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Incidence of Major Bleeding in Patients with Pulmonary Thromboembolism Treated with Fixed Dose Alteplase 100 mg

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ABSTRACT

Background: Acute pulmonary thromboembolism (PTE) is a critical cardiopulmonary condition associated with high mortality and morbidity. In massive PTE, recently referred to as high risk PTE, the routine protocol for thrombolysis with recombinant tissue plasminogen activator (alteplase) is 100 mg over 2 hours. However, there are concerns about bleeding in patients with low body weight (< 50 kg), elderly patients, and Asians.
Method: We performed a retrospective study in patients who were diagnosed with intermediate or high risk PTE, and who were treated with a fixed dose of alteplase (100 mg) in a single center at Chungbuk National University Hospital between July 2008 and April 2018.
Results: A total of 42 patients were reviewed, 4 patients dropped out, and 38 patients were included in the analysis. There were 18 males (47.4%), and the average age of the patients was 70.68 years (± standard deviation 13.15). Major bleeding was seen in 10/38 patients (26.3%), and 30/38 patients (78.9%) were successfully discharged.
Conclusion: The major bleeding risk was higher in our study (26.3%) than in a previously published meta-analysis (9.24%). Therefore, we suggest reducing the dose of alteplase in patients who are elderly, Asian, or have cardiovascular disease. Further prospective studies of efficacy and bleeding rate after low dose alteplase should be considered.

Keywords: Pulmonary Thromboembolism; Bleeding; Thrombolysis; Dose

INTRODUCTION

In Europe, 1–2 per 1,000 individuals have venous thromboembolism, which results in a mortality rate of 17%.[1,2] In the United States, the prevalence rate of pulmonary thromboembolism (PTE) was 0.4%, and the annual incidence was estimated at 600,000 cases.[3] In Korea, the incidence of PTE was 229.36 per 100,000 and the age-sex adjusted standardized incidence rate was 151.28 per 100,000 in a tertiary hospital during the 10-year period from 2006 to 2015.[4] Also, a previous study from Korean Health Insurance Review and Assessment service database showed the increasing incidence of PTE in Korea.[5] In this study, the annual age- and sex-adjusted incidence (ASR) of venous thromboembolism (VTE) from

2009 to 2013 in Korea increased yearly. In 2009, ASRs of VTE, deep vein thrombosis, and PTE were 21.3, 8.1, and 13.2 cases per 100,000 individuals and these increased to 29.2, 12.7, and 16.6 cases per 100,000, respectively, in 2013.

Among patients with PTE, thrombolytic therapy is indicated for those with high risk PTE (shock or hypotension). This therapy includes streptokinase, urokinase, or recombinant tissue-type plasminogen activator (rt-PA).[6] The rt-PA drugs include alteplase, reteplase, tenecteplase, and desmoteplase, and there is no particular difference in their therapeutic effects. Alteplase is the only drug currently approved by the Food and Drug Administration for patients with high risk PTE.[7] Alteplase has high specificity and acts rapidly to reduce the resistance of pulmonary blood vessels, with a short half-life, and produces no allergic reactions or hypotensive effects.[8]

The general regimen of alteplase for patients with high risk PTE is 100 mg over 2 hours, or a 10-mg bolus followed by 90 mg over 2 hours.[1] Alteplase initiates local fibrinolysis by binding to fibrin in a thrombus, and converts entrapped plasminogen to plasmin. The details of alteplase metabolism have not yet been revealed,[9] and adjusting the dose according to liver and renal function is not recommended.[10]

Nowadays, the incidence of PTE is increasing, especially in elderly patients due to their co-morbidities (cancer, immobilization, fracture, and surgery). There is no routine protocol for dose reduction of alteplase in patients with low body weight, decreased renal function, age over 65, and those with a high risk of bleeding.[4] We have concerns about the bleeding risk when using fixed dose alteplase in these vulnerable patients.

In acute myocardial infarction and stroke, there is evidence about dose reduction of alteplase. In the STREAM trial, in which fibrinolysis was performed in myocardial infarction patients, the incidence of intracranial hemorrhage increased in patients older than 75 years. Therefore, when using rt-PA in patients aged > 75 years, a 50% dose reduction is warranted.[11] The alteplase dose used for patients with stroke is 0.9 mg/kg in most countries, and this dose is particularly low (0.6 mg/kg) in Japan. In the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) trial, compared with standard dose alteplase (0.9 mg/kg), the low dose alteplase (0.6 mg/kg) did not meet any non-inferiority criteria for the outcome of death or disability at 90 days.[12]

Interestingly, in the MOPETT trial of thrombolysis in intermediate-risk PTE, alteplase was used at ≤ 50% of the standard dose.[13] The success rate of thrombolysis was 100%, and the percentage of pulmonary hypertension after thrombolysis was significantly lower than that of the conventional anticoagulation group (16% vs. 63%, $P < 0.001$).

Recent studies halved the dose of alteplase to 50 mg, and have shown no significant difference in efficacy, while there was a decrease in major bleeding.[14,15] This dose reduction protocol has not been established for patients with high risk PTE. In a Korean retrospective study, a low dose thrombolytic regimen was as efficient as the standard dose with a lower bleeding risk.[16]

The frequency of bleeding caused by thrombolysis in previous studies reported to be 0%–23%, and a meta-analysis showed a mortality rate of 2.17%, and an incidence of major bleeding events of 9.24%.[17,18]

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The purpose of our study was to evaluate the major bleeding incidence in intermediate to high-risk PTE patients to whom fixed dose alteplase 100mg was administered.

METHODS

Subjects

We reviewed 42 patients with high risk PTE who had been treated with alteplase 100 mg in Chungbuk National University Hospital, Korea from July 1, 2008 to April 30, 2018. However, one patient voluntarily discharged without performing thrombolysis and we were unable to search the details of medical records of three patients who received alteplase. Thus, the medical records of 38 patients were included in the retrospective analysis. The final diagnosis of PTE was confirmed by chest computed tomography (CT) and echocardiography. Thrombolytic therapy was used in cases when: 1) systolic blood pressure was less than 90 mmHg, or mean arterial pressure was less than 65 mmHg; 2) circulatory shock requiring cardiopulmonary resuscitation occurred; 3) right ventricular (RV) failure occurred with hypoxia, or hypoxemia; or 4) RV dysfunction was ongoing.

Methods

We reviewed the medical records and extracted the following data: clinical symptoms; vital signs; laboratory findings (including arterial blood gas analysis, N-terminal pro-brain natriuretic peptide [NT-proBNP], troponin T, D-dimer, hemoglobin); imaging findings (such as chest X-ray, chest contrast CT, including of the pulmonary artery with deep veins, and echocardiography).

Severity of illness was assessed by the duration of intensive care unit hospitalization, and the sequential organ failure assessment (SOFA) score on the day of thrombolysis.

The data was analyzed for overall treatment success rate, incidence of bleeding, and hospital mortality. Criteria of successful thrombolysis were as follows: hemodynamic stability (i.e., the systolic blood pressure was maintained above 90 mmHg, even after stopping inotropes or vasopressors); improved oxygen saturation; and echocardiographic RV dysfunction improved or was absent during hospitalization and follow-up. The consequences of major bleeding were defined as: 1) fatal bleeding; 2) intracranial hemorrhage; 3) bleeding sufficient to require surgery; 4) reduction in hemoglobin by 2 g/dL or more, or the need for transfusion of two or more units of packed red blood cells.[19] Any bleeding that did not match the above criteria was classified as minor bleeding. Thus, patients were categorized into three groups: 1) non-bleeding; 2) minor bleeding; and 3) major bleeding.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 25.0, SPSS Inc., Chicago, IL, USA). General descriptive statistics were used to determine the mean, standard deviation, and frequency. For categorical data, the nominal variables were analyzed with the χ^2 test or Fisher's exact test. Student's *t*-test was used for continuous variables, and the Mann-Whitney U test was also performed when normal distribution could not be assumed, because there were few observations or variances. For the multivariate analysis, logistic regression was used. The two-sided test and analysis of variance were used, and statistical significance was defined as $P < 0.05$.

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Ethics statement

The Institutional Review Board of Chungbuk National University Hospital approved the study protocol and waived the need for informed consent because the study was retrospective, and no patients were at risk (approval No. 2018-05-020). The study was performed in accordance with the Declaration of Helsinki.

RESULTS

Patient characteristics

A total of 38 patients were reviewed for this study. A fixed dose of alteplase (100 mg) was used, as per the guidelines; it was administered over 2 hours, or as a 10-mg bolus followed by the remaining 90 mg over 2 hours.[20] There were 22 patients without bleeding, 6 patients with minor bleeding, and 10 patients with major bleeding. The mean age of these three groups was similar (71, 67, and 73 years, respectively; $P = 0.659$) (**Table 1**). The SOFA score was significantly higher in the non-bleeding group (8.2 points), and the incidence of cardiovascular disease (70%) was higher in patients with major bleeding than in the other groups. Of the 38 patients, aspirin was used by 10 patients, 5 of whom had major bleeding. Other characteristics did not differ between the three groups.

Diagnostic tests and laboratory findings

There were no differences in average systolic blood pressure among the three groups. One of the arterial blood gas parameters, partial pressure of carbon dioxide, was lower in the

Table 1. Baseline characteristics of patients with PTE who received alteplase 100 mg

Characteristics	Total (n = 38)	Non-bleeding (n = 22)	Minor bleeding (n = 6)	Major bleeding (n = 10)	*P* value
Men	18 (47.4)	13 (59.1)	2 (33.3)	3 (30)	0.321
Age, yr	70.68 ± 13.15	70.86 ± 15.78	66.50 ± 7.26	72.80 ± 9.15	0.659
< 65	8 (21.0)	6 (27.3)	1 (16.7)	1 (10.0)	
65–75	14 (36.8)	6 (27.3)	4 (67.7)	4 (40.0)	
≥ 75	16 (42.1)	10 (45.5)	1 (16.7)	5 (50.0)	
Body weight, kg	63.55 ± 12.09	62.24 ± 14.62	63.97 ± 12.10	66.17 ± 5.38	0.819
< 50	3	3	0	0	
≥ 50	19	10	3	6	
BMI, kg/m^2	23.83 ± 4.04	23.00 ± 4.87	23.90 ± 1.86	23.83 ± 4.04	0.448
< 18.5	2	2	0	0	
18.5–25	10	6	2	2	
≥ 25	10	5	1	4	
SOFA score	6.24 ± 4.39	8.27 ± 4.53	2.00 ± 0.00	3.71 ± 1.60	0.009
Risk of PTE					
High	34 (89.5)	20 (91.0)	4 (66.7)	10 (100.0)	
Intermediate	4 (10.5)	2 (9.0)	2 (33.3)	0 (0)	
Previous disease					
Hypertension	20 (52.6)	13 (59.1)	1 (16.7)	6 (60.0)	0.189
Diabetes	7 (18.4)	3 (13.6)	0 (0)	4 (40.0)	0.139
Cardiovascular disease	15 (39.5)	7 (31.8)	1 (16.7)	7 (70.0)	0.081
Pulmonary disease	4 (10.5)	2 (9.1)	1 (16.7)	1 (10.0)	0.791
Renal disease	5 (13.2)	2 (9.1)	0 (0)	3 (30.0)	0.251
Malignancy	6 (15.8)	4 (18.2)	0 (0)	2 (20.0)	0.690
Use of anticoagulation & antiplatelet agent					
Aspirin	10 (26.3)	5 (22.7)	0 (0)	5 (50.0)	0.119
P2Y12 inhibitor	2 (5.3)	2 (9.1)	0 (0)	0 (0)	0.687
Anticoagulant	3 (7.9)	3 (13.6)	0 (0)	0 (0)	0.726

Data are presented as mean ± standard deviation or number (%).
PTE = pulmonary thromboembolism, BMI = body mass index, SOFA score = sequential organ failure assessment score.

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Table 2. Clinical and laboratory findings

Variables	Total (n = 38)	Non-bleeding (n = 22)	Minor bleeding (n = 6)	Major bleeding (n = 10)	*P* value
Systolic BP, mmHg	70.41 ± 19.63	68.44 ± 24.35	82.00 ± 11.36	70.00 ± 7.56	0.169
Diastolic BP, mmHg	47.60 ± 14.19	47.31 ± 16.74	47.67 ± 16.44	48.33 ± 4.08	0.165
Mean BP, mmHg	55.48 ± 15.61	54.35 ± 18.76	59.11 ± 14.74	56.67 ± 3.65	0.155
Laboratory findings					
NT-proBNP, pg/mL	5,650 ± 8,457	6,256 ± 10,423	7,131 ± 6,564	3,845 ± 3,626	0.724
Troponin T, ng/mL	0.12 ± 0.20	0.11 ± 0.21	0.05 ± 0.07	0.19 ± 0.22	0.427
D-dimer, μg/mL	19.0 ± 29.6	26.2 ± 37.6	5.3 ± 3.1	12.0 ± 7.7	0.217
Platelets, /mL	218,500 ± 110,386	232,730 ± 133,683	241,170 ± 71,323	173,600 ± 49,916	0.330
Total bilirubin, mg/dL	0.74 ± 0.43	0.78 ± 0.45	0.52 ± 0.27	0.78 ± 0.46	0.387
Creatinine, mg/dL	1.15 ± 0.48	1.27 ± 0.49	0.84 ± 0.38	1.06 ± 0.44	0.107
pH	7.36 ± 0.12	7.32 ± 0.14	7.41 ± 0.06	7.42 ± 0.09	0.063
pCO2, mmHg	31.2 ± 11.5	33.4 ± 13.7	31.5 ± 8.4	26.2 ± 4.5	0.272
PaO2, mmHg	81.9 ± 30.7	83.3 ± 34.8	68.9 ± 22.3	85.5 ± 25.1	0.598
PF ratio	249.9 ± 168.5	223.2 ± 188.9	261.1 ± 52.2	302.9 ± 155.3	0.470
Echocardiographic finding					
Left ventricular ejection fraction, %	65.0 ± 9.2	63.5 ± 7.2	68.8 ± 7.3	65.3 ± 12.7	0.493
Right ventricular systolic pressure, mmHg	47.0 ± 17.6	45.4 ± 17.9	54.7 ± 17.9	44.1 ± 17.4	0.496

Data are presented as mean ± standard deviation.
BP = blood pressure, NT-proBNP = N-terminal pro-brain natriuretic peptide, pCO2 = partial pressure of carbon dioxide, PaO2 = partial pressure of oxygen, PF ratio = PaO_2/FiO_2 ratio.

group with major bleeding, but all groups showed respiratory alkalosis, with no statistically significant differences. Other blood tests such as NT-proBNP, troponin T, D-dimer, platelets, total bilirubin, creatinine, and other results of arterial blood gas analysis revealed no differences, and the PaO_2/FiO_2 ratio (PF ratio) was similar (**Table 2**).

On echocardiography, left ventricular ejection fraction was normal, and RV systolic pressure indicated mild pulmonary hypertension, with no differences among the three groups.

Bleeding complication associated with thrombolytic therapy

The overall frequency of major bleeding was 26.3% (10/38 patients). Only one patient with major bleeding had intracranial hemorrhage, and in the other 9 patients there was a reduction of hemoglobin by 2 g/dL or more, or transfusion of two or more units of packed red blood cells (RBCs).

Six patients (15.8%) had minor bleeding. Bleeding sites varied, and included an intravenous or atrial-line site, gastrointestinal tract, epistaxis, and other sites (**Table 3**). No deaths were caused by bleeding.

Table 3. Number of patients with bleeding complications

Complications	Minor bleeding (n = 6)	Major bleeding (n = 10)
Major bleeding	0	10
Intracranial hemorrhage	0	1
Necessity of surgery	0	0
Hb reduction ≥ 2 or transfusion ≥ 2 pRBC	0	9
Bleeding site		
IV or A-line site	2	3
GI bleeding	1	2
Gum bleeding	0	0
Hematuria	0	0
Epistaxis	1	0
Intracranial hemorrhage	0	1
Others	2	5

Hb = hemoglobin, pRBC = packed red blood cell, IV = intravenous, A-line = arterial-line, GI = gastrointestinal.

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Table 4. Clinical outcomes of patients treated with alteplase 100 mg

Outcomes	Total (n = 38)	Non-bleeding (n = 22)	Minor bleeding (n = 6)	Major bleeding (n = 10)	*P* value
ICU stay, day	3.25 ± 3.52	3.14 ± 2.77	0.40 ± 0.90	5.11 ± 5.00	0.050
Treatment success	31 (81.6)	16 (72.7)	6 (100.0)	9 (90.0)	0.298
Hospital discharge	30 (78.9)	15 (68.2)	6 (100.0)	9 (90.0)	0.244
Mortality	8 (21.0)	7 (31.8)	0 (0)	1 (10.0)	0.212

Data are presented as mean ± standard deviation or number (%).
ICU = intensive care unit.

Treatment success

The average length of stay in the intensive care unit was 3.25 (± 3.52) days (**Table 4**). Treatment success was achieved in 31/38 patients (81.6%), and 30/38 patients (78.9%) were successfully discharged from the hospital. The mean duration of intensive care unit admission was 3.14 (± 2.77) days in patients with no bleeding, 0.40 (± 0.90) days in patients with minor bleeding, and 5.11 (± 5.00) days in patients with major bleeding, with no statistically significant difference, but the group with major bleeding showed a tendency to stay in the intensive care unit ($P = 0.050$). Treatment success rates were 72.7% (16/22 patients) in the groups with non-bleeding, 100% (6/6 patients) in the groups with minor bleeding, and 90% (9/10 patients) in the major bleeding group, with no significant difference between the three groups ($P = 0.298$) (**Table 4**).

DISCUSSION

This retrospective study aimed to investigate major bleeding risk of thrombolysis with fixed dose of alteplase (100 mg) in patients with PTE according to current guidelines. The incidence of major bleeding was higher in our study (26.3%) than in a previously published meta-analysis (9.24%).[18] In aspect of efficacy, the overall success rate of thrombolysis was 81.6% and mortality rate was 21% and these were similar in the three groups, but generally showed good results in the minor bleeding group.

Compared with previous studies, the most distinctive features of the patients in our study was that the average age was almost 70 years, with 78.9% (30/38 patients) older than 65 years, and only Asian population being considered. We hypothesized that age influenced the higher bleeding incidence rate observed in the present study. As Korea has an aging society, PTE prevalence is on the rise due to increasing co-morbidities, especially cancer and major fracture.[21]

All-cause mortality was not increased in patients 65 years and older. However, the incidence of major bleeding was about 13% in elderly patients and only 3% in younger patients.[18] The major bleeding event rate was increased more than four times, according to a previous meta-analysis. In previous studies that used alteplase 100 mg, the mean age of enrolled patients was less (range, 55.98–64.68 years) than that of our present study and those enrolled in Western countries.[22-25] Moreover, those data showed low incidences of major bleeding (events range, 0%–15%).

In our retrospective study, there were only 8 patients < 65 years and we could not reach a significant statistical difference in the incidence of major bleeding due to this small number.

In the MOPETT trial, the total alteplase dose of 50 mg was administered in patients with moderate PTE weighing more than 50 kg.[13] Of this dose, 10 mg was administered as a

bolus, and the remaining 40 mg over 2 hours. In patients weighing less than 50 kg, the total alteplase dose was 0.5 mg/kg, and in another study that compared the use of alteplase and urokinase in terms of bleeding complications, alteplase dose of 50–100 mg was administered in patients with high risk PTE.[9] In trials, 8.3% of the patients had major bleeding.[13,16]

There is no established guideline for dose reduction of thrombolytics according to body mass index (BMI). However, one study has shown that using thrombolytic agents in patients with a BMI of less than 18.5 kg/m^2 tends to increase the bleeding risk.[26] In addition, Asians have a lower BMI than Westerners, and tend to have higher bleeding risk in cardiovascular and cerebrovascular disease, while Westerners have a higher tendency of thromboembolic risk.[27,28]

In our 10-year data, there were missing data of weight in 16 patients, therefore it was not suitable to analyze the differences in the incidence of major bleeding events according to the weight or BMI of patients.

Another notable point in our data is that major bleeding events were more common in patients with cardiovascular disease (**Supplementary Tables 1** and **2**) indicating the tendency of major bleeding in patients who used antiplatelet agents (such as aspirin) before thrombolysis. The current anticoagulant use (for example, warfarin or novel oral anticoagulant) is suggested as a relative contraindication in the current guideline, however, there are no precautions for taking aspirin. Based on our data, dose reduction should be considered in those patients on aspirin and with cardiovascular disease.

Our study has several limitations as it was retrospective, single center, and had a relatively small number of patients.

In conclusion, we suggest reducing the dose of alteplase in patients who are elderly, Asian or have cardiovascular disease. Further prospective studies evaluating the efficacy of low dose alteplase are recommended.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Differences in major bleeding incidence according to variables

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Supplementary Table 2

Logistic regression analysis of major bleeding risk

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