Factors Determining the Efficacy of Recombinant Human Thrombomodulin in the Treatment of Sepsis-Induced Disseminated Intravascular Coagulation

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Recombinant human thrombomodulin (rhTM) is an anti-coagulant used to treat disseminated intravascular coagulation (DIC). The efficacy of rhTM in patients with sepsis-induced DIC has been proved in some clinical trials, but the determining factors are not known. The aim of this study was to identify patients for whom rhTM will be effective and the factors that determine rhTM efficacy in alleviating DIC. A single-center, retrospective, observational study was conducted in patients with sepsis-induced DIC who were treated with rhTM in Okayama Saiseikai General Hospital (Okayama, Japan) between January 2010 and December 2019. Among 67 patients who were treated with rhTM, DIC was resolved in 24 patients. The multivariate logistic regression analysis revealed that age (odds ratio (OR) 1.05; 95% confidence interval (CI) 1.00–1.10; p < 0.05) and acute physiology and chronic health evaluation II scores (OR 0.88; 95% CI 0.78–0.98; p < 0.05) were factors that determined rhTM efficacy in alleviating DIC. Overall, our study provides valuable information on factors that should be considered before rhTM administration to patients with sepsis-induced DIC for a better management of healthcare costs.

Key words recombinant human thrombomodulin; disseminated intravascular coagulation; sepsis; efficacy; resolution; health economics

INTRODUCTION

Disseminated intravascular coagulation (DIC) is a systemic process that can cause thrombosis, hemorrhage, and ultimately multiple organ dysfunction syndromes. 1, 2) It is an acquired disorder that occurs in various clinical conditions such as sepsis from infectious disease. 3) As infectious disease-induced DIC can cause severe bleeding and high mortality, 4–6) several randomized controlled trials on pharmacological therapeutic agents for DIC have been conducted. 7–11) However, therapeutics such as recombinant human activated protein C, recombinant tissue factor pathway inhibitor, and plasma-derived activated protein C do not improve 28-d mortality. 7–11) Recently, antithrombin III (AT) and recombinant human thrombomodulin (rhTM) have been used to treat patients with sepsis-induced DIC. 12–17) Although there are no comparative studies on the efficacy of AT and rhTM, high-dose AT therapy has been reported to increase the frequency of bleeding complications in patients with sepsis, 12, 13) but mortality remained unchanged in the AT-treated group (albeit a small sample size) compared with that in the placebo group in a Japanese study. 14) In contrast, rhTM has been studied in a sufficient number of subjects; it has a low risk of bleeding 15–17) and immediate treatment with rhTM may alleviate DIC. 18) In the past, the Sequential Organ Failure Assessment (SOFA) score, used to assess the status of patients in the intensive care unit (ICU), has been reported to be associated with DIC resolution. 19) The identification of multiple factors related to the resolution of DIC can help improve the poor prognosis of DIC. However, studies on other factors that influence DIC severity are limited. Therefore, in this study, we examined factors that can determine the efficacy of rhTM in patients with sepsis-induced DIC.

PATIENTS AND METHODS

Ethics Statement This retrospective study conforms to the principles of the Declaration of Helsinki. Prior approval to conduct this retrospective study was obtained from the Institutional Review Board in Okayama Saiseikai General Hospital.

Definition DIC was diagnosed if the DIC score was 4 or more at the start of rhTM administration, according to the Japanese Association for Acute Medicine (JAAM)-DIC diagnostic criteria. 20, 21) A DIC score of <4 at the end of rhTM administration was defined as DIC resolution, whereas a DIC score of ≥4 was defined as DIC non-resolution. Sepsis was defined according to the Sepsis-3 criteria. 22)

Patients All patients admitted to the ICU in Okayama Saiseikai General Hospital between January 2010 and December 2019 were screened for eligibility. We enrolled patients with suspected or documented infection and an acute increase in the SOFA score of ≥2 points on admission. The exclusion criteria were unknown DIC scores due to missing data, DIC score of <4 at rhTM administration, stay in ICU for >48 h, and administration of rhTM for conditions other than sepsis.

Assessment of Factors Related to DIC Resolution We retrospectively collected the data of patient characteristics (age, body weight, and sex) and medical history (hypertension, diabetes, cardiovascular disease, chronic kidney disease, and malignancy) at the time of hospitalization for both DIC resolution; health economics
tion and DIC non-resolution groups. We also collected medical records at the time of entry to the ICU: C-Reactive protein level; white blood cell count; hemoglobin, platelet, and lactate levels; SOFA scores; acute physiology and chronic health evaluation II (APACHE II) score; systemic inflammatory response syndrome; prothrombin time (value of patient/value of healthy individual); fibrin/fibrinogen degradation product (FDP); and DIC score on rhTM administration. rhTM is administered at a dose of 380 U·kg⁻¹·d⁻¹ to all patients with DIC, except those with chronic kidney disease, to whom an adjusted dose of 130 U·kg⁻¹·d⁻¹ was administered. Furthermore, we examined the effects of administration duration of rhTM and concomitant drugs that could directly affect the DIC score (AT, heparin, and transfusion).

**Statistical Analysis** Continuous variables are presented as median and interquartile ranges, and Mann–Whitney U-test

![Fig. 1. Flowchart of Patients in the DIC Resolution and DIC Non-resolution Groups](image)

**rhTM, recombinant human thrombomodulin; DIC, disseminated intravascular coagulation; ICU, intensive care unit.**

**Table 1. Characteristics of Patients Treated with rhTM for Sepsis-Induced DIC**

| DIC resolution group (n = 24) | DIC non-resolution group (n = 43) | p-Value |
|------------------------------|----------------------------------|---------|
| Age, years                   | 83 (74–85)                      | 72 (64–82) | 0.01 |
| Female, n                    | 10/24                           | 11/43    | 0.27 |
| Hypertension, n              | 9/24                            | 15/43    | 1.00 |
| Diabetes, n                  | 8/24                            | 11/43    | 0.58 |
| Cardiovascular disease, n    | 3/24                            | 8/43     | 0.73 |
| Chronic kidney disease, n    | 4/24                            | 5/43     | 0.71 |
| Malignancy, n                | 6/24                            | 10/43    | 1.00 |
| C-Reactive protein, mg/dL    | 18.2 (12.8–23.4)                | 14.7 (11.1–24.0) | 0.72 |
| White blood cell count, /µL | 11445 (5430–18818)              | 13010 (9160–19220) | 0.39 |
| Hemoglobin, g/dL             | 9.6 (8.9–11.6)                  | 11.1 (9.5–12.6) | 0.08 |
| Platelet count, 10⁹/µL       | 7.0 (5.8–10.6)                  | 6.1 (3.9–9.7) | 0.22 |
| Lactate, mg/dL               | 2.3 (1.6–3.7)                   | 2.6 (1.6–3.7) | 0.80 |
| SOFA score                   | 8.5 (6.8–13.0)                  | 11.0 (9.0–13.0) | 0.06 |
| APACHE II score              | 16 (12–19)                      | 21 (17–24) | 0.01 |
| SIRS score                   | 2 (1–3)                         | 2 (1–3)  | 0.55 |
| Prothrombin ratio            | 1.3 (1.2–1.5)                   | 1.4 (1.2–1.6) | 0.32 |
| FDP, µg/mL                   | 23.1 (14.4–46.3)                | 31.9 (22.1–53.5) | 0.20 |
| DIC score                    | 5 (5–6)                         | 6 (5–7)  | 0.09 |
| rhTM dosage, unit/d          | 15600 (8898–19820)              | 13120 (8480–19100) | 0.56 |
| rhTM dose of 380 U·kg⁻¹·d⁻¹, n | 16/24                           | 29/43    | 1.00 |
| rhTM dose of 130 U·kg⁻¹·d⁻¹, n | 8/24                            | 14/43    | 1.00 |
| Duration of administration of rhTM, d | 5 (4–7)                      | 5 (3–6)  | 0.28 |
| Combination of antithrombin III, n | 13/24                       | 22/43    | 1.00 |
| Combination of heparin, n    | 3/24                            | 6/43     | 1.00 |
| Red blood cell transfusion, n | 8/24                            | 23/43    | 0.13 |
| Platelet transfusion, n      | 7/24                            | 17/43    | 0.44 |
| Plasma transfusion, n        | 4/24                            | 21/43    | 0.01 |

Continuous variables are presented as median (interquartile range). p-Values were calculated using Fisher’s exact probability test or Mann–Whitney U test. rhTM, recombinant human thrombomodulin; DIC, disseminated intravascular coagulation; SOFA, Sequential Organ Failure Assessment; APACHE II, acute physiology and chronic health evaluation II; SIRS, systemic inflammatory response syndrome; FDP, fibrin/fibrinogen degradation product.
was used to assess differences between the DIC resolution and DIC non-resolution groups. Categorical variables are reported as frequency or percentage, and Fisher’s exact probability test was used. To investigate the determining factors of rhTM efficacy, univariate and multivariate logistic regression analyses were performed. In the multivariate logistic regression analysis, the forced entry method was employed using the factors that were significantly different in the univariate logistic regression analysis ($p < 0.05$). To estimate sensitivity, specificity, and cut-off values for independent predictors obtained using multivariate logistic regression analysis, area under receiver-operator characteristics (ROC) curve analysis was performed. All statistical analyses were performed with JMP version 15.2.0 (SAS Institute, Cary, NC, U.S.A.). All recorded $p$-values were two-sided, and results with a $p$-value of $<0.05$ were considered statistically significant.

RESULTS

Comparison of Clinical Characteristics of Patients in the DIC Resolution and DIC Non-resolution Groups During the 10-year study period from January 2010 to the end of December 2019, 122 patients were admitted into the ICU for sepsis-induced DIC. Sixty-seven patients met the inclusion criteria (Fig. 1), and 24 of these patients were in the DIC resolution group. Table 1 shows the clinical characteristics of the patients enrolled in this study. The average age of patients in the DIC non-resolution group (median age, 72 years) was considerably lower than that of patients in the DIC resolution group (median age, 83 years) ($p < 0.05$). Furthermore, the average APACHE II score in the DIC non-resolution group (median score, 21) at the time of entry to the ICU was higher than that in the DIC resolution group (median score, 16) ($p < 0.05$). Twenty one of the 43 patients in the DIC non-resolution group and four of the 24 patients in the DIC resolution group received plasma transfusion ($p < 0.05$). There were no significant differences in other clinical characteristics between the two groups.

Factors Influencing the Efficacy of rhTM The clinical characteristics of patients were evaluated using the logistic regression analysis (Table 2). In the univariate logistic regression analysis, age (odds ratio (OR) 1.05; 95% confidence interval (CI) 1.00–1.09; $p < 0.05$), APACHE II score at the time of entry to the ICU (OR 0.89; 95% CI 0.81–0.98; $p < 0.05$), and plasma transfusion (OR 0.21; 95% CI 0.06–0.72; $p < 0.05$) were found to be associated with DIC resolution. To identify the effects of confounding factors—age, APACHE II score, and plasma transfusion—we preformed multivariate logistic regression analysis (Table 3). The results revealed that age (OR 1.05; 95% CI 1.00–1.10; $p < 0.05$) and APACHE II score at the time of entry to the ICU (OR 0.88; 95% CI 0.78–0.98; $p < 0.05$) were independent predictors of DIC resolution by rhTM administration.

Sensitivity, Specificity, and Cut-Off Values of Predictors Estimated Using the ROC Curve Analysis To estimate the predictive ability of independent predictors (age and APACHE II score) obtained using the multivariate logistic regression analysis, the area under the ROC curves (AUC) was calculated. The AUC for age plus the APACHE II score was 0.75 (95% CI 0.63–0.87) (Fig. 2). When the cut-off value for age plus the APACHE II score was 84 years and 23, the sensitivity and specificity were 79 and 60%, respectively.

DISCUSSION

This study was conducted to identify the factors determining the efficacy of rhTM for DIC resolution in patients with sepsis-induced DIC. Our findings emphasize three main points. First, age, APACHE II score, and plasma transfusion were significantly different between the DIC resolution and DIC non-resolution groups (Table 1). However, there were no significant differences between these two groups with regard to any other factors investigated in this study. These findings are similar to those of a previous study, which reported that the number of patients who received plasma transfusion in the
DIC resolution group (5/19, 26.3%) was significantly lower ($p = 0.004$) than that in the DIC non-resolution group (11/14, 78.6%). Second, the multivariate logistic regression analysis revealed that age and the APACHE II scores were independent factors associated with DIC resolution (Table 3). Finally, the cut-off value for age and the APACHE II score was 84 years and 23, respectively.

In this study, age was identified as one of the factors determining the efficacy of rhTM. It has been reported that patients with DIC complicated by acute respiratory distress syndrome treated with rhTM have a higher survival rate at older age.24) The results of the multivariate analysis in our study (Table 3) show that the OR for age is 1.05 (CI: 1.00–1.10) and the rate of resolution of DIC in older adults is high, which supports this report. However, it has been reported that the rate of DIC resolution was improved in patients who received rhTM, but no significant difference was observed in the survival rate.23) In addition, elderly people reportedly have a high mortality rate due to sepsis, and the mortality rate increases with age.26–28) In order to examine the relationship between the effectiveness of rhTM and age, patients treated with rhTM should be analyzed by age group and the association between efficacy and mortality should be investigated.

The APACHE II score was identified as another factor involved in the efficacy of rhTM. Previous reports have shown that rhTM improved survival in patients with APACHE II scores between 24 and 30, while no improvement in mortality was seen with rhTM treatment in very severe or mildly ill patients (those with APACHE II scores <24 and ≥30).29) Particularly in mildly ill patients with low APACHE II scores, improvement in DIC in both the rhTM-treated group and the control group has been observed.30) From these results, we cannot exclude the possibility we were not truly evaluating the efficacy of rhTM. In our study, patients in the DIC resolution group had lower APACHE II scores than those in the non-resolution group; to clarify the relationship between the effectiveness of rhTM and APACHE II score, the number of cases should be increased, and the effectiveness of rhTM should be evaluated based on severity of illness according to the APACHE II score. The SOFA score is another established index for measuring the severity of illness in patients admitted to the ICU.31) A previous study has shown that patients with high SOFA scores have poor prognosis.30) Although we did not observe any significant difference in the SOFA score in our study, there may be a correlation between the SOFA score and the APACHE II score as the latter is based on the respiratory state, renal function, average blood pressure, and consciousness state.

Although several studies have shown that rhTM is effective in DIC resolution, some questions about whether rhTM lowers the mortality rate persist.18,19,29) The Sepsis Congulopathy Asahi Recombinant LE Thrombomodulin (SCARLET) randomized clinical trial showed that rhTM did not reduce 28-d all-cause mortality.33) However, as the SCARLET trial was conducted in countries other than Japan, the selection criteria for patients with DIC were different from those in Japan. Although observational studies have reported reduced mortality in rhTM-treated patients,32) the effect of confounding factors, including differences in patient background between rhTM-treated and target patients, cannot be ruled out. Thus, there is a need for randomized controlled trials based on the Japanese DIC criteria.

As patients with septic shock-induced DIC have been occasionally treated with a combination of rhTM and AT,32–35) we examined the use of AT in our study subjects. There were no significant differences between patients receiving AT and rhTM when almost half of the patients in both groups were treated with AT. Hence, we concluded that the effects of the combination of AT and rhTM on patients with septic shock-induced DIC were not significant.

As both AT and rhTM are expensive, the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 recommend that rhTM and AT should be sparingly used.26) Our results (Table 3) suggest that older age and lower APACHE II score were independent factors for DIC resolution, with cut-off values of 84 years of age and an APACHE II score of 23. These findings could facilitate the selection of patients for whom rhTM should be used preferentially and help reduce healthcare costs.

This study had some limitations. First, as the classification of patients into the DIC resolution and DIC non-resolution groups was performed only on the basis of the DIC score at the end of rhTM administration, there is a high probability of bias in DIC classification. To eliminate these biases, it is necessary to conduct a prospective observational study and predetermine the timing of blood collection and evaluation in both groups. Second, organ dysfunction and pathogenesis of DIC were not examined in this study. Third, several other factors associated with DIC were not investigated such as anti-thrombin III activity; fibrinogen; and plasma levels of soluble fibrin, plasmin-plasmin inhibitor complex, and thrombin anti-thrombin III complex. Finally, the number of subjects in this study was small; therefore, the evaluated statistical power might be insufficient. To resolve this problem, further analyses with more patients are needed.

In conclusion, our study showed that age and the APACHE II score were possible factors determining the efficacy of rhTM for the resolution of DIC associated with sepsis. Future studies further increase the number of cases and examine DIC resolution classified by age and APACHE II score.
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Conflict of Interest  The authors declare no conflict of interest.

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