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Effects of longer use of recombinant human soluble thrombomodulin on outcomes of patients with disseminated intravascular coagulation based on a national administrative database

Atsuhiko Murata, MD, PhD[1)], Shinya Matsuda, MD, PhD[1)]

[1)]*Department of Preventive Medicine and Community Health, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan.*

Abstract

It remains unclear whether longer-term use of recombinant human soluble thrombomodulin (rhs-TM) enhances outcomes in patients with disseminated intravascular coagulation (DIC). This study investigated whether longer use of rhs-TM influenced outcomes in patients with DIC based on a national administrative database. Between 2010 and 2012, 6,354 patients with DIC were treated with rhs-TM at 735 hospitals in Japan. Patients were divided into two groups according to duration of use of rhs-TM: < 7 days (n = 4,685) and ≥ 7 days (n = 1,669). The in-hospital mortality rate, length of stay (LOS) and medical costs during hospitalization in these two groups were compared. Overall mortality rates were similar in the (odds ratio 1.05; 95% confidence interval (CI): 0.93 – 1.19, $p = 0.358$). LOS was significantly longer and medical costs during hospitalization significantly higher in patients treated with rhs-TM for ≥ 7 than < 7 days. The unstandardized coefficient for LOS was 15.97 days (95% CI, 13.77 – 18.16 days; $p < 0.001$) whereas that for medical costs during hospitalization was 11650.5 US dollars (95% CI, 10350.0 – 12950.9 US dollars; $p < 0.001$). Longer treatment with rhs-TM did not affect the mortality rate of patients with DIC but significantly increased LOS and medical costs during hospitalization. Additional prospective studies are required to confirm the efficacy of longer treatment with rhs-TM for patients with DIC.

Key words: Disseminated intravascular coagulation; recombinant human soluble thrombomodulin (rhs-TM); Outcomes; Administrative Database

❖Introduction

Disseminated intravascular coagulation (DIC) is a syndrome characterized by the systemic activation of coagulation, leading to widespread microvascular thrombosis, which compromises organ perfusion and can contribute to organ failure[1,2)]. This critical condition is usually induced by some triggering event, such as severe infection, acute promyelocytic leukemia, solid cancers, inflammatory disease, or trauma[1,2)]. Management of DIC requires prompt treatment combined with therapy for the underlying disease, all of which are critically important to increase survival rates and improve patient prognosis[1-4)].

Although the treatment of DIC is primarily focused on the treatment of associated underlying medical conditions, clinical practice guidelines have indicated the need for anticoagulant therapy[5)]. Recombinant human soluble thrombomodulin (rhs-TM) was approved in 2008 in Japan as a novel biological agent to treat DIC[6)]. Recent reports have suggested that rhs-TM treatment has improved the prognosis of patients with DIC[7,8)], with rhs-TM treatment expected to replace traditional management protocols in Japanese patients with DIC[9)].

Manufacturers of rhs-TM have recommended that patients with DIC be treated with this agent for < 7 days, owing to a lack of data about longer use in these patients[10)]. Indeed, previous studies have assessed the efficacy of rhs-TM for < 7 days in patients with DIC[7,8)]. The promise shown by this agent in patients with DIC suggests that longer treatment with rhs-TM may further improve patient prognosis and/or survival rate. Thus, we retrospectively investigated the effects of longer

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term use of rhs-TM on clinical outcomes in patients with DIC using a national administrative database developed in the Japanese case-mix system project called the Diagnosis Procedure Combination (DPC).

❖Methods

Administrative database associated with the DPC system

Japanese case-mix projects based on the DPC system were introduced at 82 academic hospitals (the National Cancer Center, the National Cardiovascular Center, and 80 university hospitals) in 2003[11-15]. Reimbursement from health insurance using the DPC system is common practice in Japan. According to the administrative database of the DPC system, the number of acute-care hospitals has increased. Data on inpatients have been collected annually, with the Ministry of Health, Welfare and Labour of Japan reporting that this database includes approximately 55% of hospital inpatients throughout Japan[16].

The Japanese DPC system collects important information during hospitalization, in addition to data required for health insurance reimbursement. The administrative database includes financial data, claim information, and discharge summary (including the principal diagnosis, complications, and comorbidities during hospitalization. All data are coded using the International Classification of Diseases and Injuries, 10th Revision (ICD-10) code. Additionally, this administrative database contains comprehensive medical information, including all interventional or surgical procedures, medications, and devices, indexed according to the Japanese codes assigned by the Ministry of Health, Labour and Welfare of Japan, as well as the date and amount of daily care delivered[11-15].

Study setting

The study included 6,354 patients with infectious disease-associated DIC treated with rhs-TM at 735 hospitals participating in the DPC (83 academic and 652 community hospitals) between 2010 and 2012. These hospitals are dispersed throughout Japan and play leading roles in providing acute care medicine, advancing medical research, and educating students and medical residents[11-15]. These 6,354 patients were divided into two groups according to the duration of use of rhs-TM: < 7 days (n = 4,685) and ≥ 7 days (n = 1,669).

A comprehensive survey of hospitals participating in the DPC was conducted by a DPC research group, which has worked on the DPC data utilization project for research purposes, independent of the Ministry of Health, Labour and Welfare, Japan. DPC-participating hospitals sent all anonymized data to the DPC research group, which then sent these data to the server in our department[13]. The use of DPC data was permitted by all institutions and hospitals that provided detailed data. The research protocol of the study was approved by the Ethics Committee of Medical Care and Research of the University of Occupational and Environmental Health, Kitakyushu, Japan.

Study variables

Study variables included patient age, sex, comorbid conditions, and use of ambulance transportation and intensive care unit (ICU); drugs used to treat infectious diseases, including antimicrobial, antifungal, and antiviral agents; supportive care, including central venous catheterization, vasopressor, artificial ventilation, and continuous hemodiafiltration; transfusions with platelet concentrates and fresh-frozen plasma; hospital type, size and region; the proportion of hospitals with emergency centers; in-hospital mortality; length of stay (LOS); and medical costs during hospitalization.

Age was stratified as < 60 years, 60-79, and ≥ 80 years. The severity of comorbid conditions was assessed using the Charlson Comorbidity Index (CCI), which is widely used for recording comorbidities and has been validated in various studies[11-15]. The CCI score was calculated for each patient as in studies showing associations between the CCI and ICD-10 codes[11-15]. The CCI score was expressed as the score of all comorbid conditions and was initially evaluated as a continuous variable. However, categorical variables defining four categories of severity of chronic comorbid conditions were created to simplify the presentation of the results: 0, none; 1, mild; 2, moderate; and ≥ 3, severe[11-15]. Patients were treated according to clinical practice guidelines for DIC and infectious diseases[5,17]. Hospital type was classified as academic or community[11-15]. Hospital size was categorized based on the number of hospital beds as small (< 200 beds), medium (200-600 beds), or large (> 600 beds)[11-15]. Hospital region was classified as urban, defined as a prefecture with a ≥ 50% degree of population concentration, or rural, defined as a prefecture with a < 50% degree of population concentration[18]. To analyze medical costs during hospitalization, we assumed an exchange rate of

approximately 100 yen per US dollar (May 2014).

Main measure outcomes and statistical analysis

The main measure of interest in this investigation was to compare outcomes in patients treated with rhs-TM for < 7 and ≥ 7 days. Categorical variables were compared using the chi-squared test, and continuous variables were compared using Student's t test. Simple and multiple logistic regression models were used to estimate the odds ratios (ORs) and their 95% confidence intervals (CIs) for in-hospital mortality. Generalized propensity score analysis was performed to control for selection bias with regard to baseline characteristics of the patients in the two groups. The propensity score method has been widely used in observational studies to deal with possible biases[11,14,19,20]. A multinomial logistic regression model with logit as the link function was used to calculate generalized propensity scores, using patient characteristics, such as age, sex, chronic comorbid conditions, use of ambulance transportation and ICU, drugs for infectious diseases, supportive care, and transfusion. Propensity score models were developed between patient groups, and propensity scores were categorized into deciles as described[20-22]. Hospital characteristics were also considered confounding factors in the multiple logistic regression models. In additional analyses, multiple linear regression models were used to identify the effect of treatment duration with rhs-TM on LOS and medical costs during hospitalization, considering propensity scores and hospital characteristics.

All statistical analyses were performed using the STATA statistical software package, version 11.0 (Stata Corporation, College Station, TX, USA). A p value of < 0.05 was considered statistically significant.

❖Results

The clinical characteristics and presentations of patients and hospitals are shown in Table 1. The percentage of patients aged ≥ 80 years and the percentage using ambulances were higher in patients treated with rhs-TM for < 7 than ≥ 7 days. In contrast, the percentages using the ICU and receiving supportive care and transfusion were significantly higher in patients treated with rhs-TM for ≥ 7 than < 7 days. Regarding patients treated with rhs-TM for ≥ 7 days were more likely treated at academic than community hospitals and at large than medium or small sized hospitals, and were less likely treated at hospitals in urban than rural regions.

Patient outcomes in the two groups are compared in Table 2. The in-hospital mortality rate was significantly higher in patients treated with rhs-TM for ≥ 7 than < 7 days (45.6% vs 38.3%; $p < 0.001$). Mean LOS was significantly longer (50.4 vs 31.5 days; $p < 0.001$) and mean medical costs during hospitalization significantly higher (39642.9 vs 24260.8 US dollars; $p < 0.001$) in patients treated with rhs-TM for ≥ 7 than < 7 days.

The logistic regression analysis for in-hospital mortality is shown in Table 3. Simple logistic regression showed that treatment with rhs-TM for ≥ 7 days was associated with a significantly higher in-hospital mortality rate (OR 1.35, 95% CI: 1.20-1.51; $p < 0.001$). This association was no longer observed, however, after adjustment for patient characteristics and hospital status (OR 1.05, 95% CI: 0.93-1.19; $p = 0.358$).

The linear regression analysis for LOS and medical costs during hospitalization are presented in Table 4. There was a consistently significant association between duration of rhs-TM treatment and LOS. Multivariate regression analysis showed that longer treatment with rhs-TM was significantly associated with increasing LOS in patients with DIC. The unstandardized coefficient was 15.97 days (95% CI, 13.77-18.16 days; $p < 0.001$). Moreover, longer use of rhs-TM was significantly associated with increasing medical costs in patients with DIC after adjustment for potentially confounding clinical variables. The unstandardized coefficient was 11650.5 US dollars (95% CI, 10350.0-12950.9 US dollars; $p < 0.001$).

❖Discussion

Using data obtained from a national administrative database, we assessed the effects of longer use of rhs-TM on outcomes in patients with DIC. We found that longer use of rhs-TM did not affect in-hospital mortality rate although it was associated with significant increases in LOS and medical costs during hospitalization.

Although the reason remains unclear, the underlying diseases in these patients may be associated with the obtained results. Treatment with rhs-TM has been reported to improve the prognosis of patients with sepsis-induced DIC without increasing bleeding risk[23)24)], and administration of rhs-TM was found to reduce 28-day mortality rate in patients with DIC associated with

Table 1 Characteristics of patients and hospitals

	All patients (n=6,354)	< 7 days (n=4,685)	≥ 7 days (n=1,669)	*p* value
Patient characteristics				
Age categories (%)				
Less than 60 years	14.0	14.7	12.2	0.008
60-79 years	47.1	46.1	49.9	
80 years or more	38.9	39.2	37.9	
Sex (%)				
Male	54.5	53.4	57.7	0.002
Female	45.5	46.6	42.3	
Comorbid conditions (%)				
None (CCI; 0)	45.0	46.2	41.8	<0.001
Mild (CCI; 1)	25.4	25.7	24.5	
Moderate (CCI; 2)	16.8	16.1	18.8	
Severe (CCI; 3 or more)	12.8	12.0	14.9	
Use of ambulance (%)	51.8	53.2	47.9	<0.001
Use of intensive care unit (%)	21.6	20.6	24.6	0.001
Drugs for infectious diseases (%)				
Antimicrobial drugs	98.3	98.1	99.0	0.013
Antifungal drugs	4.5	3.6	7.1	<0.001
Antiviral drugs	4.0	3.6	5.3	0.002
Supportive care (%)				
Central venous catheterization	63.4	60.6	71.4	<0.001
Vasopressor	62.0	61.0	64.8	0.005
Artificial ventilation	40.6	38.8	45.7	<0.001
Continuous hemodiafiltration	8.6	8.1	10.1	0.011
Transfusion (%)				
Platelet concentrates	26.9	22.8	38.4	<0.001
Fresh-frozen plasma	20.8	19.0	26.1	<0.001
Hospital characteristics				
Hospital type (%)				
Community hospitals	80.9	81.5	79.2	0.036
Academic hospitals	19.1	18.5	20.8	
Hospital size (%)				
Small sized hospitals	4.5	4.8	3.7	0.006
Medium sized hospitals	62.3	63.0	60.3	
Large sized hospitals	33.2	32.2	36.0	
Hospital region (%)				
Rural region	35.8	34.6	39.0	0.001
Urban region	64.2	65.4	61.0	
Emergency center (%)				
Without emergency center	57.7	57.4	58.7	0.348
With emergency center	42.3	42.6	41.3	

CCI: charlson comorbidity index.

Table 2 Outcomes in patients with disseminated intravascular coagulation treated with recombinant human soluble thrombomodulin for < 7 and ≥ 7 days

	All patients (n=6,354)	< 7 days (n=4,685)	≥ 7 days (n=1,669)	*p* value
In-hospital mortality (%)	40.2	38.3	45.6	<0.001
Mean length of stay (days)	36.5	31.5	50.4	<0.001
Mean medical costs (US dollars)	28301.2	24260.8	39642.9	<0.001

Table 3 Logistic regression analysis on mortality of patients

	Odds Ratio	95% confidence interval	*p* value
In-hospital mortality			
Simple logistic regression			
< 7 days	1.00 (Reference)		
≥ 7 days	1.35	1.20–1.51	<0.001
Multivariate logistic regression†			
< 7 days	1.00 (Reference)		
≥ 7 days	1.05	0.93–1.19	0.358

† Odds ratios adjusted for propensity score (age, sex, chronic comorbid conditions, use of ambulance and intensive care unit, drugs for infectious diseases, supportive care, and transfusion) and hospital characteristics (hospital type, size, region and presence of emergency center).

Table 4 Linear regression analysis on length of stay and medical costs of patients

	Coefficient	95% confidence interval	*p* value
Length of stay (days)			
Simple linear regression			
< 7 days	Reference		
≥ 7 days	18.9	16.72–21.08	<0.001
Multivariate linear regression†			
< 7 days	Reference		
≥ 7 days	15.97	13.77–18.16	<0.001
Medical costs (US dollars)			
Simple linear regression			
< 7 days	Reference		
≥ 7 days	15382.1	14010.3–16753.9	<0.001
Multivariate linear regression†			
< 7 days	Reference		
≥ 7 days	11650.5	10350.0–12950.9	<0.001

† Coefficient adjusted for propensity score (age, sex, chronic comorbid conditions, use of ambulance and intensive care unit, drugs for infectious diseases, supportive care, and transfusion) and hospital characteristics (hospital type, size, region and presence of emergency center).

severe sepsis[25]. These results show the efficacy of rhs-TM for patients with DIC associated with infectious diseases. However, a recent study reported that the severity of underlying disease was the most important predictor of survival rate in patients with DIC, even those treated with rhs-TM, suggesting that the treatment of the underlying disease, and DIC, is critically important[26]. Additionally, current clinical practice guidelines have highlighted the importance of underlying diseases in the treatment of patients with DIC[27]. Even if longer treatment with rhs-TM can enhance outcomes in patients with DIC, these findings may be masked by the severity of the underlying. Additionally, it is plausible that both longer treatment of DIC and the underlying diseases resulted in increasing LOS and medical costs during hospitalization. Therefore, prospective clinical studies may be needed to confirm the efficacy of longer rhs-TM treatment in patients with DIC, with comparisons considering the severity of underlying diseases.

The clinical data used represent a major strength of the current study. One of the benefits of the national database is that it enables evaluation of a large number of hospitals in an unbiased manner, because our investigation involved a nationally representative sample of patients in a community setting[11-15]. Additionally, detailed medical data, including all procedures and medications, have been coded with the original Japanese payment codes[11-15]. These data are recorded on a daily basis for each patient[11-15]. Therefore, this administrative database also enables interested parties to evaluate clinical outcomes in response to detailed medical treatments.

This study also had several potential limitations. It could not consider the characteristics of the clinicians involved in treatment, because our administrative database does not include data such as clinicians' level of skill, type of specialty or years in practice. These clinicians' backgrounds may affect the duration of rhs-TM treatment for DIC. Additionally, we could not accurately determine the doses of rhs-TM administered to patients. Additional clinical studies evaluating the efficacy of longer treatment with rhs-TM of patients with DIC may be required to include data on clinicians' characteristics and does of rhs-TM.

In conclusion, this study demonstrated that longer treatment with rhs-TM did not affect mortality rates in patients with DIC, although it was associated with significantly increased LOS and medical costs during hospitalization. Prospective studies are required to confirm the efficacy of longer rhs-TM treatment for patients with DIC.

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