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Full Length Article

Antithrombin supplementation and risk of bleeding in patients with sepsis-associated disseminated intravascular coagulation

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ABSTRACT

Introduction: Although antithrombin is commonly used for the treatment of sepsis-associated disseminated intravascular coagulation (DIC) in Japan, the factors influencing the incidence of bleeding complications have not been sufficiently studied. The purpose of this survey was to identify the factors that predict clinically relevant bleeding in patients receiving antithrombin for DIC.
Methods: We analyzed data from 1026 sepsis-associated DIC patients with a baseline antithrombin activity ≤70% who underwent antithrombin supplementation at two dosages (1500 IU/day or 3000 IU/day) for three consecutive days. The patients' demographic characteristics, parameters before and after the treatment, and co-administered anticoagulants were analyzed in relation to the bleeding events.
Results: Overall, 55 patients (5.36%) experienced bleeding events (major bleeding: 1.75%). Logistic regression analysis revealed that sustained DIC > 7 days was significantly associated with bleeding (odds ratio: 2.761, $P = 0.001$). In contrast, the higher dose of antithrombin or the co-administration of recombinant thrombomodulin or heparins were not associated with bleeding events.
Conclusion: A higher dose of antithrombin or the concomitant use of other anticoagulants were not associated with bleeding events. On the other hand, sustained DIC lasting more than one week was associated with an increased risk of bleeding in patients with sepsis-associated DIC.

1. Introduction

Recent studies have repeatedly demonstrated a beneficial effect of antithrombin on sepsis-associated intravascular coagulation (DIC) [1–3]. A randomized controlled study conducted by the Japanese Association for Acute Medicine (JAAM) revealed that the DIC resolution rate in patients treated with a supplementation dose of antithrombin (1500 IU/day for 3 days) was more than twice of that of the patients who were treated without antithrombin (53.3% vs. 20.0%, $P = 0.015$) [4]. However, an increase in the bleeding risk has been the major concern associated with this treatment [5], and the global guidelines for severe sepsis management [6], the British guidelines [7] and the Italian guidelines [8] for DIC management do not recommend the use of antithrombin for DIC. Indeed, the large randomized controlled trial KyberSept [9] found a significant increase in the incidence of bleeding in patients receiving high-dose (30,000 IU in total over 4 days) antithrombin (placebo: 12.8% [major bleeding: 5.7%] vs. antithrombin: 22.0% [major bleeding: 10.0%], $P < 0.01$). In a recent meta-analysis, Allingstrup et al. [10] also demonstrated a significant increase in bleeding events (relative risk [RR], 1.58; 95% confidence interval [CI], 1.35–1.84). The risk of bleeding might differ between patients with and those without DIC. In a subgroup analysis of the KyberSept trial [11], though bleeding complications were significantly higher in the antithrombin-treated group of patients without DIC (20.2% vs. 8.7%, $P = 0.003$), the difference was not significant among patients with DIC (18.4% vs. 11.3%, $P = 0.14$). Similar findings have been reported for other anticoagulants. Umemura et al. [3] found that the bleeding risk was 5.7% in septic patients not receiving anticoagulant vs. 7.6% in septic patients treated with an anticoagulant (RR, 1.33; 95% CI, 1.12–1.57; $P < 0.01$). The corresponding risks in patients with sepsis-associated

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DIC were comparable (6.1% vs. 7.7%; RR, 1.26; 95% CI, 0.86–1.85; $P = 0.23$). Despite the increased prevalence of anticoagulant therapy for patients with sepsis-associated DIC, the bleeding risk associated with a supplementation dose of antithrombin has not been sufficiently examined. Thus, the objective of this study was to elucidate the factors associated with bleeding complications in such patients.

2. Patients and methods

2.1. Treatment

The Japanese health care system approved the use of antithrombin concentrate for patients with DIC and an antithrombin activity of 70% or less in 1987. For standard use, either 1500 IU/day or 3000 IU/day of AT is administered for 3 consecutive days, and this treatment is called "supplementation therapy."

2.2. Data set

Data from multi-institutional, post-marketing surveys performed between 2006 and 2014 by Nihon Pharmaceutical were utilized for the analysis [12,13]. A total of 1026 sepsis-associated DIC patients treated with antithrombin concentrate (Nihon Pharmaceutical Co. Ltd., Tokyo, Japan) were registered in the survey. Patients were treated with antithrombin supplementation therapy when the patients met the JAAM-DIC criteria [14] and baseline antithrombin activity was ≤70%. Platelet count, prothrombin time (PT), fibrinogen/fibrin degradation products (FDP), systemic inflammatory response syndrome (SIRS) score, JAAM-DIC score, sepsis-related organ failure assessment (SOFA) score and antithrombin activity were evaluated at the time of the diagnosis of DIC (Day 1) and after antithrombin supplementation (Day 4). Standard sepsis care was performed, and platelet concentrate and fresh frozen plasma were used as substitution therapy, if necessary [15]. The survey was conducted in accordance with the Declaration of Helsinki and Good Vigilance Practice and Good Post-marketing Study Practice. Although the Japanese Ministry of Health, Labour and Welfare judged that the patients' agreement was not necessary for this survey, the patients' agreement and consent were obtained when required by the ethics committee of each hospital.

2.3. Study outcomes

Bleeding events were recorded from the day of DIC diagnosis until Day 28. Major bleeding was defined as bleeding that was either fatal, involved a critical organ, or was associated with a decrease in the hemoglobin level of 2.0 g/dL or more or required the infusion of 2 or more units of blood. The patients who presented bleeding at diagnosis were not included in the study. The DIC was judged to have been resolved if the JAAM-DIC score decreased to <4 and DIC resolution rate was calculated on Days 4 and 7. Patients were judged as 'sustained DIC' if the score was >4 on Day 7.

2.4. Measurements

The platelet count and other coagulation tests were measured at local laboratories. The following methods were used for the measurements: the electric impedance method was used for the platelet count, the scattered light detection method was used for the PT, and latex immunoassays were used for the FDP. To measure the antithrombin activity, the plasma anti-Factor Xa activity or the anti-thrombin activity was assessed (chromogenic substrate method, reference intervals: 70% to 120%).

2.5. Statistical analysis

The numerical values in the text and tables represent the median and interquartile range (IQR). The univariate association was evaluated using the Fisher exact test, the unpaired Wilcoxon signed-rank test (Mann-Whitney *U* test). The relationship between bleeding events and the various predictive factors was analyzed using logistic regression analysis (enter method). The following variables were analyzed for their possible association with bleeding: age, baseline DIC score, sustained DIC, antithrombin dose and co-administration of thrombomodulin. The analysis was conducted using the bleeding event (yes, 1; no, 0) as the dependent variable and age, baseline DIC score, sustained DIC (yes, 1; no, 0), antithrombin dose of 3000 IU/day (yes, 1; no, 0) and co-administration of recombinant thrombomodulin (yes, 1; no, 0) as additional factors. Results were reported as the odds ratio (OR), Wald result, *P* values, and 95% CI. A P value < 0.05 was considered to denote statistical significance. The above-mentioned analyses were performed using SPSS 13.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

Table 1 summarizes the baseline characteristics of the study proportion. Fifty-five patients (5.36%) experienced a bleeding event which was major in 18 patients (1.75%). The digestive tract was the most common bleeding site, followed by the soft tissue and respiratory tract. Vascular bleeding was recognized in two cases, and intracranial bleeding was recognized in one case, all of which were regarded as major bleeding (Table 2).

The respiratory tract was the most common suspected source of infectious followed by the digestive tract. There was no statistical difference in the infectious sites between patients with and without

Table 1
Subject baseline demographics and characteristics.

		Non-bleeding ($n = 971$)	Bleeding ($n = 55$)	*P*-value
Sex	Male	560	30	0.676
	Female	411	25	
Suspected source of infection				
Respiratory tract		347	14	0.146
Digestive tract		234	11	0.626
Urinary tract		102	9	0.179
Biliary tract		97	5	1.000
Antithrombin dose				
1500 IU/day × 3 days		854	48	0.832
3000 IU/day × 3 days		117	7	
Co-administered anticoagulants				
Thrombomodulin		81	2	0.308
Heparin (total)		243	15	0.749
Unfractionated heparin		170	10	0.856
Low-molecular weight heparin		75	5	0.610
Median (inter quartile range [IQR])				
Age, years		75 (65–82)	67 (58–80)	0.020*
Body weight (kg)		50.5 (45–60)	50.0 (42.7–60.1)	0.367
Baseline DIC score		5 (4–6)	6 (5–8)	0.001**
Baseline platelet count ($\times 10^4/mm^3$)		6.8 (3.9–10.6)	5.9 (3.7–8.2)	0.055
Baseline FDP (μg/mL)		23.4 (11.7–44.1)	27.9 (13.1–65.8)	0.177
Baseline PT ratio		1.35 (1.20–1.62)	1.50 (1.29–1.81)	0.008**
Baseline SIRS score		3 (2–3)	3 (2–3)	0.782
Baseline AT activity		47.0 (38.0–56.0)	44.0 (33.0–54.0)	0.132
Baseline SOFA score		9 (5.5–12)	9 (6–12)	0.958

DIC: disseminated intravascular coagulation, FDP: fibrinogen/fibrin degradation products, PT: prothrombin time, SIRS: systemic inflammatory response syndrome, AT: antithrombin, SOFA: sepsis-related organ failure assessment.
** *P*-value < 0.01 (Fisher's exact test or unpaired Wilcoxon signed-rank test [Mann–Whitney *U* test]).
* *P*-value < 0.05.