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Full Length Article

The efficacy and associated bleeding complications of recombinant antithrombin supplementation among intensive care unit patients

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ABSTRACT

Introduction: The aim of this study was to evaluate the efficacy and complications of recombinant antithrombin (rAT) supplementation for adult patients with disseminated intravascular coagulation (DIC) compared with conventional plasma derived AT (pAT) treatment in the intensive care unit.
Materials and methods: This study was performed in a single national university hospital in Japan. Adult patients from April 2015 to March 2016 with DIC were divided into two groups based on the type of AT agent used: the pAT group (n = 24) and the rAT group (n = 21). Patient demographics, medical history, diagnosis, blood tests, various clinical scores, AT activity, complications, and clinical outcome were collected and analyzed retrospectively.
Results: Significantly higher SIRS and APACHEII scores were confirmed in the rAT group than the pAT group. The initial dose of AT was significantly higher in the rAT group than in the pAT group. ATIII values before and after initial supplementation and during their ten-day clinical course were statistically similar between two groups. During the same period, 10 bleeding adverse events were found and there was no significant difference between both groups. Significantly more cases of the rAT group were administered with recombinant thrombomodulin concomitantly than those of the pAT group. Despite significantly more severe patients in rAT group, the clinical outcomes were the same in each group.
Conclusions: Compared with pAT, the supplementation of rAT indicates clinical effectiveness without increasing the risk of bleeding complications in adult DIC patients with low AT activity.

1. Introduction

Antithrombin (AT) is a serine protease inhibitor which forms complexes to inactivate thrombin and factors IIa, VIIa, IXa, Xa, XIa, and XIIa [1–3]. In addition, the anti-inflammatory properties of AT have been shown to play an important role in prevention of worsening systemic inflammation such as sepsis, post cardiopulmonary bypass, and reperfusion injury in organ transplantation [2]. The AT agent possesses not only an anticoagulation effect on thrombin and other coagulation factors, but also anti-inflammatory activity in sepsis [4].

In Japan, antithrombin administration is officially approved for maintaining adequate levels of plasma ATIII in patients with hereditary or acquired AT deficiency, especially in disseminated intravascular coagulation (DIC) [5]. The recent Japanese expert consensus recommends AT supplementation for septic DIC patients with <70% of AT activity [5]. Indeed, a number of previous studies demonstrate the clinical advantages of replacement therapy by AT supplementation [5–12]. The Survival Sepsis Campaign guidelines have globally improved the quality of clinical management for sepsis over the past decade [13], but specific anticoagulation therapy including AT therapy has yet to be recommended worldwide [13,14].

The recombinant AT (rAT) agent has been officially approved for commercial use in Japan since July 2015, and it is expected to prevent plasma-product-related complications. At Saga University Hospital, the conventional type of AT (pAT) has been completely replaced with rAT since November 2015. The recommended volume of rAT is calculated based on body weight (36 IU/kg), which is equivalent to the volume of conventional therapy by pAT (1500 IU/day or 30 IU/kg) [15].

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However, few studies about the efficacy and safety of rAT for DIC patients with low AT level have been performed.

The aim of this study was to retrospectively evaluate the efficacy and bleeding complications of rAT supplementation compared with treatment by pAT among intensive care unit patients.

2. Materials and methods

2.1. Study design and patients

This is a retrospective observational study performed in the two ICUs of a single national university hospital in Japan. The study was certified by the institutional review board of Saga University Hospital (20160705). Patients 18 years of age and older who received an AT agent during their ICU stay from April 2015 to March 2016 were included in the present study. During this period, pAT was replaced with rAT starting in November 2015 in this hospital. All cases were divided into two groups based on the type of AT agent: pAT group (n = 24 cases) and rAT group (n = 21 cases).

2.2. Variables related to patient demographics, medical history, and diagnosis

Patient data including age, sex, and past medical histories such as malignancy, ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM) and liver cirrhosis (LC) were collected. Sepsis was defined as an infection induced condition with more than a two-point increase in the systemic inflammatory response syndrome (SIRS) score. Infection sources were categorized according to the results of blood cultures in combination with clinical manifestations.

2.3. Blood testing and various clinical scores

The following blood test results were analyzed were: white blood cell (WBC) count, platelet (PLT) count, C-reactive protein (CRP), prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time (APTT), fibrinogen (FIB), fibrin degradation products (FDP), and D-dimer (DD).

In addition to blood tests, we calculated various clinical scores to evaluate the patient's severity as follows: SIRS score, sequential organ failure assessment score (SOFA) score, acute physiology and chronic health evaluation (APACHE) II score, and Japanese association for acute medicine (JAAM) disseminated intravascular coagulation (DIC) score. All variables described above were recorded before AT administration on the first day of treatment. DIC was defined when a patient's DIC score was >4 points.

Table 1
Patient characteristics in each group.

	pAT group (n = 24)	rAT group (n = 21)	P-value
Age, year old,*	75 [58–82]	75 [63–83]	0.793
Male, n (%)	15 (62.5)	14 (66.7)	0.771
Body weight, kg,**	60.6 ± 11.6	60.3 ± 12.5	0.936
Past medical history			
Malignancy, n (%)	7 (29.2)	9 (42.9)	0.338
IHD, n (%)	2 (8.3)	3 14.3	0.435
COPD, n (%)	1 (4.2)	0 (0.0)	0.533
DM, n (%)	6 (25.0)	9 (42.9)	0.205
LC, n (%)	3 (12.5)	6 (28.6)	0.166
Sepsis, n (%)	16 (66.7)	16 (76.2)	0.482
Infection sources			
Digestive, n (%)	5/16 (31.3)	7/16 (43.8)	0.296
Respiratory, n (%)	3/16 (18.8)	3/16 (18.8)	
Urinary, n (%)	0/16 (0.0)	1/16 (6.3)	
Biliary, n (%)	0/16 (0.0)	2/16 (12.5)	
Others, n (%)	7/16 (43.8)	2/16 (12.5)	
Unknown, n (%)	1/16 (6.3)	1/16 (6.3)	
Positive blood culture, n (%)	8/15 (53.3)	9/12 (75.0)	0.226

IHD: ischemic heart disease, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, LC: liver cirrhosis.
*Median [IQR], **Mean ± SD, P-value < 0.05.

Table 2
Blood tests and clinical scores on the first day of AT therapy.

	pAT group (n = 24)	rAT group (n = 21)	P-value
WBC, /μL,*	8950 [8025–11,575]	13,800 [8650–21,750]	0.028
Platelet, 10^4/μL,*	7.8 [5.1–11.1]	8.0 [4.0–14.8]	0.829
Alb, g/dL,*	2.4 [1.9–2.8]	2.4 [2.1–2.8] (n = 20)	0.868
CRP, mg/dL,**	12.5 ± 8.6 (n = 23)	17.5 ± 11.0	0.099
PT-INR,*	1.44 [1.27–1.74]	1.53 [1.33–2.04] (n = 20)	0.389
APTT, second,*	51.6 [42.8–89.2]	53.2 [47.0–92.2]	0.585
Fibrinogen, mg/dL,**	371.0 ± 204.6	420.0 ± 222.4 (n = 20)	0.451
FDP, μg/mL,*	23.7 [16.2–36.7] (n = 23)	38.1 [18.6–104.0]	0.159
DD, μg/mL,*	8.14 [6.17–17.25] (n = 16)	15.96 [8.72–54.38] (n = 17)	0.031
SIRS, pts,*	2 [1–3]	3 [2–3]	0.007
SOFA, pts,*	12 [9–14]	11 [9–14]	0.973
APACHEII, pts,**	23.2 ± 9.4	29.1 ± 6.6	0.020
JAAM DIC score, pts,*	5 [3–6]	6 [4–8]	0.298
JAAM DIC, n (%)	18 (75.0)	16 (76.2)	0.926

WBC: white blood cell, Alb: albumin, CRP: C-reactive protein, PT-INR: international normalized ratio of prothrombin time, APTT: activated partial thromboplastin time, FDP: fibrinogen and fibrin degradation products, DD: D-dimer, SIRS: systemic inflammatory response syndrome, SOFA: sequential organ failure assessment, APACHEII: acute physiology and chronic health evaluation, JAAM: Japanese association for acute medicine, DIC: disseminated intravascular coagulation.
*Median [IQR], **Mean ± SD, P-value < 0.05.

2.4. AT administration and measurement of plasma AT value

Data on the treatment of AT included the initial dose, the initial dose of AT adjusted for BW, the timing of AT treatment before or after surgery, the route of administration, and the number of treatment days. The recommended injection dose of pAT used in Saga University Hospital was 1500 international unit (IU) or 30 IU/kg, whereas that of rAT was 36 IU/kg. There is no institutional protocol on AT supplementation. Therefore, the indication of AT was determined by each physician in charge.

Plasma ATIII levels were measured in all patients before initial AT administration (day 0). However, after the first injection of AT, the timing and the number of tests for the ATIII level was dependent on each individual physician. We retrospectively analyzed the ATIII data from day 0 to day 10, which was categorized as follows: “Day 0”, “Day 1–2”, “Day 3–5” and “Day 6–10”. Since the number and timing of blood sampling varied, the highest ATIII value was used for the analysis from each category.

Table 3
Variables for AT administration in the intensive care unit.

	pAT group (n = 24)	rAT group (n = 21)	P-value
Initial dose, unit,*	1500 [1500–1500]	1800 [1800–2400]	<0.001
Initial dose of AT adjusted for BW, unit/kg,*	26.1 [22.6–28.8]	33.9 [31.2–37.1]	<0.001
Timing of the AT therapy			
Before operation, n (%)	3 (12.5)	2 (9.5)	0.565
After operation, n (%)	14 (58.3)	5 (23.8)	0.019
Type of DIV			
Intermittent, n (%)	20 (83.3)	19 (90.5)	0.400
Continuous, n (%)	4 (16.7)	2 (9.5)	
Total days of therapy, day,*	2 [1–3]	2 [1–4]	0.461

DIV: intravenous drip.
*Median [IQR], **Mean ± SD, P-value < 0.05.