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Abstract

Background: Antithrombin and recombinant human thrombomodulin (rhTM) are individually reported to improve survival in sepsis-induced disseminated intravascular coagulation (DIC). However, continuing controversy exists as to which agent is superior and whether concomitant therapy is superior to individual administration. **Methods:** This post hoc analysis included adult patients with sepsis-induced DIC from a nationwide multicenter registry database in Japan. We categorized patients into 4 groups: patients who received (1) individual administration of antithrombin, (2) individual administration of rhTM, (3) both, and (4) neither. In-hospital mortality was compared between every 2 groups among the 4 groups by Cox proportional hazards model adjusted with propensity scores. **Results:** In total, 1432 patients with sepsis-induced DIC were included. Although both antithrombin and rhTM were associated better outcome compared with no anticoagulants, mortality benefits were similar between each individual anticoagulant. Similarly, no significant difference in mortality was detected between individual administrations and concomitant therapy. **Conclusion:** Antithrombin and rhTM might have comparable efficacy in reducing mortality in patients with sepsis; however, concomitant therapy appeared to offer no additional survival benefit.

Keywords

anticoagulants, sepsis, retrospective studies, disseminated intravascular coagulation, combination

Background

Sepsis almost invariably complicates deranged blood coagulation disorders ranging from subclinical activation to distinct systemic dysfunction of blood coagulation, that is, disseminated intravascular coagulation (DIC). Sepsis-induced DIC plays a crucial role in inducing multiple organ dysfunction syndrome and is associated with an increased risk of death.^{1,2} Although the management of DIC should be directed primarily at the treatment of the underlying disorders, it is often difficult to control coagulation disorders in patients with sepsis-induced DIC. Therefore, anticoagulant therapy is considered to be effective as supportive therapy against DIC to improve clinical outcomes.³ Actually, much evidence based on previous observational studies and post hoc subgroup analyses of randomized

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controlled trials suggests that anticoagulant therapies may improve mortality in patients with sepsis-induced DIC.⁴⁻¹¹

However, we have little knowledge about which anticoagulant is the most effective for sepsis-induced DIC. Antithrombin and recombinant human thrombomodulin (rhTM) are commonly used anticoagulant agents for sepsis-induced DIC and are often coadministered. According to the recent studies based on the Diagnosis Procedure Combination (DPC) database in Japan, 37.7% of patients treated with antithrombin were reported to receive coadministration of rhTM, and 45.9% of patients treated with rhTM were reported to receive coadministration of antithrombin.^{12,13} Both agents were reported to be associated with lower risk of death in sepsis-induced DIC by recent large-scale observational studies^{10,11}; however, due to a lack of definitive clinical evidence, continuing controversy exists about which agent is superior and whether concomitant therapy is superior to individual administration.

The present study was designed to compare safety and efficacy between the individual administration of antithrombin or rhTM and to evaluate whether the concomitant administration of both agents over individual administration could reduce the rate of death in sepsis-induced DIC.

Materials and Methods

Study Population

This investigation was a post hoc subgroup analysis of a nationwide multicenter retrospective cohort study conducted in 42 intensive care units (ICUs) in Japan between January 2011 and December 2013.¹⁰ Patients were consecutively included in the registry if they were equal to or older than 18 years and diagnosed with having severe sepsis or septic shock according to the Sepsis-1 criteria proposed by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus conference in 1991.¹⁴ Among them, we included patients with sepsis-induced DIC in this study. The patients were considered to have DIC if they fulfilled the Japanese Association for Acute Medicine (JAAM) DIC criteria on the day of ICU admission.¹⁵

The exclusion criteria were as follows: use of warfarin/acetysalicylic acid/thrombolytic therapy before study entry; history of fulminant hepatitis, decompensated liver cirrhosis, or other serious liver disorder; history of hematologic malignant disease; other conditions associated with coagulation disorder; treatment with any chemotherapy at study entry; and patients with missing data for main analysis.

This study followed the principles of the Declaration of Helsinki and was approved by the institutional review board of each participating hospital. Because of the anonymous and retrospective nature of this study, the board of each hospital waived the need for informed consent. This study was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR ID: UMIN000012543).

Sepsis Definitions

In this study, "sepsis" meant severe sepsis and septic shock in the conventional criteria (sepsis-1). Severe sepsis was defined according to the definitions set and revised by the ACCP/SCCM consensus conference in 1991: combination with a suspected or proven infection, 3 or more signs of systemic inflammation, and more than 1 organ dysfunction. Septic shock was also defined according to the ACCP/SCCM consensus in 1991 as sepsis-induced hypotension persisting despite adequate fluid resuscitation and requiring catecholamine infusions to improve hemodynamic status.¹⁴

Data Collection

Patients were followed up until hospital discharge or death. A case report form was developed for the study, and the following information was obtained: age, sex, scores for illness severity on the day of ICU admission, source of ICU admission, preexisting comorbidities, primary source of infection, and therapeutic interventions such as immunoglobulin, low-dose steroid, renal replacement therapy, and low-dose heparin for prophylaxis against deep vein thrombosis (DVT). We evaluated the severity of illnesses according to the Acute Physiology and Chronic Health Evaluation II score and the Sequential Organ Failure Assessment (SOFA) score at study entry. The primary outcome measure was all-cause in-hospital mortality. We also recorded bleeding complications as secondary outcomes. Bleeding complications included the occurrence of intracranial hemorrhage, transfusion requirements related to bleeding, and bleeding requiring surgical intervention.

Patient Categorization

To compare the efficacy and safety between antithrombin, rhTM, and concomitant therapy with both agents, we categorized the study patients into 4 treatment groups: (1) patients who received individual administration of antithrombin (antithrombin group), (2) patients who received individual administration of rhTM (rhTM group), (3) patients who received both antithrombin and rhTM (concomitant group), and (4) patients who received neither agent (nonanticoagulant group). For study purposes, we compared the primary and secondary outcomes between every 2 groups among these 4 study groups.

Statistical Analysis

Due to the retrospective nature of the study, there were baseline imbalances between the groups; therefore, an adjusted analysis was performed using propensity scores.¹⁶⁻¹⁸ The propensity score for the likelihood of undergoing therapies that patients actually received was calculated using multivariable logistic regression analysis including age, sex, disease severity, source of ICU admission, medical history of severe conditions, new organ dysfunctions, types and volume of ICUs, primary source of infection, causal microorganisms, and other therapeutic interventions as covariates. The detailed combinations of the

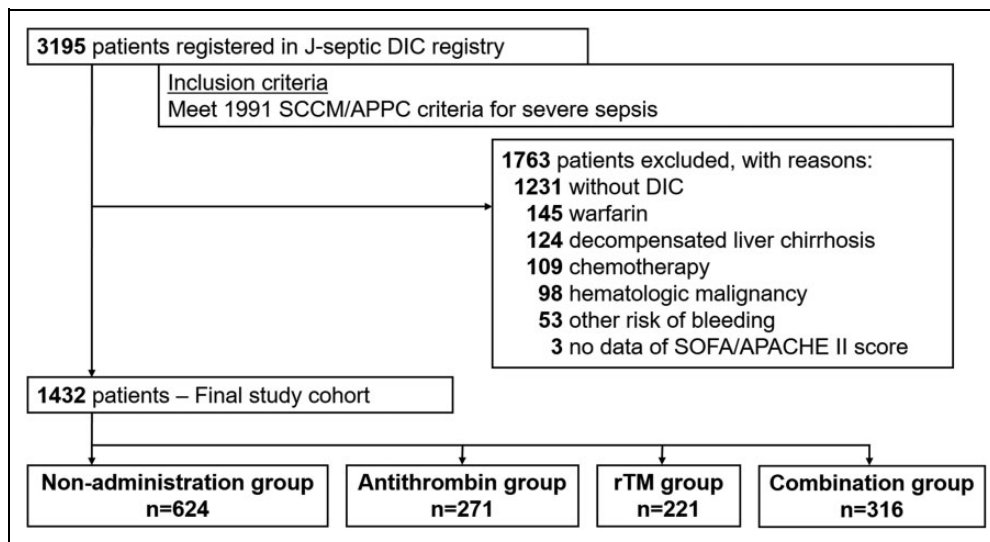


Figure 1. Patient flow diagram. APACHE indicates Acute Physiology and Chronic Health Evaluation; DIC, disseminated intravascular coagulation; rTM, recombinant human thrombomodulin; SCCM/ACCP, Society of Critical Care Medicine/American College of Chest Physicians; SOFA, Sequential Organ Failure Assessment.

variables are described in Table S1. We compared the in-hospital mortality between every 2 groups among the 4 groups by Cox proportional hazards model adjusted with inverse probability of treatment weighting (IPTW) using the propensity score. For secondary outcomes of bleeding complications, we compared one group to every other group by logistic regression analysis adjusted by IPTW estimation.

Descriptive statistics are summarized as group medians with the first and third quartiles for continuous variables and frequencies with percentages for categorical variables. Univariate differences between groups were assessed using the Kruskal-Wallis test or χ^2 test. All hypotheses were 2-sided, and a P value of $<.05$ indicated statistical significance. All statistical analyses were conducted using STATA Data Analysis and Statistical Software version 14.0 (StataCorp, College Station, Texas).

Results

Study Population and Categorizations

The patient flow diagram is shown in Figure 1. During the study period, 3195 consecutive patients fulfilled the inclusion criteria and were registered in the J-SEPTIC DIC registry database. After excluding 1763 patients without DIC and 352 patients who met at least 1 exclusion criterion, we included 1432 patients as the final study cohort. Among them, 271 (20.6%) patients received individual administration of antithrombin, 221 (14.4%) patients received individual administration of rhTM, 316 (20.6%) patients received both antithrombin and rhTM, and 624 (40.7%) received neither agent.

Baseline Characteristics

Table 1 shows the baseline characteristics of the study population categorized by the presence and types of anticoagulant

therapy. There were no significant differences in age and sex distribution between the groups. Baseline disease severity indicated by SOFA and JAAM DIC scores were significantly different between the 4 groups and tended to be lower in the nonadministration group. We also found the percentage of concomitant use of therapeutic interventions other than anticoagulants, such as immunoglobulin, low-dose steroid, renal replacement therapy, and low-dose heparin for prophylaxis against DVT to be significantly different between the groups.

Mortality

The main results in this study using Cox proportional hazards analyses adjusted by propensity score to evaluate the difference in in-hospital mortality between every 2 groups among the 4 groups are shown in Table 2. We also show the propensity score-adjusted survival curves for the 4 groups in Figure 2. The adjusted hazard ratios (HRs) of in-hospital mortality for the antithrombin group and rhTM group compared to the nonanticoagulant group were 0.68 (95% confidence interval [CI]: 0.51-0.91; $P = .008$) and 0.72 (95% CI: 0.52-0.99; $P = .044$), respectively, indicating significant survival benefits associated with all 3 types of anticoagulant therapies. In contrast, we detected no significant difference in in-hospital mortality between the antithrombin and rhTM groups (adjusted HR: 0.95, 95% CI: 0.60-1.49; $P = .748$) or between the individual administration groups and the concomitant group (HR: 1.03, 95% CI: 0.65-1.66; $P = .826$ for antithrombin vs concomitant, and HR: 1.09, 95% CI: 0.66-1.82; $P = .625$ for rhTM vs concomitant).

Bleeding Complications

We summarized the findings for differences in the risk of bleeding complications between every 2 groups among the 4

Table 1. Baseline Characteristics of the 4 Groups.^a

Variable	Nonanticoagulant n = 624	Antithrombin n = 271	rhTM n = 221	Concomitant n = 316	P Value
Patient characteristics					
Age, years	73 (63-81)	72 (63-80)	72 (62-78)	72 (62-80)	.424
Sex, male	353 (56.6%)	152 (56.1%)	122 (55.2%)	171 (54.1%)	.907
Illness severity					
APACHE II score	23 (17-30)	24 (17-29)	23 (17-29)	24 (18-30)	.887
SOFA score	9 (7-13)	11 (8-13)	10 (8-13)	12 (9-14)	<.001
JAAM DIC score	5 (4-6)	6 (4-7)	6 (5-7)	6 (5-8)	<.001
ISTH overt-DIC score	4 (3-5)	4 (4-5)	4 (4-5)	5 (4-6)	<.001
Source of ICU admission					
Emergency department	307 (49.2%)	133 (49.1%)	82 (37.1%)	134 (42.4%)	<.001
Ward	156 (25.0%)	74 (27.3%)	45 (20.4%)	80 (25.3%)	
Other hospital	161 (25.8%)	64 (23.6%)	94 (42.5%)	102 (32.3%)	
Preexisting comorbidities					
Immunocompromised	63 (10.1%)	19 (7.0%)	31 (14.0%)	39 (12.3%)	.055
Chronic kidney disease	71 (11.4%)	21 (7.7%)	13 (5.9%)	16 (5.1%)	.003
Chronic heart failure	28 (4.5%)	17 (6.3%)	16 (7.2%)	9 (2.8%)	.079
Chronic respiratory disorder	28 (4.5%)	10 (3.7%)	5 (2.3%)	7 (2.2%)	.223
Liver insufficiency	7 (1.1%)	2 (0.7%)	3 (1.4%)	4 (1.3%)	.909
Site of infection					
Abdomen	212 (34.0%)	113 (41.7%)	67 (30.3%)	107 (33.9%)	.067
Lung	131 (21.0%)	46 (17.0%)	45 (20.4%)	51 (16.1%)	
Urinary tract	123 (19.7%)	44 (16.2%)	54 (24.4%)	77 (24.4%)	
Bone/soft tissue	56 (9.0%)	35 (12.9%)	25 (11.3%)	41 (13.0%)	
Central nervous system	19 (3.0%)	6 (2.2%)	8 (3.6%)	7 (2.2%)	
Other/unknown	83 (13.3%)	27 (10.0%)	22 (10.0%)	33 (10.4%)	
Therapeutic interventions					
Immunoglobulin	96 (15.4%)	127 (46.9%)	78 (35.3%)	196 (62.0%)	<.001
Low-dose steroid	121 (19.4%)	81 (29.9%)	75 (33.9%)	120 (38.0%)	<.001
Renal replacement therapy	154 (24.7%)	115 (42.4%)	90 (40.7%)	177 (56.0%)	<.001
Low-dose heparin	28 (4.5%)	38 (14.0%)	8 (3.6%)	17 (5.4%)	<.001
Interventions for source control	235 (37.7%)	141 (52.0%)	99 (44.8%)	153 (48.4%)	<.001

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; DIC, disseminated intravascular coagulation; ICU, intensive care unit; ISTH, International Society of Thrombosis and Hemostasis; JAAM, Japanese Association for Acute Medicine; rhTM, recombinant human thrombomodulin; SOFA, Sequential Organ Failure Assessment.

^aData are presented as the median (first and third quartiles) for continuous variables and number (%) for categorical variables. Differences between groups were assessed using the Kruskal-Wallis or χ^2 test.

Table 2. Propensity Score-Adjusted Comparison of In-hospital Mortality.

Treatment	Reference	HR	95% CI	P Value
Antithrombin	vs Nonanticoagulant	0.68	0.51-0.91	.008
rhTM	vs Nonanticoagulant	0.72	0.52-0.99	.044
Concomitant	vs Nonanticoagulant	0.66	0.47-0.91	.012
Antithrombin	vs rhTM	0.95	0.60-1.49	.748
Antithrombin	vs Concomitant	1.03	0.65-1.66	.826
rhTM	vs Concomitant	1.09	0.66-1.82	.625

Abbreviations: CI, confidence interval; HR, hazard ratio; rhTM, recombinant human thrombomodulin.

groups in Table 3. We observed a significantly higher risk of bleeding complications in the antithrombin group compared to the nonanticoagulant group, whereas the rhTM group was not associated with a higher risk of bleeding complications compared to the nonanticoagulant group. We also found that the risk of bleeding complications in concomitant therapy was not

significantly different compared to that for the individual administration of each agent.

Discussion

Recently, multiple lines of evidence have clarified that anticoagulant therapy against sepsis-induced DIC can improve mortality.^{3,8,10,11,19} Antithrombin and rhTM are the most commonly used agents against sepsis-induced DIC, and these 2 agents are often coadministered in Japan. However, a continuing controversy remains about whether 1 agent is superior to the other and whether concomitant therapy with these 2 agents is superior to individual administration. The current propensity score-adjusted study provided the evidence that (1) there was no difference in survival benefit between the individual administration of antithrombin or rhTM, (2) concomitant administration of antithrombin and rhTM showed no additional beneficial effects or interactions over the individual administration of these agents, and (3) concomitant

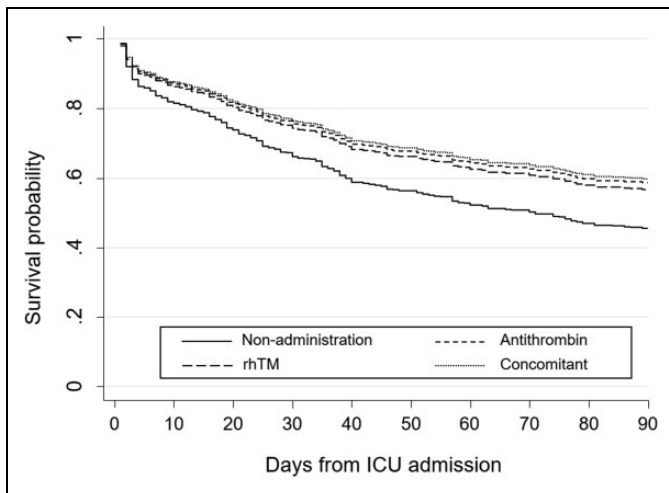


Figure 2. Adjusted estimated survival curves according to the types and presence of anticoagulant therapy. rhTM indicates recombinant human thrombomodulin.

Table 3. Propensity Score-Adjusted Comparison of Bleeding Complications.

Treatment	Reference	OR	95% CI	P Value
Antithrombin	vs Nonanticoagulant	2.10	1.30-3.41	.002
rhTM	vs Nonanticoagulant	1.10	0.60-2.01	.749
Concomitant	vs Nonanticoagulant	2.12	1.17-3.86	.013
Antithrombin	vs rhTM	1.91	1.06-3.44	.031
Antithrombin	vs Concomitant	0.99	0.55-1.78	.973
rhTM	vs Concomitant	0.52	0.26-1.03	.061

Abbreviations: CI, confidence interval; OR, odds ratio; rhTM, recombinant human thrombomodulin.

administration of these agents caused no additional adverse effects over those of individual administration.

Differences in Mortality Between Antithrombin and rhTM

Multiple evidence based on previous observational studies and post hoc subgroup analyses of randomized controlled trials suggested the association of survival benefits with anticoagulant therapies for sepsis-induced DIC.⁴⁻¹¹ The current study also demonstrated significant reductions in mortality in all 3 groups of anticoagulant therapies compared to the nonanticoagulant group.

However, there has been a great deal of controversy about which agent, antithrombin or rhTM, is more effective in improving patient outcomes because only a few studies have investigated the superiority of 1 agent over the other. Our study showing no significant difference in mortality between antithrombin and rhTM agreed with a recent large-scale observational study based on the Japanese DPC database,²⁰ and these lines of evidence provide a robust indication that these 2 agents offer almost comparable survival benefit for patients with sepsis-induced DIC.

Significance of Concomitant Administration of Anticoagulants

In our study population, 316 patients received the concomitant administration of antithrombin and rhTM, which was equal to 53.8% of the total number of patients who received antithrombin and 58.8% of the total number of patients who received rhTM. Another database in Japan reported by Tagami et al showed that 37.7% of the sepsis-induced DIC patients who received antithrombin were coadministered rhTM, and 45.9% of the sepsis-induced DIC patients who received rhTM were coadministered antithrombin.^{12,13} These findings might reflect the current Japanese clinical situation in which the concomitant administration of these 2 agents was widely performed as adjunct management for sepsis-induced DIC. Therefore, clinical evidence to evaluate the superiority of concomitant administration over individual administration is strongly required.

Antithrombin exerts its anticoagulant properties by controlling the activity of thrombin and a large number of coagulation factors including factors VIIa, IXa, Xa, XIa, and XIIa.²¹ In contrast, rhTM forms a high-affinity complex with circulating thrombin and activates protein C, which inactivates coagulation factors Va and VIIIa, thereby suppressing further thrombin generation.²² Previous studies reported that these 2 independent anticoagulant pathways neither affect nor disturb each other.²³ Therefore, the concomitant administration of antithrombin and rhTM could possibly exert additive and synergistic anticoagulant effects. Actually, several animal studies demonstrated that concomitant therapy with antithrombin and rhTM could modulate cell death, decrease the circulating levels of damage-associated molecular patterns, and lead to reduced organ damage and mortality.^{24,25}

Nevertheless, despite these theoretical advantages of the concomitant administration of antithrombin and rhTM, the efficacy of concomitant therapy remains a topic of controversy because of a lack of definitive clinical evidence.^{26,27} We have provided the best evidence so far that the survival benefit associated with concomitant therapy was almost comparable to that of the individual administration of antithrombin or rhTM in the clinical situation. However, we cannot offer a clear explanation for why concomitant therapy was not associated with a greater effect on mortality despite the line of pathophysiological advantage reported by past basic studies. One possible reason might be that the individual administration of these agents already has sufficient efficacy to improve the patient's condition, so that any additional benefit from coadministration of the other agent might be concealed.

Adverse Events

Bleeding was the most significant adverse event associated with anticoagulant therapy. In this study, we showed that the individual administration of antithrombin was associated with a higher risk of bleeding complications compared to nonuse of an anticoagulant. These findings agreed with those of previous studies showing an association between antithrombin

administration and an increased risk of bleeding complications.^{28,29} Therefore, anticoagulant therapy including antithrombin should be administered only inpatients who can be expected to receive sufficient survival benefits despite the potentially increased risk of bleeding.

Limitations of This Study

Because of the retrospective study design, baseline characteristics and therapeutic interventions, including the concomitant use of low-dose heparin for prophylaxis of DVT, were different between the 4 groups. Therefore, we developed a propensity score approach to cope with the nonrandomized effect of anticoagulant therapies. However, it is hard to remove the effects of observed confounding completely because multiple unmeasured variables may account for the outcome differences observed in this study. Further multicenter prospective randomized trials are therefore required to gather definitive evidence of the difference in clinical outcomes between individual and concomitant anticoagulant therapy against sepsis-induced DIC.

Conclusion

The present study using the multicenter nationwide J-Septic DIC registry in Japan suggested that individual administration of antithrombin or rhTM had comparable efficacy in reducing mortality, but concomitant administration of these 2 agents might offer no additional survival benefit. Our findings raise some concerns about the routine use of concomitant anticoagulant therapy against sepsis-induced DIC.

Authors' Note

Y.U. contributed to the study design; acquisition, analysis, and interpretation of the data; and drafting of the manuscript. K.Y. conceived and designed this study and was responsible for drafting, editing, and submission of the manuscript. M.H., D.K., and S.F. assisted with the design of the study and interpretation of the data. All authors reviewed and revised the manuscript and approved the final version of the manuscript. The data sets supporting the conclusions of this article are available in the University Hospital Medical Information Network Individual Case Data Repository (UMIN000012543, <http://www.umin.ac.jp/icdr/index-j.html>). Please contact the corresponding author to access the data. Trial registration: UMIN000012543. Retrospectively registered 10 December 2013. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplementary material for this article is available online.

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