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Full Length Article

Multicenter clinical experience with recombinant soluble thrombomodulin for disseminated intravascular coagulation associated with severe acute cholecystitis

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ABSTRACT

Background: Severe acute cholecystitis (AC) is defined by the association of organ dysfunction, including hematological dysfunction, with AC. Severe AC is often complicated by disseminated intravascular coagulation (DIC), the diagnostic criteria of which overlap with AC-associated hematological dysfunction. Since the diagnosis of DIC often delays definitive surgical management of severe AC, treatment of DIC in this setting is clinically important. Recombinant human soluble thrombomodulin (rTM) is a new agent that has proven clinically useful for treating DIC. However, the relevance of rTM to sepsis-induced DIC caused by AC has not been clinically evaluated. This retrospective multicenter study aimed to determine the clinical impact of rTM on sepsis-induced DIC caused by AC.

Methods: This retrospective multicenter study initially included 68 consecutive patients and proceeded between July 2014 and December 2017. The inclusion criterion was sepsis-induced DIC caused by severe AC due to benign disease. Sixteen of the 68 patients were excluded in this study due to having advanced malignant tumors. Finally, 42 patients were enrolled in this study. We treated DIC with AC using Recomodulin® Injection (rTM) at doses of 130 or 380 U/kg/day.

Results: 17 and 25 patients were treated with and without rTM, respectively. Values on days 3 and 7 did not significantly differ between the groups for PT-INR ($P = 0.38$ and $P = 0.16$, respectively) and FDP ($P = 0.06$ and $P = 0.08$, respectively), and PLT was significantly increased in the rTM group at day 7 ($P = 0.03$). Resolution rates of DIC on day 7 were significantly higher in the group treated with, than without rTM (94.1% [16/17] vs. 68.0% [17/25], $P = 0.04$). Two patients in each group died of sepsis-induced DIC associated with severe AC, and thus mortality rates did not significantly differ.

Conclusions: rTM can may be improve the resolution rate of sepsis-induced DIC due to severe AC. Future studies should include more patients to validate our findings.

1. Introduction

Early laparoscopic cholecystectomy (LC) is the gold standard of treatment for acute cholecystitis (AC) [1–3]. However, the Tokyo Guidelines 2018 (TG18) [4] recommend appropriate antibiotics and general supportive care as first-line treatment for severe (Grade III) AC caused by complications imposed by substantially dysfunctional organs. The criteria for severe AC include neurological, cardiovascular, respiratory, renal, hepatic, or hematological dysfunction, which often delays LC. On the other hand, a mortality rate of 30–40% is associated with disseminated intravascular coagulation (DIC), which is the thrombotic occlusion of microvessels [5,6] that results from systemic activation of the coagulation pathway [7,8]. Severe AC is often complicated with DIC because the diagnostic criteria overlap with hematological dysfunction. Therefore, treating DIC before proceeding with LC is clinically important. Recombinant human soluble

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thrombomodulin (rTM) is a new agent that has proven clinically useful for treating DIC [9–17]. However, the relevance of rTM to sepsis-induced DIC caused by AC has not been clinically evaluated. This retrospective multicenter study aimed to determine the clinical impact of rTM on sepsis-induced DIC caused by AC.

2. Patients and methods

This retrospective multicenter study initially included 68 consecutive patients (median age, 78 years; range, 49–88 years; male, 11) and proceeded between July 2014 and December 2017 at Osaka Medical College, Osaka Saiseikai Nakatsu Hospital, Osaka Kaisei Hospital, and Moriguchi Keijinkai Hospitals. The inclusion criterion was sepsis-induced DIC caused by severe AC. Patients with malignant tumors were excluded to avoid the influence of such tumors on DIC scores [17–19]. Therefore, sixteen of the 68 patients were excluded in this study due to having advanced malignant tumors. Finally, 42 patients were enrolled in this study.

Patients provided written, informed consent to participate in this clinical trial. In addition, an announcement regarding our study was displayed at each hospital, asking patients to notify their physician if they did not wish to be included in this analysis. These measures were taken for the purpose of patient information, although this study is based on anonymized patient data without a correspondence table which does not require IRB approval according to ethical guideline of The Japanese Society of Gastroenterology.

2.1. Diagnosis and treatment of acute cholecystitis

All enrolled patients were assessed by non-invasive computed tomography (CT) and abdominal ultrasound, and diagnosed with severe AC according to TG18 on admission day. Severe AC was defined as the onset of dysfunction of at least one of the following six criteria: decreased consciousness level, cardiovascular symptoms (hypotension requiring dopamine > 5 mg/kg or any dose of norepinephrine), respiratory dysfunction (PaO_2/FiO_2 ratio < 300), renal dysfunction (oliguria; serum creatinine > 2.0 mg/dL), hepatic dysfunction (PT-INR > 1.5), or hematological dysfunction (platelets < $10^{10}/mm^3$).

AC was treated using appropriate intravenous antibiotics. Endoscopic (ERGBD) or percutaneous transhepatic gallbladder drainage (PTGBD) was also implemented depending on the status of each patient or the judgment of the attending physician. A duodenoscope was initially advanced into the ampulla of Vater. An ERCP catheter (MTW Endoskopie, Düsseldorf, Germany) was then inserted into the common bile duct, then a 0.025-in., VisiGlide guidewire (Olympus Medical Systems, Tokyo Japan) and a 0.035-in., RadiFocus guidewire M (Terumo, Tokyo Japan) were advanced into the gallbladder through the cystic duct. Thereafter, ERGBD proceeded via a 7-Fr nasal biliary tube or a 7-Fr pigtail plastic stent. Percutaneous transhepatic gallbladder drainage was achieved using a 7-Fr Amplatz Universal Drainage Catheter (Cook Medical, Tokyo Japan).

2.2. Diagnosis and treatment of DIC

We diagnosed DIC due to severe AC based on the criteria of the Japanese Association for Acute Medicine (JAAM) [20], which assigns 1 DIC point for each of the following: systemic inflammatory response syndrome (SIRS) score ≥ 3 [21], mild thrombocytopenia (platelets, ≥8.0 to < 12.0 × 10^{10}/L, or > 30% decrease within 24 h of admission), prolonged prothrombin time-international normalized ratio (≥1.2), and mildly elevated fibrin/fibrinogen degradation product (FDP) values (≥10 to < 25 μg/mL). Three DIC points were also assigned for each of severe thrombocytopenia (< 8.0 × 10^{10}/L or > 50% decrease within 24 h) and extremely elevated FDP values (≥25 μg/mL). We treated DIC with AC using Recomodulin® Injection (rTM; Asahi Kasei Pharma Corporation, Tokyo, Japan) at doses of 130 or 380 U/kg/day. The dose of rTM depended on creatinine clearance. In patients with renal failure, 130 U/kg/day of rTM was injected. Patients received rTM from the day of admission until the day of DIC resolution defined as the achievement of DIC scores ≤3 according to the JAAM criteria. Whether rTM was used depended on attending physicians.

2.3. Definitions and statistical analysis

The characteristics of the patients, DIC scores, and laboratory data were compared using Mann-Whitney *U* tests, Wilcoxon signed rank tests, and Fisher's exact tests between groups that had received rTM. The main outcome of the study was the DIC resolution rate after seven days of treatment. The DIC score, inflammatory laboratory data, SOFA, and the resolution rate were calculated before admission (day 0), and on days 3 and 7 after starting treatment. Adverse events associated with treating DIC using rTM, such as intestinal bleeding, were also evaluated [17–19]. Adverse events associated with procedures including ERGBD and PTGBD were evaluated according to the severity grading system of the American Society for Gastrointestinal Endoscopy lexicon [22]. Differences with $P < 0.05$ were considered significant. Continuous variables are expressed as means. All data were statistically analyzed mainly using SPSS version 13.0 statistical software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Characteristics of the patients

Table 1 shows that 17 (median age, 78 years; range, 49–88 years; male, 11) and 25 (median age, 70 years; range, 55–92 years; male, 17) patients were treated with and without rTM, respectively. The etiology of AC such as gallstones did not significantly differ between the groups ($P = 0.85$). The failure of other organs also did not significantly differ between the groups. Median SOFA scores on admission day were 5 (range, 4–8) and 4 (range, 4–8) in the groups treated or not treated with rTM, respectively.

Laboratory findings associated with DIC scoring or AC inflammation such as fibrin degradation products (FDP), platelets (PLT), PT-INR,

Table 1
Patient's characteristics.

	rTM group (n = 17)	Non-rTM group (n = 25)	P-value
Median age (yo, range)	78 (49–88)	70 (55–92)	0.19
Gender (male: female)	11: 6	17: 9	0.96
Etiology of cholecystitis (n)			
Stones	12	17	0.85
Other	5	8	
Heat failure (n)	3	4	0.88
Renal failure (n)	3	6	0.62
SOFA score (range)	5 (4 to 8)	4 (2 to 14)	0.22
DIC score (range)	5 (4 to 8)	4 (4 to 8)	0.07
SIRS (n)	16	20	0.20
FDP (μg/ml)	29.0 (10.0 to 86.8)	28.6 (6.0 to 115.1)	0.33
PLT (×10^3/L)	7.9 (5.0 to 20.1)	10.6 (7.0 to 30.7)	0.36
PT-INR	1.20 (0.99 to 1.49)	1.29 (1.2 to 2.04)	0.26
WBC (/μL)	12,200 (3260 to 24,010)	11,320 (1000 to 39,190)	0.11
CRP (mg/dL)	17.5 (0.48 to 40.73)	16.0 (1.26 to 31.6)	0.40
Drainage (n)			0.06
ERGBD	1	3	
PTGBD	5	10	

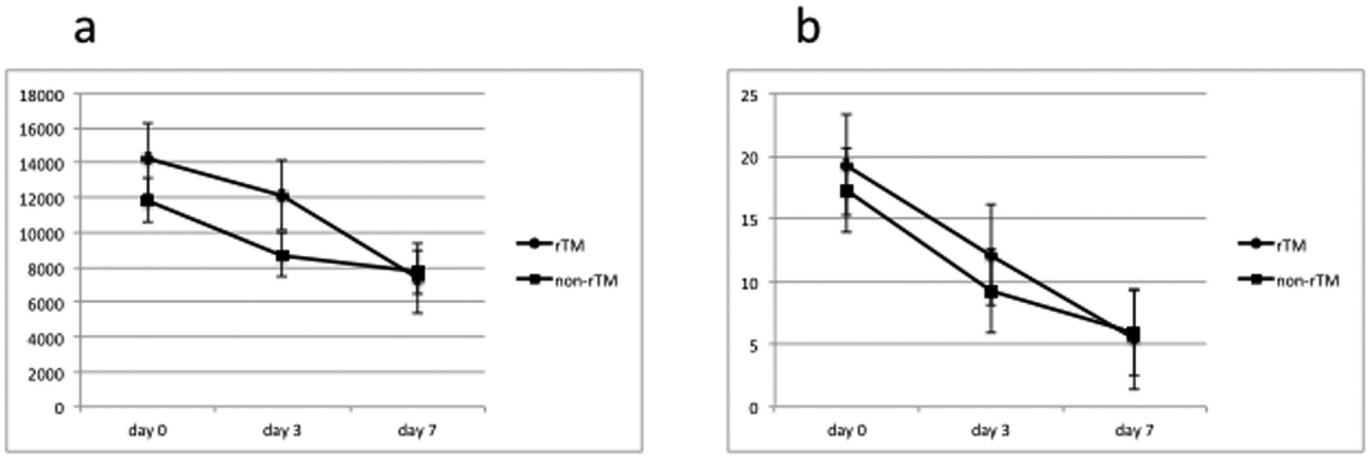

Fig. 1. Summary of changes in mean inflammatory data levels
(a. White blood cell count, b. C-reactive protein)
There are no significant differences on day 3 and 7. (rTM vs non-rTM: WBC, day 3 P = 0.07, day 7 P = 0.34; CRP, day 3 P = 0.05, day 7 P = 0.13).

white blood cells (WBC), C-reactive protein (CRP), total bilirubin (T-Bil), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) also did not significantly differ between the groups on admission day. Although more patients in the group that did not receive rTM tended to require gallbladder drainage, the difference did not reach significance (P = 0.06). Severe adverse events associated with procedures did not arise in either group.

Fig. 1 summarizes changes in inflammation among patients with AC. The data did not significantly differ between the groups on days 0, 3, and 7. Fig. 2 summarizes changes in coagulation markers. Values on days 3 and 7 did not significantly differ between the groups for PT-INR (P = 0.38 and P = 0.16, respectively) and FDP (P = 0.06 and P = 0.08, respectively), and PLT was significantly increased in the rTM group at day 7 (P = 0.03). Fig. 3 summarizes changes in DIC scores. Resolution rates of DIC on day 7 were significantly higher in the group treated with, than without rTM (94.1% [16/17] vs. 68.0% [17/25], P = 0.04). Two patients in each group died of sepsis-induced DIC associated with severe AC, and thus mortality rates did not significantly differ between the groups (11.8% [2/17], 4.0% [2/25], P = 0.68).

4. Discussion

Treatment is not attempted when severe AC is characterized by infected bile juice, which is systemic and fatal. Among the treatment strategies established in TG2018 [3], first-line treatment for severe AC comprises antibiotics and general organ support. Second-line treatment comprises a surgical approach except when patients have poor performance status (PS). However, when severe AC is complicated with sepsis-induced DIC according to the diagnostic criteria, including a low PLT count, invasive procedures such as surgery might be contraindicated even with good PS. Therefore, both gallbladder drainage and the resolution of sepsis-induced DIC are extremely important for patients with severe AC complicated with sepsis-induced DIC.

According to the Japan Septic Disseminated Intravascular Coagulation study [24], rTM has a positive clinical impact on sepsis-induced DIC. That study found that among 1784 of 3195 patients with sepsis-induced DIC, 645 were treated with rTM and 1139 were not. Survival analysis revealed a higher survival rate in a propensity score-matched group treated with rTM, than a propensity score-matched control group (hazard ratio, 0.781; 95% confidence interval, 0.624–0.977; P = 0.03). However, rTM was also developed to treat DIC in the setting of gastroenterology and Ito et al. found that rTM was effective against sepsis-induced DIC in this setting [23]. That retrospective study included 53 patients with sepsis-induced DIC (rTM, 25; non-rTM, 28). Compared with the non-rTM group, rTM significantly improved all parameters except FDP within 7 days. Ito et al. thus concluded that rTM would be useful for treating DIC from a gastroenterological perspective. Suetani et al. evaluated the ability of rTM to treat acute cholangitis-induced DIC [13]. That study found higher DIC resolution rates on day 9 in the rTM group (n = 30) than in the non-rTM group (n = 36) (83.3% vs. 52.8%, P < 0.01). Mean DIC scores on day 7 and mean SIRS scores on day 3 were significantly lower in the rTM group than in the control group (2.1 ± 2.1 vs. 3.5 ± 2.3, P = 0.02 and 1.1 ± 1.1 vs. 1.8 ± 1.1, P = 0.03, respectively). These findings collectively indicated that rTM is useful for treating sepsis-induced DIC. However, a heterogeneous primary infection site might impose limitations because the treatment guidelines for each disease differ.

To the best of our knowledge, this is first description of the outcomes of rTM therapy among patients with severe AC. The resolution rate of DIC on day 7 was significantly higher in the group treated with rTM. This outcome might allow patients to undergo earlier LC, which is the gold standard treatment for AC. In addition, we excluded patients with complicating malignant tumors. Patients complicated with a large tumor burden, metastasis, and massive bone marrow infiltration are at risk of developing DIC [19]. Clotting abnormalities appear to be induced by factors released by tumor cells. An excess of such factors can activate coagulation pathways and result in the persistent consumption of PLT and coagulation factors as well as increased fibrinolysis, leading to DIC and visceral dysfunction. The effects of tumors were not completely excluded in these previous studies; thus, we excluded patients with malignancies and investigated patients who had only AC. Therefore, our results might be more reliable. However, the extremely low mortality rate did not significantly differ between the rTM and non-rTM groups in the present multicenter study, possibly because of the small patient cohort. Therefore, the present findings should be confirmed by a larger, randomized study. There were several limitations in our study. First, our study was retrospective nature and included small sample size. Second, although significant differences were not observed in drainage between both groups, this difference may be influenced to the resolution of DIC.

In conclusion, rTM may be improve the resolution rate of sepsis-induced DIC due to severe AC. Future studies should include more patients to validate our findings.

5. Addendum

Takeshi Ogura wrote a paper. Takeshi Ogura, Takaaki Eguchi, Mio Amano, Tatushi Sano, Nobu Nishioka, Akira Miyano, Masahiro Tsujimae, Hirohisa Tanimura, Tadahiro Yamada, Yoshihiko Terashima,

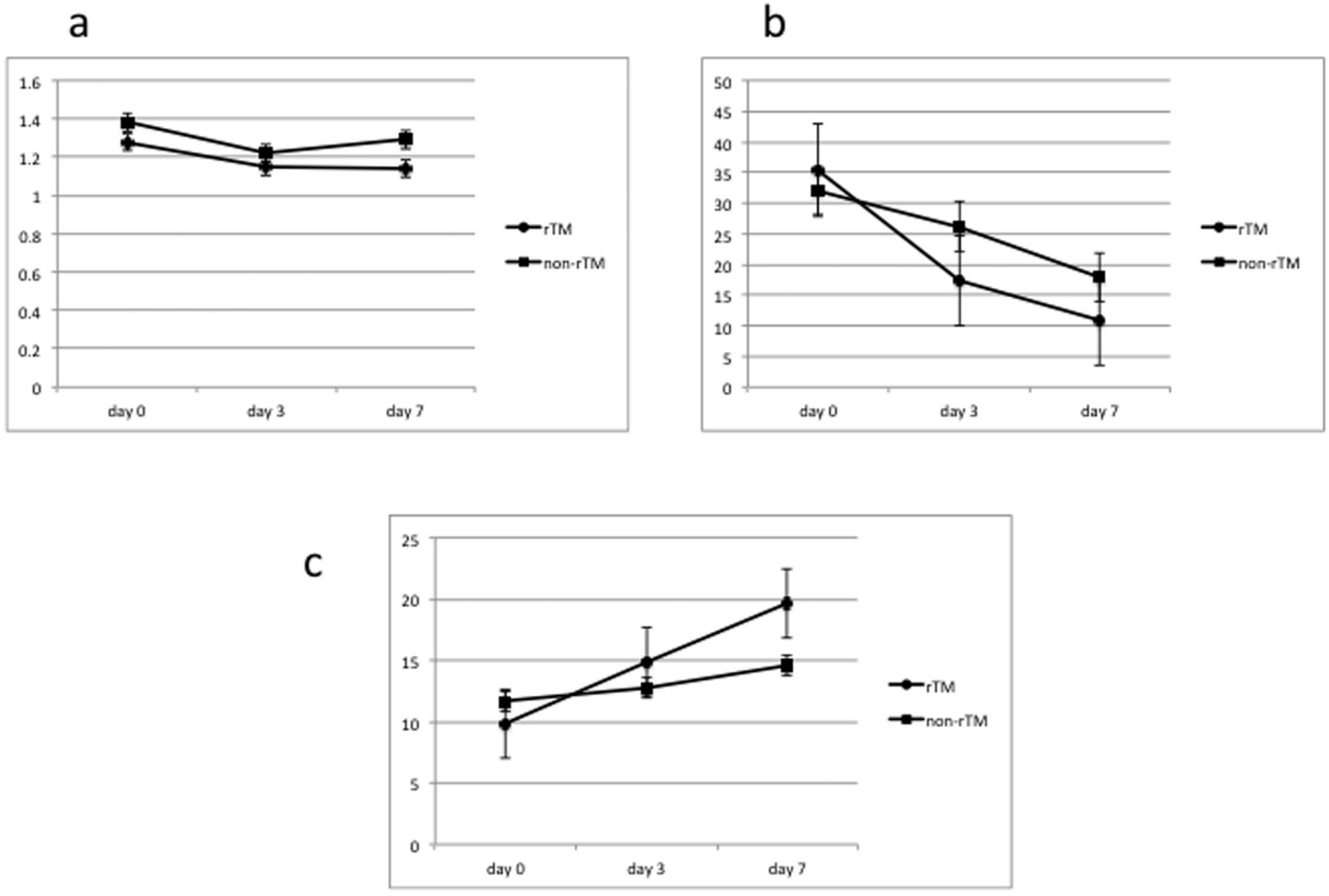

Fig. 2. (a. PT-INR, b. fibrin degradation products, c. blood platelets)
No significant differences are seen between the groups in PT-INR (day 3, P = 0.38; day 7, P = 0.16) and in FDP (day 3 P = 0.06, day 7 P = 0.08). PLT counts are significantly higher in the rTM group than in the non-rTM group on day 7 (day 3, P = 0.09; day 7, P = 0.03).

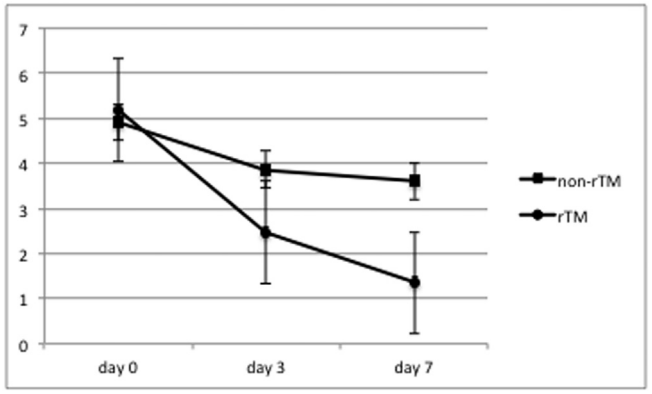

Fig. 3. The resolution of DIC at day 7 was significantly higher in the rTM group than in the non-rTM group [93.8% (15/16), 68.0% (17/25), P = 0.007].

Okada Akihiko, Kazuhide Higuchi played roles of interpretation of data for the work, revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with Ethical Standards

Funding: None.

Conflict interest: The authors declare that they have no conflict of interest.

Research involving human rights: All procedures performed in studies involving participants were in accordance with the ethical standards of the Institute Committee of Osaka Medical College.

Informed consent: Informed consent was obtained from all individual participants included in this study.

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