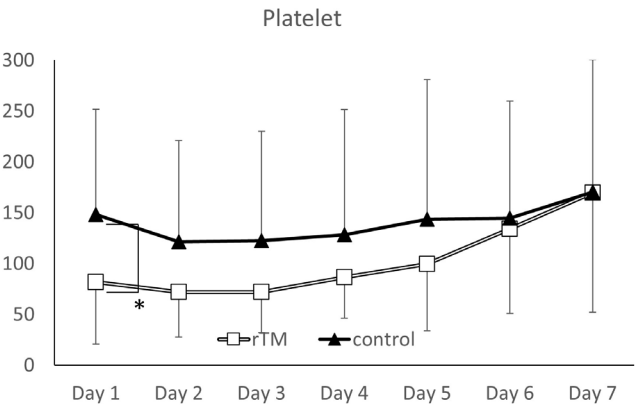

Figure 2. Comparisons and time course change of platelet counts
At the start of treatment, platelet counts were significantly lower in the rTM group. However, on Day 6, the platelet count recovered to the control group's level (approximately 100×10^3/μL).
***p<0.05; comparison between groups**

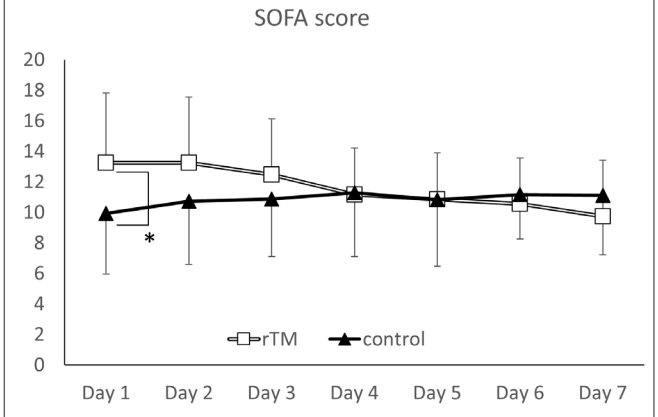

Figure 4. Comparisons and time course change of SOFA scores
SOFA scores were significantly higher at the start of treatment in the rTM group. SOFA scores tended to decrease with time in the rTM group.
***p<0.05; comparison between groups**

Table 2. Multiple logistic regression analysis of administered pharmacological treatments associated with the 60-day survival in patients with disseminated intravascular coagulation due to severe acute pancreatitis

Variables	Survivors n=22	Dead n=16	B	SE	Odds Ratio	95% CI	p
rTM	11	2	1.26	0.56	12.46	1.80-159.98	0.009*
Gabexate mesilate	15	12	0.42	0.50	2.34	0.35-21.03	0.385
Nafamostat mesilate	3	1	0.44	0.67	2.39	0.21-62.40	0.496
Urinastatin	3	3	− 0.17	0.51	0.71	0.09-5.33	0.734
Antithrombin III	12	8	−0.36	0.41	0.49	0.09-2.31	0.375

*p<0.05. Statistically significant P-value determined by logistic regression. Note: Odds ratio for all variables were given in reference to no-use of respective pharmacological agent. The Nagelkerke's R-square of the model was 0.25. B: estimated coefficient; SE: standard error; CI: confidence interval

By comparing SOFA scores, which is a scoring system for organ disorders, a significantly high value was observed in the rTM group on the 1st day (rTM 13.2±4.6, control 9.9±4.0, P=0.030) (Figure 4). Regarding parameters that are the basis of SOFA, a recovery tendency was observed in the rTM group in GCS scores in addition to changes in the platelet count described above. There was no difference between the groups in the total bilirubin concentration, creatinine concentration, P/F ratio and haemodynamics. A white blood cell count improvement was recognised from around Day 4; however, there were no statistically significant differences regarding inflammation markers, including CRP.

Results of multivariate logistic regression analysis on medical treatments, with 60-day survival as the dependent variable, demonstrated a significant improvement in patients administered rTM (Table 2).

Discussion

Since rTM is not assumed to be a remedy for acute pancreatitis, reports give only few descriptions of rTM for the treatment of acute pancreatitis. Eguchi et al. (9) described the first clinical data showing the significant effectiveness of rTM in preventing necrotising pancreatitis in patients with severe acute pancreatitis.

rTM is a soluble protein purified by genetic recombination (6). rTM inhibits the production of thrombin, mainly by promoting the activation of protein C, and exerts a therapeutic effect on DIC, a state in which the balance of the coagulation fibrinolysis system is broken due to the presence of excessive thrombin (10). In addition, it is known that rTM has a strong anti-inflammatory effect, and it is suggested that it may be useful for the treatment of systemic inflammatory diseases such as severe acute pancreatitis (6). In sepsis, which is accompanied by systemic inflammation, rTM has been shown to be beneficial as a therapeutic agent for septic DIC (11-14). A retrospective study on rTM conducted in Japan confirmed an improvement in survival in sepsis patients (11-14). In our study, comparing the DIC score and the DIC reversal rate, DIC that is secondary to severe acute pancreatitis showed a tendency toward improvement in the group with rTM use, which may be related to improved survival.

In the group receiving rTM, platelet counts were significantly low at the start of treatment; SOFA scores were high. These results showed the presence of severity in the rTM group in this study. Despite the high severity, the reason for the relatively good survival in the rTM group is unknown.

The main pathology of severe acute pancreatitis is multiple organ failure due to cell death and systemic inflammatory reaction caused by various cytokines (15). Resulting from pancreatic cell injury, the elevation of blood lipase concentration, which is contained in pancreatic juice, and increase in the concentration of multiple inflammatory cytokines were observed (2, 16). High mobility group box 1 (HMGB1), a nuclear-chromatin-binding protein, is a regulator of the nucleosome structure and is one of the cytokines released during acute pancreatitis (15). HMGB1 released from dead cells acts as a damage-associated molecular pattern; it causes excessive inflammatory and immune responses and becomes a lethal mediator (17, 18). rTM binds to HMGB1 in a part of the constitutive domain and can inactivate the activation effect of HMGB1 on inflammatory cells (19). rTM decreases the HMGB1 concentration in lung lavage fluid and contributes to improvement of the survival rate in a lipopolysaccharide-induced lung injury model in mice (20). Since the meta-analysis has shown that serum HMGB1 concentration is related to the severity of severe acute pancreatitis (21), the relative improvement of prognosis shown in this study might be related to the inhibitory effect of rTM on the HMGB1 activity.

In severe acute pancreatitis, a low value of antithrombin is a risk factor (22). It is also pointed out that the administration of antithrombin may improve survival (22). In this study, it may be the reason why the rTM group had a good prognosis, as the number of people who received antithrombin was significantly higher in the rTM group. However, in a multivariate analysis, antithrombin was not significantly associated with the 60-day survival rate among some DIC therapeutics.

As compared with the incidence of DIC described in reports on severe acute pancreatitis in Japan in recent years (44%), the incidence of DIC in this study (88%) was considered to be remarkably high (9). In our hospital ICU, due to a limited number of beds, patients with complications of acute respiratory failure or acute renal impairment are often accepted preferentially, and due to such patient selection, this study may include patients with greater severity.

As for the limitations of this study, it was not a prospective study, it had an insufficient target number of patients, and the data for comparing the two groups included data of patients who died within 7 days (In some comparisons, especially on the 7th day, the data were insufficient). In Japan, rTM was approved for use in 2008, which was before the 1st day of our study period. However, rTM became widely used in clinical practice relatively late. There was a possibility that the date of treatment was relatively recent in the rTM group. There was no noticeable difference in patient background, but this may explain the difference in the treatment given to the rTM group and the control group, and it may also have influenced the results. Regarding the effect of rTM on severe acute pancreatitis, randomised control trials or larger observational studies are required.

Conclusion

In patients with severe acute pancreatitis combined with DIC, it was suggested that rTM may improve survival. The effect of improving prognosis could be related to promoting DIC treatment, especially platelet count recovery. No adverse reactions associated with rTM administration were observed in the subjects of the study, which is considered to be an easy-to-use therapeutic agent for severe acute pancreatitis. It was a surprising result that the prognosis improved despite the high severity at the beginning of treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Miyazaki University (#O-0151).

Informed Consent: The ethics committee waived the need for written informed consent from participants because of the retrospective design of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – T.Y.; Design – T.Y.; Supervision – M.T., T.S., I.T.; Resources – T.Y., M.T., T.S., I.T.; Materials – T.Y.; Data Collection and/or Processing – T.Y.; Analysis and/or Interpretation – T.Y., M.T., T.S., I.T.; Literature Search – T.Y., M.T., T.S., I.T.; Writing Manuscript – T.Y., M.T., T.S., I.T.; Critical Review – T.Y., M.T., T.S., I.T.

Conflict of Interest: The authors have no conflicts of interest to declare.

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