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ORIGINAL ARTICLE

Retrospective Study

Thrombomodulin in the management of acute cholangitis-induced disseminated intravascular coagulation

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Abstract

AIM: To evaluate the need for thrombomodulin (rTM) therapy for disseminated intravascular coagulation (DIC) in patients with acute cholangitis (AC)-induced DIC.

METHODS: Sixty-six patients who were diagnosed with AC-induced DIC and who were treated at our hospital were enrolled in this study. The diagnoses of AC and DIC were made based on the 2013 Tokyo Guidelines and the DIC diagnostic criteria as defined by the Japanese Association for Acute Medicine, respectively. Thirty consecutive patients who were treated with rTM between April 2010 and September 2013 (rTM group) were compared to 36 patients who were treated without rTM (before the introduction of rTM therapy at our hospital) between January 2005 and January 2010 (control group). The two groups were compared in terms of patient characteristics at the time of DIC diagnosis (including age, sex, primary disease, severity of cholangitis, DIC score, biliary drainage, and anti-DIC drugs), the DIC resolution rate, DIC score, the systemic inflammatory response syndrome (SIRS) score, hematological values, and outcomes. Using logistic regression analysis based on multivariate analyses, we also examined factors that contributed to persistent DIC.

RESULTS: There were no differences between the rTM group and the control group in terms of the patients' backgrounds other than administration. DIC resolution rates on day 9 were higher in the rTM group than in the control group (83.3% *vs* 52.8%, $P < 0.01$). The mean DIC scores on day 7 were lower in the rTM group than in the control group (2.1 ± 2.1 *vs* 3.5 ± 2.3, $P = 0.02$). The mean SIRS scores on day 3 were significantly lower in the rTM group than in the control group (1.1 ± 1.1 *vs* 1.8 ± 1.1, $P = 0.03$). Mortality on day 28 was 13.3% in the rTM group and 27.8% in the control group; these rates were not significantly different ($P = 0.26$). Multivariate analysis identified only the absence of biliary drainage as significantly associated with persistent DIC ($P < 0.01$, OR = 12, 95%CI: 2.3-60). Although the difference did not reach statistical significance, primary diseases (malignancies) ($P = 0.055$, OR = 3.9, 95%CI: 0.97-16) and the non-

use of rTM had a tendency to be associated with persistent DIC (P = 0.08, OR = 4.3, 95%CI: 0.84-22).

CONCLUSION: The add-on effects of rTM are anticipated in the treatment of AC-induced DIC, although biliary drainage for AC remains crucial.

Key words: Disseminated intravascular coagulation; Acute cholangitis; Thrombomodulin; Biliary drainage; Anticoagulant therapy

Core tip: To evaluate the need for thrombomodulin (rTM) in the management of acute cholangitis (AC)-induced disseminated intravascular coagulation (DIC), we retrospectively compared patients treated with rTM (rTM group) and without rTM (control group). DIC resolution rates were higher in the rTM group (P < 0.01). Multivariate analysis identified only the absence of biliary drainage as significantly associated with persistent DIC (P < 0.01), while there was a trend towards an association between persistent DIC and a lack of rTM (P = 0.08). Therefore, the add-on effects of rTM are anticipated in the treatment of AC-induced DIC, although biliary drainage remains crucial.

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INTRODUCTION

In recent years, there have been several reports on the efficacy of recombinant human soluble thrombomodulin (rTM) for the treatment of disseminated intravascular coagulation (DIC) associated with infection[1-4]. Various disorders that cause infections were described in these reports, but none of the studies focused on a single disease. Treatment of the primary disease causing DIC remains the most important factor in the resolution of the pathological conditions that underlie infectious DIC[5], and the prognosis of patients with DIC may be markedly affected by the outcome of treatment of the primary disease. Thus, it is crucial to focus on the primary disease to accurately assess the treatment outcomes of patients with infectious DIC.

In acute cholangitis (AC)-induced DIC, the treatment for AC, including biliary drainage, can immediate resolve DIC. However, some patients still have poor outcomes, and further improvements in therapy are needed. The utility of rTM for the treatment of DIC remains unclear. Our PubMed search on rTM therapy for AC-induced DIC, using terms such as "disseminated intravascular coagulation", "acute cholangitis", and "thrombomodulin", yielded only a single-arm case series that we previously reported[6]. We had reported favorable outcomes in patients who received a therapeutic regimen of rTM for AC-induced DIC. However, the prior series had a small sample size; in this study, we therefore compared a larger group of patients who were treated with and without rTM to evaluate the role of anti-DIC therapy with rTM for AC-induced DIC. This is the first comparative study of rTM in the treatment of AC-induced DIC.

MATERIALS AND METHODS

Patients

Thirty consecutive patients who were diagnosed as having AC-induced DIC and who were treated with rTM at St. Marianna University School of Medicine Hospital between April 2010 and September 2013 were enrolled in this study (rTM group). They were compared to 36 patients with AC-induced DIC who were treated without rTM (before the introduction of rTM therapy at our hospital) between January 2005 and January 2010. Detailed data were available from medical records, which allowed these 36 patients to serve as historical controls for the analysis (control group).

The rTM group included 22 men and 8 women with a mean age ± SD of 77.0 ± 7.7 years. AC was diagnosed and graded according to the 2013 Tokyo Guidelines[7] for the management of AC. AC was severe in 28 patients and moderate in 2 patients, while no patients had mild AC. The primary diseases causing AC were choledocholithiasis in 20 patients, malignant biliary stricture in 9 (pancreatic carcinoma in 5 patients, cholangiocarcinoma in 2, lymph node metastasis of gastric cancer in 1, and malignant lymphoma in 1), and primary sclerosing cholangitis in 1. Based on the DIC diagnostic criteria defined by the Japanese Association for Acute Medicine[8] (Table 1), DIC was diagnosed when the DIC score was 4 or above. The mean DIC score ± SD at the time of DIC diagnosis was 5.4 ± 1.4. The dose of rTM was 380 units/kg per day in 26 patients, while 4 patients received rTM at a reduced dose of 130 units/kg per day, due to renal dysfunction. The duration of rTM treatment was 6 d in all patients. Other anti-DIC drugs used (besides TM) were antithrombin (AT) in 26 patients, gabexate mesilate (GM) in 14 patients, and nafamostat mesilate (NM) in 4 patients (including duplicate counts). The antibiotics used were meropenem (MEPM) in 19 patients, sulbactam/cefoperazone (CPZ/SBT) in 5 patients, doripenem in 5 patients, and tazobactam/piperacilin (TAZ/PIPC) in 1 patient. Biliary drainage was performed in 25 patients but not in 5 patients. Of the patients who did not undergo biliary drainage, 4 patients did not consent, and the presence of cholangitis after the clearance of bile duct stones precluded this procedure in 1 patient.

Table 1 Diagnostic criteria for disseminated intravascular coagulation as defined by the Japanese Association for Acute Medicine

	Score
Systemic inflammatory response syndrome criteria[1]	
≥ 3	1
0-2	0
Platelet count (× 10^3/L)	
< 80 or > 50% decrease within 24 h	3
≥ 80 and < 120; or > 30% decrease within 24 h	1
≥ 120	0
Prothrombin time (Value of patient/Normal value)	
≥ 1.2	1
< 1.2	0
Fibrin/fibrinogen degradation products (mg/L)	
≥ 25	3
≥ 10 and < 25	1
< 10	0
Diagnosis	
≥ 4 points	DIC

[1]Systemic inflammatory response syndrome criteria: Fever of more than 38 ℃ or less than 36 ℃; Heart rate of more than 90 beats per min; Respiratory rate of more than 20 breaths per minute or a $PaCO_2$ level of less than 32 mmHg; Abnormal white blood cell count (> 12000/μL or < 4000/μL or > 10% bands). DIC: Disseminated intravascular coagulation.

The control group included 21 men and 15 women with a mean age ± SD of 75.7 ± 9.4 years. AC was severe in 32 patients and moderate in 4 patients, while no patients had mild AC. The primary diseases causing AC were choledocholithiasis in 19 patients, malignant biliary stricture in 15 patients (pancreatic carcinoma in 6, cholangiocarcinoma in 5, gallbladder cancer in 2, and hepatocellular carcinoma in 2), bilio-jejunal anastomotic stricture in 1, and bile duct stricture due to a hepatic cyst in 1 patient. The mean DIC score ± SD at the time of DIC diagnosis was 5.2 ± 1.2. The anti-DIC drugs used were GM in 30 patients, NM in 18, AT in 16, and danaparoid sodium (DS) in 6 (including duplicate counts). The antibiotics used were MEPM in 14 patients, SBT/CPZ in 14, imipenem/cilastatin in 7, and TAZ/PIPC in 1. Biliary drainage was performed in 24 patients.

Measurements

The rTM group of 30 patients and the control group of 36 patients were compared in terms of patient characteristics [including age, sex, primary disease (malignant/benign)], severity of cholangitis at the time of diagnosis, DIC score at the time of diagnosis, proportion of patients undergoing biliary drainage, and anti-DIC drugs, the DIC resolution rate, the DIC score, the systemic inflammatory response syndrome (SIRS) score, hematological values [platelet count (Plt), fibrin/fibrinogen degradation products (FDP), prothrombin time-international normalized ratio (PT-INR), fibrinogen (Fib), C-reactive protein (CRP), total bilirubin (T-bil)], and treatment outcomes. The day of DIC diagnosis and treatment initiation was designated as day 1, and hematological values were assessed on days 1, 3, 5, 7, and 9. Moreover, DIC resolution was defined as a decrease in the DIC score to 3 or less. The DIC and SIRS scores were expressed as mean ± SD, and hematological data were expressed as median values (quartiles).

A multinomial logistic regression analysis based on the univariate and multivariate analyses was used to identify factors that contributed to the failure of DIC resolution in patients with AC-induced DIC.

Written informed consent was obtained from all patients. This study was approved by the ethics committee of our hospital.

Statistical analysis

Statistical analyses were performed using the χ^2 test, Fisher's exact test, Welch's t test, the Mann-Whitney U test or the Wilcoxon single rank test, as appropriate. Variables that were found to have a potentially significant association with persistent DIC ($P < 0.2$) by univariate analysis were selected for entry into a multiple logistic regression model. P values < 0.05 were regarded as statistically significant. Statistical analyses were performed using the Prism 5 program (Graph Pad Software, Inc., CA, United States) and SPSS (version 19; SPSS, Chicago, IL, United States).

RESULTS

Patient characteristics

There were no significant differences between the rTM group and the control group with respect to age, sex, primary disease, severity of cholangitis, DIC score, SIRS score, or the proportion of patients who underwent biliary drainage at the time of DIC diagnosis. With regards to anti-DIC agents other than rTM that were used, the proportion of patients who received AT was significantly higher in the rTM group, while a higher proportion of patients in the control group received GM, NM and DS were higher (Table 2).

DIC resolution rate

The DIC resolution rate on day 9 was 83.3% (25/30) in the rTM group and 52.8% (19/36) in the control group (significantly higher in the rTM group; $P = 0.009$). The DIC resolution rates on day 7 were 76.7% (23/30) and 50.0% (18/36), respectively, and again, were significantly higher in the rTM group ($P = 0.041$).

DIC scores

Both the rTM and control groups showed a significant decrease in DIC scores from day 3 onward, compared to those on day 1. The comparison between the rTM and control groups revealed no difference in the mean DIC scores at the time of diagnosis, which were 5.4 ± 1.4 in the rTM group and 5.2 ± 1.2 in the control group ($P = 0.524$). However, the mean DIC scores on day 7 were 2.1 ± 2.1 and 3.5 ± 2.3 ($P = 0.018$), and the mean DIC scores on day 9 were 1.8 ± 1.9 and 3.3 ± 2.4, respectively ($P = 0.009$). The mean DIC scores on days 7 and 9 were

Table 2 Comparison of patient characteristics between the recombinant human soluble thrombomodulin and control groups

	rTM group (n = 30)	Control group (n = 36)	P value
Age (yr)	77.0 ± 7.7	75.7 ± 9.4	0.554
Sex (Male/Female)	22/8	21/15	0.203
Primary disease (Benign/Malignant)	21/9	21/15	0.327
Severity of cholangitis (Severe/Moderate)	28/2	32/4	0.845
DIC score	5.4 ± 1.4	5.2 ± 1.2	0.523
SIRS score	2.4 ± 1.3	2.6 ± 1.0	0.599
Biliary drainage	25	24	0.123
Anticoagulant drug			
AT	26	16	< 0.001
GM	14	30	0.002
NM	4	18	0.004
DS	0	6	0.019
Antibiotics			
MEPM	19	14	0.048
IPM/CS	0	7	0.031
DRPM	5	0	0.037
SBT/CPZ	5	14	0.047
TAZ/PIPC	1	1	0.556

DIC: Disseminated intravascular coagulation; SIRS: Systemic inflammatory response syndrome; rTM: Recombinant human soluble thrombomodulin; AT: Antithrombin; GM: Gabexate mesilate; NM: Nafamostat mesilate; DS: Danaparoid sodium; MEPN: Meropenem; IPM/CS: Imipenem/Cilastatin; DRPM: Doripenem; SBT/CPZ: Sulbactam/Cefoperazone; TAZ/PIPC: Tazobactam/Piperacilin.

significantly lower in the rTM group (Figure 1A).

SIRS scores

Compared to day 1, both the rTM and control groups showed a significant decrease in SIRS scores from day 3 onward. There were no differences between the rTM and control groups in terms of the mean SIRS scores at the time of diagnosis, which were 2.4 ± 1.3 in the rTM group and 2.6 ± 1.0 in the control group (P = 0.599). However, the scores on day 3 were 1.1 ± 1.1 and 1.8 ± 1.1 (P = 0.027), respectively, and were significantly lower in the rTM group. Subsequently, the mean SIRS scores in the rTM group remained significantly lower (Figure 1B).

Hematological values

The median hematological values (day 1/day 9) in the rTM group were as follows: Plt, 70.5 (58.8-94.0)/182.0 (80.5-266.5) × 10^3/μL (P < 0.001); FDP, 20.8 (10.8-43.2)/8.8 (5.9-17.9) μg/mL (P = 0.010); PT-INR, 1.27 (1.21-1.52)/1.18 (1.14-1.24) (P = 0.024); Fib, 293.5 (203.5-449.3)/373.0 (284.8-452.3) mg/dL (P = 0.092); CRP, 8.9 (5.9-15.1)/3.6 (2.0-7.8) mg/dL (P < 0.001); and T-bil, 3.8 (1.8-5.4)/1.9 (1.2-3.1) mg/dL (P = 0.023). The Plt, FDP, PT-INR, CRP, and T-bil values on day 9 showed significant improvement compared to those on day 1. In contrast, the median hematological values (day 1/day 9) in the control group were as follows: Plt, 88.5 (70.3-134.5)/155.0 (73.3-249.0) × 10^3/μL (P = 0.024); FDP, 35.4 (14.0-51.5)/21.0 (11.2-36.5) μg/mL (P = 0.155); PT-INR, 1.34 (1.24-1.67)/1.21 (1.08-1.47) (P = 0.054); Fib, 399.0 (243.0-464.0)/302.0 (219.0-445.5) mg/dL (P = 0.180); CRP, 13.6 (9.8-18.2)/4.8 (2.1-8.1) mg/dL (P < 0.001); and T-bil, 4.0 (1.9-6.7)/1.7 (1.1-4.7) mg/dL (P = 0.021). The Plt, CRP and T-bil values on day 9 showed significant improvement compared to the Day 1 values. A comparison of the median hematological values between the rTM and control groups showed that, although the levels of Plt on day 1 were significantly lower in the rTM group (P = 0.023), the levels of Plt on day 9 were higher in the rTM group; this difference did not reach statistical significance (P = 0.699). Although there was no difference in FDP on day 1 (P = 0.157) between the two groups, from day 3 onward (P = 0.045), the level of FDP was significantly lower in the rTM group. The fluctuations in median hematological values are shown in Figure 1C.

Outcomes

The mortality rate on day 28 was 13.3% (4/30) in the rTM group and 27.8% (10/36) in the control group; although mortality was higher in the control group, the difference did not reach statistical significance (P = 0.260). In the rTM group, all 4 deaths were classified as due to malignant tumors. Of the 10 deceased patients in the control group, cancer deaths occurred in 7 patients, and deaths due to worsening DIC were observed in the remaining 3 patients.

Factors contributing to the failure of DIC resolution

The univariate analysis identified primary disease (malignancy) (P = 0.003, OR = 5.3, 95%CI: 1.8-16), absence of biliary drainage (P < 0.001, OR = 16, 95%CI: 3.9-66), non-use of rTM (P = 0.010, OR = 4.5, 95%CI: 1.5-14), and non-use of NM (P = 0.016, OR = 0.26, 95%CI: 0.088-0.76) as factors that significantly contributed to persistent DIC (Table 3). A multivariate analysis was performed, incorporating the factors that were identified by univariate analysis, as well as the non-use of GM (P = 0.107) and Fib < 200 mg/dL (P = 0.186), both of which were factors with P values < 0.2 in the univariate analysis; the absence of biliary drainage (P = 0.003, OR = 12, 95%CI: 2.3-60) was the only factor that was found to contribute to persistent DIC (Table 4). Although the difference did not reach statistical significance, it was observed that primary disease (malignancies) (P = 0.055, OR = 3.9, 95%CI: 0.97-16) and non-use of rTM (P = 0.080, OR = 4.3, 95%CI: 0.84-22) tended to be associated with persistent DIC.

DISCUSSION

Since May 2008, rTM has been available in Japan as a novel therapeutic agent for DIC. In recent years, there have been several reports on the efficacy of rTM, which binds to thrombin and activates protein C to exert an anticoagulant effect[9,10], for the treatment of infectious

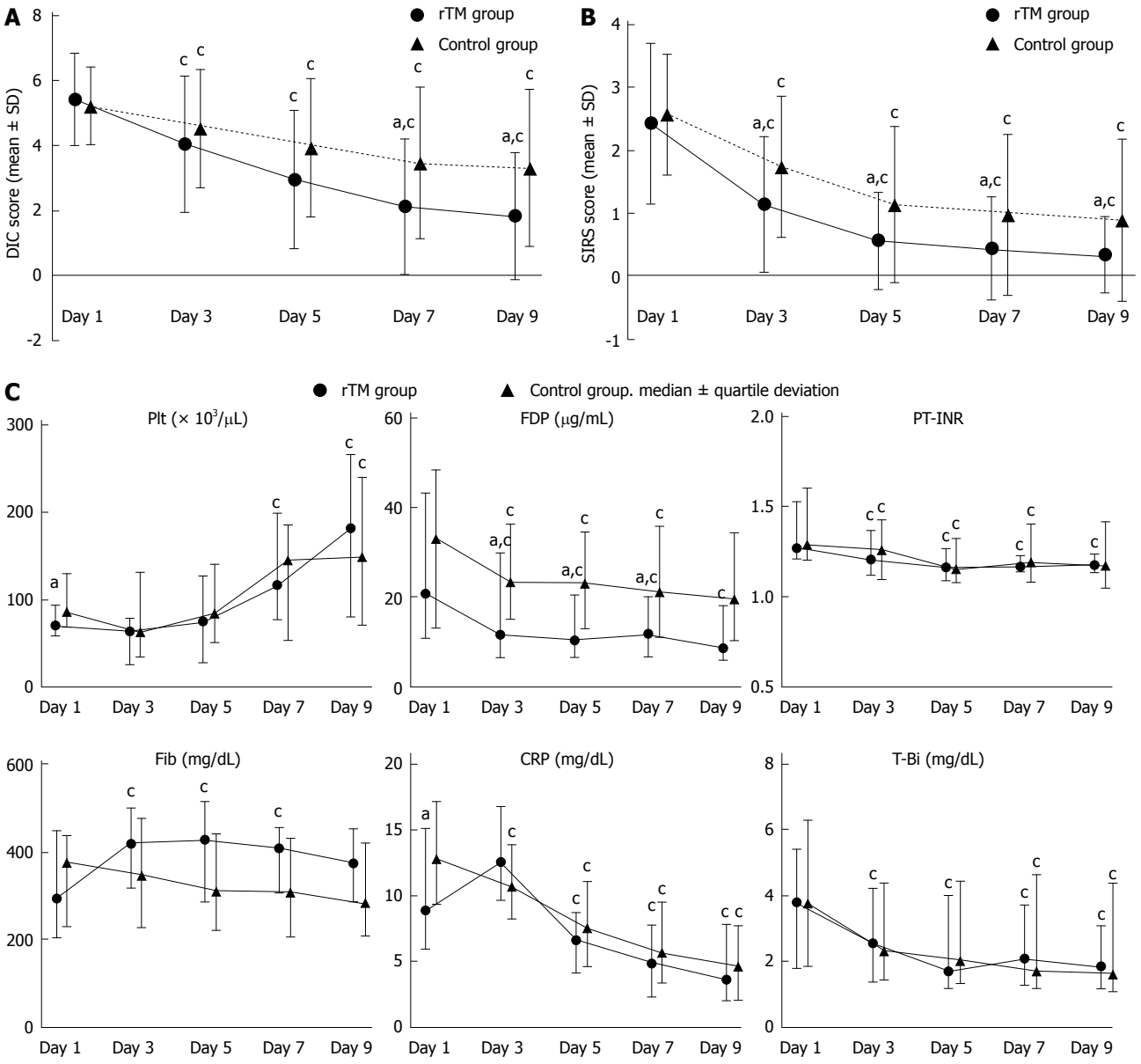

Figure 1 Comparison of the mean values of the disseminated intravascular coagulation scores (A), the systemic inflammatory response syndrome scores (B) and serum parameters between the recombinant human soluble thrombomodulin group and the control group (C). [a]*P* < 0.05 *vs* control group; [c]*P* < 0.05 *vs* baseline. DIC: Disseminated intravascular coagulation; rTM: Recombinant human soluble thrombomodulin; SIRS: Systemic inflammatory response syndrome; FDP: Fibrin/fibrinogen degradation products; PT-INR: Prothrombin time-international normalized ratio; Fib: Fibrinogen; CRP: C-reactive protein; T-Bil: Total bilirubin.

DIC[1-4]. In addition to this anticoagulant effect, rTM also elicits an indirect anti-inflammatory effect through activated protein C[9,11-13] and thrombin-activatable fibrinolysis[14,15]. Moreover, rTM exerting a direct anti-inflammatory effect by deactivating high mobility group box 1[16-18] and lipopolysaccharide[19] by binding to these molecules with the lectin-like domain of rTM. Thus, rTM has great potential as a drug for the treatment of infectious DIC.

However, the treatment of the underlying disease causing DIC is essential to achieve resolution of the pathological conditions that are associated with infectious DIC[5]. This is especially relevant in AC-induced DIC, where immediate biliary drainage can lead to prompt resolution of the DIC. Better therapies are needed, as there are still some DIC patients with poor outcomes; however, the usefulness of anti-DIC therapy with rTM remains unclear. Thus, we conducted the present study in patients with AC-induced DIC to evaluate the role of anti-DIC therapy with rTM by comparing outcomes between patients who did and did not receive rTM treatment.

Although there were no differences between the two groups in terms of age, sex, primary disease, severity of cholangitis, DIC score, or in the proportion of patients who underwent biliary drainage, the proportion of patients who received AT was significantly larger in the rTM group. However, the possibility of bias due to the therapeutic effects of AT must be taken into consideration when interpreting therapeutic outcomes in

Table 3 Factors associated with persistent disseminated intravascular coagulation (univariate analysis)

	Persistent DIC (n = 25)	Resolved DIC (n = 41)	P value	OR (95%CI)
Age (> 80 yr)	9	18	0.610	0.72 (0.26-2.0)
Female	7	16	0.431	0. 61 (0.21-1.8)
Primary disease (Malignant)	15	9	0.003	5.3 (1.8-16)
Severity of cholangitis (Severe)	23	37	1.000	1.2 (0.21-7.3)
DIC score (> 6)	12	15	0.442	1.6 (0.58-4.4)
SIRS score (> 3)	11	24	0.313	0.56 (0.20-1.5)
Without biliary drainage	14	3	< 0.001	16 (3.9-66)
Without rTM	19	17	0.010	4.5 (1.5-14)
Without AT	12	13	0.203	2.0 (0.71-5.5)
Without GM	5	17	0.107	0.35 (0.11-1.1)
Without NM	12	32	0.016	0.26 (0.088-0.76)
Without DS	22	37	1.000	0.79 (0.16-3.9)
Plt (< 80 × 10^3/μL)	12	24	0.452	0.65 (0.24-1.8)
FDP (> 25 μg/mL)	17	20	0.201	2.2 (0.79-6.3)
PT-INR	10	12	0.426	1.6 (0.57-4.6)
Fib (< 200 mg/dL)	7	5	0.186	2.8 (0.78-10)
CRP (> 15 mg/dL)	7	14	0.786	0.75 (0.25-2.2)
T-Bil (> 10 mg/dL)	4	3	0.412	0.49 (0.35-12)

DIC: Disseminated intravascular coagulation; SIRS: Systemic inflammatory response syndrome; rTM: Recombinant human soluble thrombomodulin; AT: Antithrombin; GM: Gabexate mesilate; NM: Nafamostat mesilate; DS: Danaparoid sodium; Plt: Platelet count; FDP: Fibrin/fibrinogen degradation products; PT-INR: Prothrombin time-international normalized ratio; CRP: C-reactive protein; Fib: Fibrinogen; T-Bil: Total bilirubin.

Table 4 Factors associated with persistent disseminated intravascular coagulation (multivariate analysis)

	P value	OR (95%CI)
Primary disease (Malignant)	0.055	3.9 (0.97-16)
Without biliary drainage	0.003	12 (2.3-60)
Without rTM	0.080	4.3 (0.84-22)
Without GM	0.680	1.5 (0.25-8.5)
Without NM	0.188	0.37 (0.083-1.6)
Fib (< 200 mg/dL)	0.403	2.2 (0.35-14)

rTM: Recombinant human soluble thrombomodulin; GM: Gabexate mesilate; NM: Nafamostat mesilate; Fib: Fibrinogen.

the rTM group. According to the Japanese guidelines for DIC treatment, which were prepared in 2009[5], AT is the most strongly recommended of all anti-DIC drugs. In the rTM group, which included patients who were treated in 2010 and thereafter, a higher frequency of AT use can be expected as a background condition. Because only a short time has elapsed since rTM became available, it is not included in the Japanese guidelines for DIC treatment. There have been many reports on the effectiveness of AT for the treatment of infectious DIC[20]. However, the KyberSept trial, reported in 2001[21], showed that the use of AT is not associated with decreased mortality, and the European guidelines for DIC treatment recommend restraint in the use of AT for the treatment of infectious DIC[22,23]. Our present univariate analysis identified only the use of rTM as a contributory factor in the successful treatment of DIC, while AT was not identified as such a factor. However, further studies are needed to determine the usefulness of AT for the treatment of AC-induced DIC; due to the retrospective nature of this study, we were unable to evaluate serum AT Ⅲ values in our patients.

The DIC resolution rate was significantly higher in the rTM group than in the control group, suggesting that rTM is highly effective for the treatment of AC-induced DIC. Although significant decreases in the DIC and SIRS scores from day 1 to day 3 were observed in both the rTM group and in the control group, a comparison between these two groups revealed that the DIC and SIRS scores had been significantly lower since days 7 and 3, respectively, in the rTM group and that greater improvements in the scores were observed in this group. The SIRS scores in particular were significantly improved in the early phase of treatment in the rTM group, which may be attributable to the anti-inflammatory effect of rTM[9,11-19]. With respect to the hematological findings, the control group showed significant improvements in Plt, CRP, and T-bil from day 1 to day 9, whereas the rTM group showed significant improvements in coagulation markers, such as FDP and PT-INR, in addition to Plt, CRP and T-bil. Although Plt levels on day 1 were significantly lower in the rTM group than in the control group, the Plt values on day 9 were higher in the rTM group. However, these differences did not reach statistical significance. Although there was no difference in FDP between the two groups on day 1, the levels of FDP were significantly lower from day 3 onward in the rTM group. These results suggest that rTM exerts a favorable anticoagulant effect. Thus, it is possible that in patients with AC-induced DIC, earlier and more marked resolution of the pathological condition may occur with the use of rTM.

There was no statistically significant difference in the mortality rate on day 28 between the two groups. However, the causes of death in all 4 patients in the rTM group were classified as malignant tumors, but the causes of death in 3 of the 10 deceased patients in

the control group were classified as being DIC-related. Based on these results, we can reasonably speculate that the resolution of DIC by rTM administration may have contributed to improved outcomes. In fact, there are reports on septic DIC describing reduced mortality at 28 d after the initiation of treatment with rTM[2,24,25]. In the present study, there were only 3 DIC-related deaths. To examine the effects of rTM on the improvement of the outcomes of patients with AC-induced DIC, multicenter studies with a larger sample size are needed.

In the present study, a multivariate analysis was performed to identify factors that contributed to persistent DIC. The absence of biliary drainage was identified as the only factor that contributed to persistent DIC. The treatment of the underlying disease causing DIC is considered to be the most important aspect of the treatment of infectious DIC[5], and the results of our study support this concept. Specifically, in patients with AC, a complete response is often achieved by biliary drainage[26,27], which is clearly the most important procedure for the clinical management of DIC. We advocate that biliary drainage be performed whenever possible. Furthermore, although the difference was not statistically significant, we observed that the non-use of rTM also tended to be associated with persistent DIC (P = 0.080, OR = 4.3, 95%CI: 0.84-22). It appears that treatment can be optimized by a combination of biliary drainage and the use of rTM. Moreover, our multivariate analysis revealed that the presence of malignant tumors also tended to be associated with persistent DIC, presumably because neoplastic as well as infectious DIC influenced the outcomes of patients in our study. Future studies are eagerly anticipated regarding the effects of rTM on neoplastic DIC due to solid cancers.

In conclusion, although biliary drainage for acute cholangitis is the most important treatment for AC-induced DIC, the use of rTM can lead to an earlier and more marked improvement in DIC and SIRS scores, which may improve clinical outcomes. However, to further examine the effects of rTM on the improvement of the outcomes of patients with AC-induced DIC, additional multicenter studies with a larger sample size are needed.

COMMENTS

Background

In acute cholangitis (AC)-induced disseminated intravascular coagulation (DIC), treatment for AC, including biliary drainage, can achieve resolution of the DIC. However, further improvements in treatment are needed, as there are still patients with poor outcomes.

Research frontiers

There have been several reports on the efficacy of recombinant human soluble thrombomodulin (rTM) for DIC that is associated with infection. However, in AC-induced DIC, the usefulness of anti-DIC therapy with rTM remains unclear.

Innovations and breakthroughs

The authors compared patients treated with rTM (rTM group) and without rTM (control group) to evaluate the role of anti-DIC therapy with rTM for AC-induced DIC. DIC resolution rates were higher in the rTM group (P < 0.01), and DIC scores were lower in the rTM group (P < 0.01). Multivariate analysis identified only the absence of biliary drainage as a contributor to the failure of DIC resolution (P < 0.01), and the non-use of rTM also tended to contribute to failure of DIC resolution (P = 0.08).

Applications

The add-on effects of rTM are anticipated in the treatment of AC-induced DIC, although biliary drainage for AC remains crucial.

Peer review

This paper is the first to demonstrate the effectiveness of rTM in cases of DIC due to acute cholangitis. Biliary drainage is the most effective procedure for the control of DIC, but rTM improves outcomes for patients. This retrospective study is original with solid data that is well analyzed.

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