Effects of Recombinant Human Soluble Thrombomodulin Treatment for Disseminated Intravascular Coagulation at a Single Institution—An Analysis of 62 Cases Caused by Infectious Diseases and 30 Cases Caused by Hematological Diseases

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Abstract

Objective Disseminated intravascular coagulation (DIC) is a clinical condition with high mortality that is characterized by the systemic activation of coagulation pathways resulting in multiple organ failure. Although no standard treatment for DIC has been established, recent reports have indicated that recombinant human soluble thrombomodulin (rTM) is effective against DIC.

Methods To elucidate the clinical characteristics and outcomes of DIC, we retrospectively analyzed 92 DIC patients who were treated with rTM at Miyazaki Prefectural Hospital over a 4-year period (62 patients had infectious diseases and 30 patients had hematological diseases). A diagnosis of DIC was made based on the diagnostic criteria of the Japanese Association for Acute Medicine (JAAM) and Japanese Ministry of Health and Welfare (JMHW) for infectious diseases and hematological diseases, respectively. In addition to treating the underlying disease, rTM was administered for six consecutive days.

Results In this study, 49 of the 92 DIC patients (53.3%) experienced resolution of DIC seven days after administration (46.8% patients with infectious disease and 66.7% with hematological disease). A higher survival rate was observed after a 28-day observation period in 69 of the 92 patients (75.0%) (72.6% of the patients with infectious disease and 80.0% of the patients with hematological disease). A lower DIC score at the initiation of rTM treatment was closely related to a higher rate of resolution of DIC.

Conclusion Our findings indicate that rTM therapy is an effective, safe and feasible treatment for DIC patients. Furthermore, making an accurate and early diagnosis of DIC and providing subsequent immediate treatment with rTM may improve the resolution of DIC.

Key words: disseminated intravascular coagulation, recombinant human soluble thrombomodulin, the criteria of the Japanese Association for Acute Medicine, the criteria of the Japanese Ministry of Health and Welfare, early treatment at a low score of DIC

Introduction

Disseminated intravascular coagulation (DIC) is a clinical condition characterized by the systemic activation of coagulation pathways, which can result in organ failure due to the generation of fibrin clots. Such clots can cause clinical bleeding owing to the consumption of platelets and coagulation factors, in addition to enhanced fibrinolysis (1-3). Between 20% and 40% of patients with severe sepsis develop DIC (1-3). In patients with DIC, the disease progresses rapidly and the outcome is poor, with a 30-40% mortality rate, due to the presence of severe underlying diseases, such as infection, sepsis, malignancy, collagen disease, trauma and hematological disease (1-3). Therefore, treating the underlying cause of DIC is essential. Moreover, supportive modalities, such as the administration of platelet concentrates, fresh frozen plasma, heparin, activated protein C (APC), protease inhibitors and antithrombin, play an important role in controlling DIC (1-4). However, no standard treatment has been established due to the absence of randomized controlled trials. It is known that APC and thrombomodulin play a crucial role in the pathogenesis of DIC. New agents against DIC, such as recombinant soluble thrombomodulin (rTM), have been developed, which are effective in treating DIC (5-9). Previously, we reported the clinical characteristics and outcomes of 35 DIC cases at our institution (10). Since that report, more DIC patients have been treated with rTM; therefore, we conducted a large cohort study. The purpose of this retrospective study is to clarify the efficacy of rTM in treating DIC.

Materials and Methods

We retrospectively analyzed 112 patients clinically diagnosed with DIC (62 men and 50 women) at our institution between 2008 and 2012. Among the 112 clinically diagnosed DIC patients, we retrospectively analyzed 62 infectious DIC patients and 30 hematological DIC patients who fulfilled the DIC criteria of the Japanese Association for Acute Medicine (JAAM) and Japanese Ministry of Health and Welfare (JMHW), respectively (11, 12).

In patients with infectious disease, DIC was evaluated using the diagnostic criteria of the JAAM (11). In the infectious disease DIC patients, DIC was diagnosed when the DIC score exceeded 4 points. Resolution of DIC was defined as a score of ≤3 points. In the hematological malignancy patients, DIC was evaluated using the diagnostic criteria of the JMHW. In the hematological disease DIC patients with thrombocytopenia, DIC was diagnosed when the DIC score exceeded 3 points in the presence of severe thrombocytopenia due to bone marrow failure. Resolution of DIC was defined as a score of ≤2 points. The following cases were excluded from the analysis of the DIC resolution rate and the change in the DIC score: cases in which the DIC score did not apply to the diagnosis according to the JAAM and JMHW DIC diagnostic criteria at baseline; and cases in which the DIC score could not be calculated due to missing data, such as laboratory test results at baseline and/or following the day after final treatment.

In addition to treating the underlying disease, we administered rTM at a dose of 380 U/kg for six consecutive days. Patients with renal insufficiency requiring hemodialysis received a lower dose of rTM; 130 U/kg was administered for six consecutive days. When the DIC could not be controlled, the administration of rTM was extended beyond the six-day period. Patients with active life-threatening bleeding resulting in shock were excluded. The exclusion criteria were as follows: fatal or life-threatening bleeding (intracranial, gastrointestinal or pulmonary bleeding). The treatment outcomes were evaluated according to the survival rate at 28 days after the initiation of treatment with rTM. The Wilcoxon signed-rank test was also used to evaluate the coagulation markers [platelet count (Plt), prothrombin time-ratio (PT-ratio), fibrinogen (FBG) level, and fibrinogen and fibrin degradation product (FDP) level], the DIC score, and the Sepsis-related Organ Failure Assessment (SOFA) score. Other coagulation markers, such as the levels of antithrombin, the thrombin-antithrombin complex (TAT), the plasmin-α2 plasmin inhibitor complex (PIC), d-dimer, α2 plasmin inhibitor (α2-PI), protein C, plasminogen activator inhibitor 1 (PAI-1) and fibrin monomer, were not fully available in our retrospective study.

This retrospective study was conducted in compliance with good clinical practices and the ethical principles of the Declaration of Helsinki. Prior approval to conduct this retrospective study was obtained from the ethics review board at our institution.

Results

Patient characteristics, laboratory findings and treatment outcomes

Infectious diseases

The clinical characteristics of the patients with infectious diseases are summarized in Table 1. The age of the patients with infectious disease at diagnosis ranged from 2 to 89 years (median age, 69 years). The cause of DIC in these patients included infections (62 cases), such as sepsis (31 cases), pneumonia (10 cases) and acute panperitonitis (5 cases), and clinical manifestations, such as bleeding (30 cases) and organ dysfunction (53 cases). Although the rate of bleeding symptoms tended to be high at the time that DIC was initially diagnosed, no severe side effects associated with the progression of bleeding were observed during the administration of rTM. The DIC scores in the patients with infectious diseases ranged from 4 to 8 points (median score, 6.0). We compared the changes in the Plt, PT-ratio, FBG level and FDP level to evaluate the efficacy of rTM in the management of DIC. The median values of Plt, PT-ratio,
FBG level and FDP level were as follows: before rTM administration= 4.8×10⁴/μL, 1.37, 330 mg/dL and 40.9 μg/mL, respectively (Table 1); after administration= 7.9×10⁴/μL, 1.21, 278 mg/dL and 17.1 μg/mL, respectively. These findings indicate that Plt, PT-ratio and FDP level are good markers for evaluating the efficacy of DIC treatment. We also compared the JAAM DIC scores, which enable earlier diagnosis, before and after rTM administration (Fig. 1A). The median DIC score before treatment was 6 points, whereas that after treatment was 4 points (Fig. 1A). Resolution of DIC was observed in 29 of 62 cases (46.8%). High survival rates were observed; 45 of 62 patients (72.6%) were alive with resolution of DIC after the 28-day observation period (Fig. 1B). Moreover, we analyzed the SOFA scores before and after rTM treatment. The SOFA score provided an objective and quantitative evaluation of organ failure, depending on the degree of six types of organ dysfunction, including the respiratory, circulatory, renal, hematological, and neurological systems. Table 1 shows the clinical characteristics and treatment outcomes of the patients with DIC caused by infectious disease.

![Figure 1](image-url)
patic and central nervous systems (13). The median SOFA score before treatment was 9 points, whereas the DIC score after treatment was 5 points (Fig. 1C).

**Hematological diseases**

The clinical characteristics of the patients with hematological diseases are summarized in Table 1. The age of the patients with hematological diseases at diagnosis ranged from 19 to 88 years (median age, 59 years). The causes of DIC in these patients included hematological diseases (30 cases), such as acute myelocytic leukemia ([AML] 21 cases), acute lymphocytic leukemia ([ALL] 2 cases) and Non-Hodgkin’s lymphoma ([NHL] 2 cases), and clinical manifestations, such as bleeding (20 cases) and organ dysfunction (26 cases). The JMHW DIC scores ranged from 3 to 9 points in the patients with hematological diseases (median score, 6). The median values of Fbg, PT-ratio, FBG and FDP were as follows: before treatment= 3.8×10^4 μL, 1.30, 156 mg/dL, and 47.5 μg/mL, respectively (Table 1); after treatment= 3.6×10^4 μL, 1.14, 236 mg/dL and 6.0 μg/mL, respectively. These findings indicate that FDP is a good marker for evaluating the efficacy of DIC treatment. The DIC scores obtained before and after the administration of rTM were compared in 30 patients with a score of ≥3 points calculated based on the JMHW DIC criteria (Fig. 2A). The median DIC score before treatment was 6 points, which decreased to 2 points after treatment (Fig. 2A). Resolution of DIC was observed in 20 of the 30 cases (66.7%). Higher survival rates were observed; 24 of the 30 patients (80.0%) were alive after the 28-day observation period (Fig. 2B).

**Treatment outcomes in all cases**

In this retrospective study, 49 of the 92 DIC patients (53.3%) experienced resolution of DIC seven days after rTM administration, and 69 of the 92 patients (75.0%) were alive with resolution of DIC after the 28-day observation period. Of the patients who did not survive, the cause of death was progression of the underlying disease. The major cause of death in the patients with infectious disease was uncontrollable progression of the underlying disease, such as sepsis (11/17), pneumonia (4/17), acute colitis (1/17) and acute hepatitis (1/17). The major cause of death in the patients with hematological malignancy was uncontrollable progression of the underlying disease, such as AML (4/6) and T-cell lymphoma (2/6). No severe side effects, including thrombosis and bleeding, were observed during the administration of rTM. Other concomitant drugs, such as serine protease inhibitors [gabexate mesylate (GM) or nafamostat mesylate (NF)], low-molecular-weight heparin (LMWH) and antithrombin, were administered in three (3 GM) and six (4 GM or 2 NF), zero and two, and 17 and three of the 62 infectious and 30 hematological DIC patients treated with rTM, respectively. The serine protease inhibitors were administered before rTM treatment. However, rTM was subsequently administered with concomitant protease inhibitors in the setting of uncontrolled progression of DIC. Moreover, antithrombin was administered at a value of ≤70% at a dose of 1,500 U/day for three consecutive days. In 12 renal insufficiency DIC patients, consisting of 10 infectious DIC patients and two hematological DIC patients, the median values of serum creatinine (Cr) were 2.4 mg/dL and 1.3 mg/dL, respectively. No exacerbation of the renal function occurred during treatment with rTM for DIC in the patients with a satisfactory resolution of DIC (50%; 6/12) and good treatment outcomes (83.3%; 10/12) during rTM treatment at a dose of 130 U/kg, including three patients under the administration of continuous hemodiafiltration (CHDF).

**Effects and impact of rTM on the treatment outcomes of DIC**

**Infectious diseases**

In the analysis of treatment outcomes, the rate of death within a 14-day period was high. Therefore, we analyzed the accumulated mortality rate of the DIC patients during the 28-day period (Fig. 3A). Among the DIC patients with infectious, 50% and 75% accumulated mortality rates were noted at days 8 and 14, respectively (Fig. 3A). To elucidate the impact on the treatment outcomes of the DIC patients, the laboratory parameters measured before rTM treatment in
the survivors (n=45) and non-survivors (n=17) were also analyzed (Table 2). The non-survivors had lower PT levels (p=0.0768) and higher DIC scores (p=0.0684) than the survivors (Table 2). Finally, we analyzed the relationship between DIC resolution and treatment outcomes with respect to the DIC score measured at the beginning of rTM administration. In the patients with infectious diseases, the DIC resolution and mortality rates were closely related to the DIC score at the start of rTM administration (Fig. 4A, B), and lower DIC scores at the initiation of rTM treatment were closely related to a lower SOFA score (Fig. 4C). Regarding the changes in the DIC scores from before to after rTM treatment in the non-survivors and survivors among the infectious DIC patients, the DIC scores of the non-survivors tended to not fully recover compared to that observed in the survivors, although the non-survivors had heterogeneous causes of various underlying diseases associated with DIC (Fig. 5A).

**Hematological diseases**

In the hematological DIC patients, 50% and 75% accumulated mortality rates were observed at days 11 and 23, respectively (Fig. 3B). Similarly, to clarify the impact on the treatment outcomes of the DIC patients, the laboratory parameters measured before rTM treatment in the survivors and non-survivors were also analyzed. Among the infectious DIC patients, the non-survivors had lower PT levels (p=0.0768) and higher DIC scores (p=0.0684) than the survivors. Similarly, among the hematological DIC patients, in order to clarify the impact on the treatment outcomes of the DIC patients, the laboratory parameters measured before rTM treatment in the survivors and non-survivors were analyzed. The non-survivors had lower FBG levels (p=0.2997) than the survivors.

**Table 2. Analysis of the Impact on the Treatment Outcomes of the DIC Patients**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Infectious disease</th>
<th>Hematological disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survivors (n=45)</td>
<td>Non-survivors (n=17)</td>
</tr>
<tr>
<td>FDP</td>
<td>40 (3-645)</td>
<td>53 (8-375)</td>
</tr>
<tr>
<td>PT-ratio</td>
<td>1.32 (0.90-3.42)</td>
<td>1.49 (0.90-2.51)</td>
</tr>
<tr>
<td>FBG</td>
<td>341 (92-844)</td>
<td>288 (95-543)</td>
</tr>
<tr>
<td>Platelet</td>
<td>5.0 (0.9-27.1)</td>
<td>3.5 (0.6-7.1)</td>
</tr>
<tr>
<td>DIC score*</td>
<td>6.0 (4-8)</td>
<td>7.0 (5-8)</td>
</tr>
</tbody>
</table>

* JAAM DIC criteria for infectious disease, JMHW DIC criteria for hematological malignancy

Data are shown as the median (min-max)

In order to elucidate the impact on the treatment outcomes of the DIC patients, the laboratory parameters measured before rTM treatment in the non-survivors and survivors among the hematological DIC patients, in order to clarify the impact on the treatment outcomes of the DIC patients, the laboratory parameters measured before rTM treatment in the survivors and non-survivors were analyzed. The non-survivors had lower FBG levels (p=0.2997) than the survivors.
Discussion

The development of multiple organ failure due to DIC results in an increased mortality rate; however, the etiology of DIC varies from infection to hematological malignancy (1-3). Therefore, controlling and resolving DIC is essential for improving poor treatment outcomes. Recently developed novel therapeutic strategies using the administration of rTM may be reasonable and appropriate for controlling the APC and TM systems in the coagulation process of DIC (5-10). In contrast to conventional therapeutic agents used against DIC, rTM exhibits anticoagulant and anti-inflammatory properties without any side effects (5-10).

TM is a transmembrane protein on the endothelial cell surface that plays an important role in the regulation of intravascular coagulation (5). First, rTM binds to thrombin to inhibit coagulation, and the thrombin-rTM complex stimulates protein C to produce APC (5). Consequently, the inactivation of factors VIIIa and Va by APC under protein S results in the cessation of further thrombin formation (5). Second, this anti-inflammatory effect is a result of the suppression by rTM of the production of the high-morbidity group box, which is the key cytokine involved in sepsis (14). Moreover, TM may exert cytoprotective effects on endothelial cells via the upregulation of extracellular signal-regulated kinase/myeloid leukemia cell-1 signaling (15).

Since the publication of our previous report (10), more DIC patients have been treated with rTM; therefore, we conducted a large cohort study. In this retrospective study, the purpose of the analysis was to clarify the efficiency of rTM treatment for DIC.

Previously, Saito et al. reported that rTM was effective and safe in a phase III, randomized, double-blind clinical trial of DIC (6). They also reported that the resolution rate of DIC was 66.1% (66.7% among the patients with infection and 65.6% among the patients with hematological disease) and that the positive treatment outcome rate was 78.1%
Previous report (10), more DIC patients have been treated with and positive treatment outcomes were consistent with those not (8).

Sepsis-induced DIC (68 patients received rTM, while 94 did reduced in-hospital mortality rate among 162 patients with that rTM treatment was significantly associated with a reservation period (6). Moreover, Yamakawa et al. reported the patients with hematological disease) after a 28-day ob-

In this retrospective study, the rates of resolution of DIC and positive treatment outcomes were consistent with those of previous reports (5-10). Since the publication of our previous report (10), more DIC patients have been treated with rTM, maintaining good resolution and treatment outcomes of DIC.

The major cause of death in the patients with infectious and hematological diseases was uncontrolled progression of the underlying disease. Moreover, death due to infection and/or a hematological cause tended to be observed within a 14-day period. In order to improve the resolution and treatment outcomes of DIC, we compared several parameters to clarify the differences between the survivors and non-survivors in our retrospective study. Among the parameters measured at the initial treatment of rTM, the non-survivors

Figure 5. A sequential analysis of the DIC score in the infectious DIC (A) and hematological DIC patients (B). Note that, regarding the sequential changes in the DIC scores from before to after rTM treatment in the non-survivors and survivors among both the infectious and hematological DIC patients, the DIC scores of the non-survivors tended to not fully recover compared to that observed in the survivors.

Figure 6. A stratified analysis of the DIC resolution rates (A) and outcomes (B) according to the JMHW DIC scores at the initiation of rTM administration in the patients with DIC caused by hematological malignancy. A. Among the DIC patients with hematological diseases, the DIC resolution scores were closely correlated with the DIC scores obtained at the initiation of rTM administration (A). Consequently, a lower DIC score at the initiation of rTM treatment was related to a higher rate of DIC resolution. The treatment outcomes were not correlated with the DIC scores obtained at the initiation of rTM administration (B).
had lower Pt levels and higher DIC scores than the survivors among the infectious DIC patients. The non-survivors also had lower FBG levels than the survivors among the hematological DIC patients. With respect to the sequential changes in the DIC scores from before to after rTM treatment in the non-survivors and survivors among both the infectious and hematological DIC patients, the DIC scores of the non-survivors tended to not fully recover compared to that observed in the survivors, although the non-survivors had heterogeneous causes of various underlying diseases associated with DIC. Therefore, obtaining early control of DIC is necessary to improve the resolution and treatment outcomes of DIC. Previously, Wada et al. (16) reported that, in their study, the efficacy of treatment in relation to the DIC score obtained when treatment was initiated was greater in the pre-DIC patients than in the DIC patients. Furthermore, in our retrospective study, the clinical findings strongly indicated that a lower DIC score at the initiation of rTM treatment was closely related to a higher rate of resolution among both the infectious and hematological DIC patients. These findings clearly show that a delay in diagnosing DIC may be lethal and fatal, thereby directly affecting the poor resolution and treatment outcomes of DIC. Therefore, obtaining an accurate and early diagnosis of DIC is essential, and providing subsequent immediate treatment with rTM may result in the early and efficient resolution of infectious and hematological DIC. In infectious DIC patients, the accurate and prompt diagnosis of DIC and subsequent immediate administration of treatment with rTM may improve the treatment outcomes of DIC. Regarding the diagnosis and treatment of DIC, the harmonization of guidelines for DIC was recently performed by the British Committee for Standards in Haematology (BCSH), Japanese Society of Thrombosis and Hemostasis (JSTH) and Italian Society for Thrombosis and Haemostasis (SISET) due to the fact that the recommendations for diagnosis and treatment differed for each of the three guidelines (17). In Japan, most emergency and hematological physicians make a diagnosis of and provide treatment for DIC according to the diagnostic criteria of the JAAM for infectious DIC and JMHW for hematological DIC. Based on this clinical experience, in our retrospective study, we made the diagnosis of and provided treatment for DIC using rTM according to the diagnostic criteria of the JAAM for infectious DIC and JMHW for hematological DIC. In the future, standardized guidelines for DIC would be a useful and powerful tool for diagnosing and treating DIC.

In conclusion, rTM was found to be efficacious in the treatment of DIC among most patients treated at Miyazaki Prefectural Hospital. Obtaining an accurate and early diagnosis of DIC and providing subsequent immediate treatment with rTM may improve the resolution of DIC. Moreover, no severe complications, such as bleeding, were observed in this study. Randomized studies with longer follow-up periods are needed to determine the treatment outcomes of DIC patients treated with rTM.

The authors state that they have no Conflict of Interest (COI).

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References


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