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Impact of Anticoagulant Therapy on Mortality for Sepsis-Associated Disseminated Intravascular Coagulation Depending on the Source of Infection

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Abstract

Introduction: Sepsis can be caused by various infections, and coexistence of Disseminated Intravascular Coagulation (DIC) exacerbates mortality. Reportedly, anticoagulant therapy could be associated with a survival benefit in patients with sepsis-associated DIC. The use of Antithrombin (AT) replacement therapy and Recombinant Thrombomodulin (RTM) preparations are typically applied as part of anticoagulant therapy, but which therapeutic modality should be prioritized is unclear.

Objectives: This study aimed to clarify whether anticoagulant therapies affect mortality depending on the source of infection and identify the suitable treatment, AT or RTM, based on the source of infection.

Patients and Methods: This single-center retrospective cohort study involved 297 patients with sepsis-associated DIC treated by either AT replacement therapy or RTM preparation. Participants were categorized into the following five groups according to the source of infection: pulmonary, intestine-related, biliary tract, urinary tract, and catheter-related bloodstream infection groups. To assess the clinical efficacy of AT or RTM depending on the source of infection, 90-day mortality was examined using a Cox proportional hazard model.

Results: AT replacement therapy reduced the mortality in pulmonary infection (Hazard Ratio (HR), 0.461; 95% Confidence Interval (CI), 0.215–0.992; P=0.048), and RTM preparation did in biliary tract infection (HR, 2.675; 95% CI, 1.037–6.900; P=0.042).

Conclusion: The impact of anticoagulant therapies showed different influence depending on the source of infection, and we suggest that it is necessary to properly use of AT replacement therapy and RTM preparations.

Keywords: Thrombomodulin; Antithrombin; Polymyxin-B Hemoperfusion; Pulmonary infection; Biliary tract infection.

Introduction

Sepsis can be caused by various infections, and the related mortality rates are substantially higher in patients with Disseminated Intravascular Coagulation (DIC) [1]. Regarding benefit profile of anticoagulant therapy in sepsis, a nationwide multicenter registry in Japan [2] was analyzed and reported that aggressive therapy of DIC were important for improving patient outcomes in addition to treating the underlying disease. For management of DIC, Antithrombin (AT) replacement therapy and Recombinant Thrombomodulin (RTM) preparations were suggested by the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 (J-SSCG 2016) [3]. However, international guidelines for management of sepsis in 2016 [4] recommended against the use of AT and provided no recommendation regarding the use of RTM for treatment of sepsis and sepsis shock. Cochrane Database Systemic Review in 2016 [5] reported that there was insufficient evidence to support AT substitution in any category of critically ill participants, and they did not find a statistically significant effect of AT including the subset of patients with sepsis and DIC. The SCARLET randomized clinical trial examined effect of RTM on mortality in patients with sepsis-associated coagulopathy concluded that administration of RTM, compared with placebo, did not significantly reduce mortality [6]. At this time, there are no clear institutional guidelines as to which therapeutics should be prioritized.

Factors that affect the prognosis include not only the severity of the disease but also the selection of appropriate treatments and the use of effective therapeutic drugs. It also seems that the mechanism of progression of disease or onset of DIC differs depending on the source of infection and implies the necessity of considering the specific characteristics in deciding treatment policies. This indicates that, if the therapeutic effect of drugs is discussed, a comparison should be made by source of infection. Therefore, we hypothesized that anticoagulant therapies may differently impact patient mortality according to different sources of infection. This study also focused on identifying which treatment, AT replacement therapy or RTM preparation, was suitable for which source of infection.

Patients and Methods

Study design

This was a retrospective cohort study of patients with sepsis-associated DIC who were admitted to Hakodate Goryoukaku Hospital during the period from May 2008 to December 2019. Patients were excluded if they were suffered from Child–Pugh C hepatic cirrhosis, hematologic diseases such as leukemia, and end-stage cancer. Our study protocol was approved by the local ethics committee in our hospital (No.2020-049), and informed consent was waived because of this study's retrospective design.

Definitions

Sepsis was diagnosed based on the Sepsis-3 criteria [7], and DIC was defined as a total score of ≥ 4 according to the Japanese Association for Acute Medicine (JAAM) DIC scoring system [8]. The Acute Physiology and Chronic Health Evaluation II (APACHE-II) [9] are used as tools to objectively assess patient clinical severity. Baseline data were collected from electronic medical records, and were calculated to confirm their diagnosis at the time when DIC treatment was planned. All patients were followed-up for 90 days after a diagnosis of sepsis with DIC.

Data collection and management

Participants were categorized into the following five groups according to the source of infection: Pulmonary, Intestine-related, Biliary tract, Urinary Tract, and Catheter-Related Bloodstream (CRBS) infection groups.

The anticoagulant therapies for DIC available in our hospital are limited to the use of AT replacement therapy or RTM preparations. For AT replacement therapy, the supplementation dose of AT was 1500 IU/day for 3 days; RTM was administrated at a dose of 380 U/kg, but the dose was reduced to 130 U/kg in patients with renal disorders. In this retrospective study, there were no predefined protocols regarding the definite indications for using AT replacement therapy or RTM preparation. Therefore, these therapeutic modalities were administered at the discretion of the attending physician.

In our series, all patients in intestine-related infection group underwent emergent surgical procedures, and sepsis-associated DIC occurred after surgery. In the biliary tract infection group, a biliary drainage applied for a treatment of biliary obstruction. Polymyxin B Hemoperfusion (PMX-HP) was indicated for patients with septic shock unresponsive to standard fluid resuscitation and the use of cardio-vascular agents; however, its enforcement was left to the discretion of the attending physician.

Statistical analysis

Results are presented as mean ± standard deviation. Overall survival time was defined as the time from DIC diagnosis to any cause death. The Kaplan–Meier method was used to estimate survival rates depending on the source of infection, and a comparison was made using a log rank test. To assess the clinical efficacy of AT replacement therapy or RTM preparation, 90-day mortality was examined using a Cox proportional hazard model with APACHE-II score, JAAM DIC score, and preparation of PMX-HP as common variables in each infection group. In the intestine-related infection group, intestine damage could be etiologically attributed to two variables, intestinal necrosis or perforation, and these variables were added to the multivariate analysis. Preparation of biliary drainage in biliary tract group and the indication of mechanical ventilation to the patient in pulmonary infection group were included as additional variables in group analysis, respectively. Hazard ratios and 95% confidence intervals were determined for these variables. In all tests, $P<0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 21.0. (Armonk, NY: IBM Corp.).

Results

Patient characteristics

In total, 297 consecutive patients who presented with sepsis-associated DIC and simultaneously treated by either AT replacement therapy or RTM preparation were assessed for inclusion in the study. Enrolled patients were categorized based on five sources of infection, and the characteristics are shown in Table 1. All patient in intestine-related infection group underwent emergency surgery owing to the clinical diagnosis of intestinal necrosis (n=23) or intestinal perforation (n=46). In biliary tract infection group, biliary drainage was performed in 64% (36/55) patients. In pulmonary infection group, mechanical ventilation was installed in 54% (42/76) patients.

Variables	Pulmonary infection	Intestine-related infection	Biliary tract infection	Urinary tract infection	CRBS infection
Patients, n	76	69	55	52	45
Age, mean (SD)	74(12)	74(10)	78(11)	74(11)	69(13)
Sex (men/ women), n	46/30	40/29	27/28	15/37	22/23
APACHE-II score, mean (SD)	21(6.5)	21(6.1)	15(4.9)	17(5.7)	19(7.6)
JAAM DIC score, mean (SD)	5.6(1.4)	5.1(1.2)	5.8(1.3)	5.7(1.4)	5.8(1.6)
Polymyxin B hemoperfusion, n (%)	13(17)	18(26)	4(7)	6(12)	9(20)
Mechanical ventilation, n (%)	41(54)	35(51)	6(11)	4(7.7)	6(13)

Surgical procedure, n (%)	0(0)	69(100)	0(0)	1(2)	0(0)
Anticoagulant therapy (RTM/AT), n	59/17	54/15	45/10	39/13	28/17
Days of RTM administration, mean (SD)	4.2(3.7)	3.3(3.0)	4.7(3.6)	3.2(2.3)	3.3(3.5)

Table 1: Patient characteristics by the source of infection. SD: Standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation; JAAM: Japanese Association for Acute Medicine; DIC: Disseminated Intravascular Coagulation; RTM: Recombinant Thrombomodulin; AT: Antithrombin; CRBS: Catheter-Related Bloodstream.

Survival (90 days) by the source of infection

Kaplan–Meier survival curves are shown in Figure 1. Comparing the mortality of the five groups, that is Pulmonary, Intestinal-related, Biliary tract, Urinary tract, and CRBS infection groups, revealed that there were significant differences in terms of the source of infection in the overall 90-day survival rates (P<0.001).

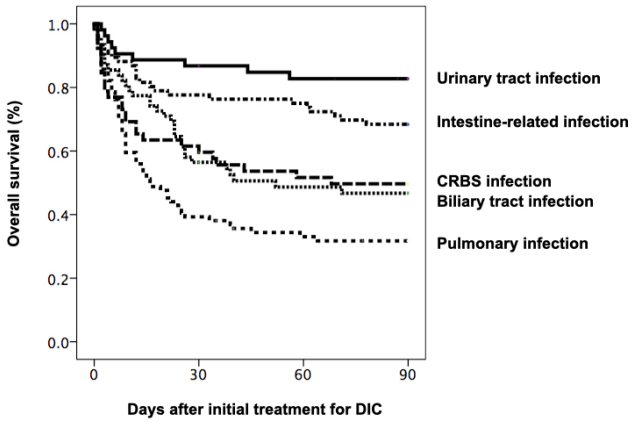

Figure 1: Kaplan-Meier survival curves for sepsis-associated DIC divided into five groups depending on the source of infection. Statistical comparison was made by a log rank test (P<0.001). CRBS: Catheter-Related Bloodstream.

Impact variables on mortality by the source of infection

In pulmonary infection group (Figure 2), AT replacement therapy and performing PMX-HP showed significant improvement in mortality (P=0.042, P=0.034). In the intestine-related infection group (Figure 3).

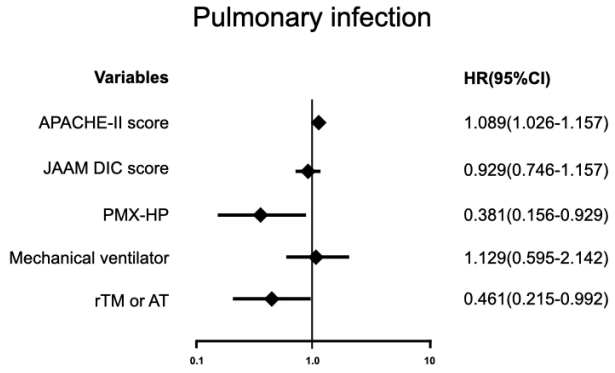

Figure 2: Patients in pulmonary infection group.

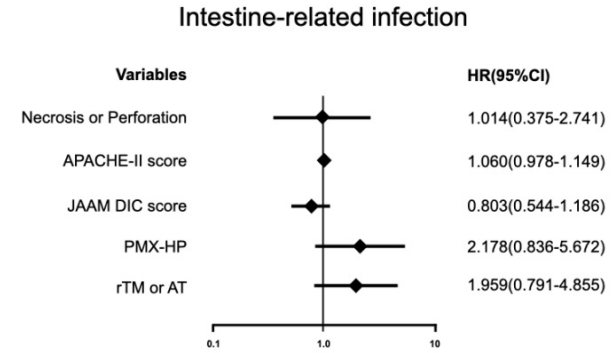

Figure 3: Patients in intestine-related infection group

There is no significant difference on mortality between the use of AT replacement therapy and RTM preparation. In the biliary tract infection group (Figure 4), the use of RTM preparation showed statistically significant impact on improving mortality (P=0.048). In the group of urinary tract (Figure 5) and CRBS infection (Figure 6), the differences of impact on mortality between AT replacement therapy and RTM preparations were not statistically significant.

Figure 4: Patients in biliary tract infection group.

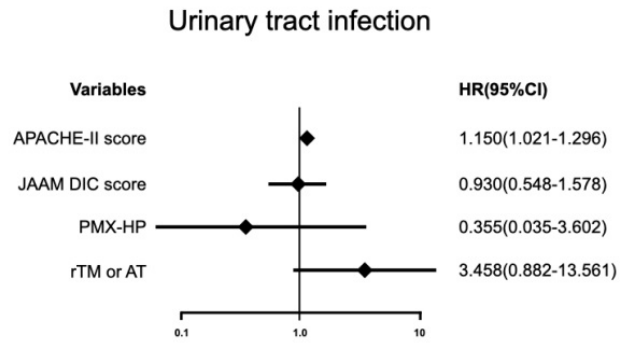

Figure 5: Patients in urinary tract infection group.

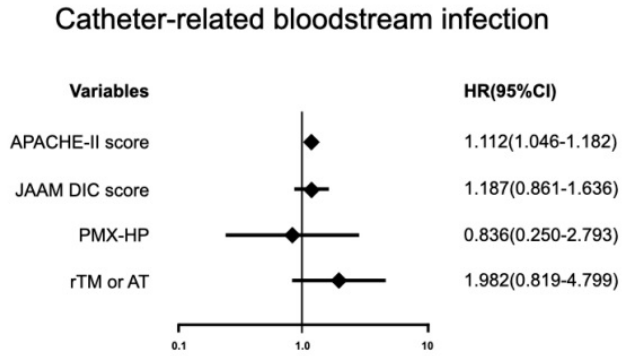

Figure 6: Patients in catheter-related bloodstream infection group.

Discussion

In our study, patients with sepsis-associated DIC were classified according to the source of infection and we investigated whether there was a difference between the outcomes of using AT replacement therapy and RTM preparation as anticoagulant therapies. As a result, the impact of these therapies highlighted the differences in their influence on mortality depending on the source of infection. Aggressive therapy of DIC has been reported to be important for improving patient outcomes [2]. However it has remained unclear which treatments, AT replacement therapy or RTM preparation, is suitable for which source of infection, and there have been no definitive reports of comparative test among various sources of infection. Therefore, in this study, the impact of RTM preparation and AT replacement therapy were analyzed together with other variables using a multivariate analysis for each source of infection. The results revealed that pulmonary and biliary tract infection showed different outcomes depending on the use of AT replacement therapy and RTM preparation.

In the pulmonary infection group, the result from the Cox proportional hazard analysis showed the use of AT replacement therapy could be favorable to reduce 90-day mortality over the use of RTM preparation. Collecting from the Japanese Diagnosis Procedure Combination (DPC) database between 2010 and 2013, the nationwide study concerning about AT replacement therapy in patients with severe pneumonia with sepsis-associated DIC reported that AT replacement therapy may be associated with reduced 28-days mortality [10]. Alternatively, the effect of RTM preparation resulted from propensity score analyses using Japanese DPC data demonstrated that there might be little association between the use of RTM and mortality in patients with severe pneumonia with sepsis-associated DIC [11]. However, a retrospective study enrolling 1,180 of patients from 42 intensive care units in Japan concluded that the use of RTM preparation was positively correlated with a reduction in mortality in patients with sepsis with severe respiratory failure [12]. Thus, an effect of RTM preparation on pulmonary infection–induced septic DIC is still controversial.

Focusing on the biliary tract infection, our data showed the use of RTM preparation had a positive effect on reduced 90-day mortality, which is favorable over AT replacement therapy for sepsis-induced DIC. Tokyo Guidelines 2018 for initial management of acute biliary infection [13] recommended the use of RTM for acute cholangitis–induced DIC, but the level of evidence in that study was relatively low. A propensity score matching analysis using a nationwide database in Japan collecting 4,094 of eligible patients proposed that RTM preparation should be used for the treatment to patients with acute cholangitis with DIC [14]. On the contrary, the efficacy of AT replacement therapy combined with RTM preparation for acute cholangitis–induced DIC reported that the concomitant use of both anticoagulant therapies may not help improve the treatment outcome [15].

Our study also found the effectiveness of performing PMX-HP on sepsis-induced DIC in pulmonary infection group. A guideline of J-SSCG 2016 [3] recommended performing PMX-HP as a standard treatment for patients with septic shock. However, the EUPHRATES randomized trial in North America [16], which was designed to test whether adding the use of PMX-HP improves survival among patients with septic shock resulted that performing PMX-HP did not reduce mortality at 28 days. From our study that categorized the source of infection into five groups, the impact of PMX-HP on reduced 90-day mortality revealed its usefulness only in pulmonary infection group. About the relationship between PMX-HP and respiratory failure, the EUPHAS trial [17] that enrolled patients with severe sepsis or septic shock because of intra-abdominal infection requiring emergency surgery reported that mean arterial pressure increased, vasopressor requirement decreased, the PaO2/FiO2 ratio increased, and 28-day mortality decreased by the early use of PMX-HP. However, regarding the intestine-related infection group, the French ABDOMIX RCT [18] failed to demonstrate clinical benefits of PMX-HP application in patients suffering from peritonitis-induced septic shock after emergency surgery. Similarly from our study, in intestine-related infection group, performing PMX-HP could not show any significant reduction of 90-day mortality. Until now, the usefulness of PMX-HP is still controversial and further analysis is required depending on the source of infection.

Several limitations associated with the present study include the following. First, our study was a single-center retrospective analysis without randomization, and the number of patients was small. Second, the source of infection was classified into five

groups, each of which could include various pathological conditions, and a bias could still be present in the form of confounders. Third, we made no definite indication for the use of AT replacement therapy or RTM preparation, and these therapeutics were administered at the discretion of the attending physician. Fourth, the administration of RTM preparation has been used until clinical improvement of DIC, but its decision is left to the discretion of the attending physician because there is no strict provision for discontinuation of medication in our institution. Fifth, performing PMX-HP was usually indicated for a patient with severe septic shock, but the decision to use was made by the discretion of the attending physician. Therefore, our date was including some patient with severe shock but not tried performing PMX-HP.

Conclusion

In conclusions, patients with sepsis-associated DIC were classified depending on the source of infection, and whether there was a difference in the therapeutic effect of AT replacement therapy and RTM preparation was examined. As a result, the outcome of using AT replacement therapy was good for pulmonary infection and that of RTM preparation was good for biliary tract infection. Therefore, we suggest that it is necessary to properly use AT replacement therapy and RTM preparations depending on the source of infection.

A summary of this report was presented at the 120th Annual Congress of the Japan Surgical Society (held in August 2020 in Yokohama).

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Author contributions

M.K. wrote the manuscript. R.A., Y.E. and S.H. revised and edited the manuscript.

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Conflict of interest

Makoto Kobayashi and the other co-authors have no conflict of interest.

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