Clinical and Experimental Emergency Medicine

Clin Exp Emerg Med 2022;9(1):47-53
https://doi.org/10.15441/ceem.21.073

Original Article

eISSN: 2383-4625

Short-term effects of fibrinolytic therapy on the hemodynamic parameters of patients with intermediate- and high-risk pulmonary embolism

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Objective We aimed to determine the effect of fibrinolytic therapy on hemodynamic parameters at 4 hours after treatment and bleeding complications in patients with intermediate- and high-risk pulmonary embolism.

Methods This single-center, retrospective, cohort study included patients with intermediate- and high-risk pulmonary embolism treated with fibrinolytics. Their demographic and clinical characteristics, complications, and vital signs at the initiation of and 4 hours after fibrinolytic therapy were evaluated. The primary outcome was the change in the patients' vital signs at 4 hours after fibrinolytic therapy, compared by the Mann-Whitney U-test.

Results Seventy-nine patients were included in this study. The systolic and diastolic blood pressures of the high-risk group at 4 hours after fibrinolytic therapy were higher than those at the initiation of fibrinolytic therapy (80 mmHg vs. 99 mmHg, P=0.029; 49 mmHg vs. 67 mmHg, P=0.011, respectively). In the intermediate-risk group, the oxygen saturation increased (94% vs. 96%, P=0.004) and pulse rate decreased (104 beats/min vs. 91 beats/min, P<0.001).

Conclusion Blood pressure at 4 hours after fibrinolytic therapy increased in patients with high-risk pulmonary embolism. Also, oxygen saturation and pulse rate improved in intermediate-risk patients.

Keywords Pulmonary embolism; Thrombolytic therapy; Blood pressure

Received: 19 April 2021
Revised: 7 June 2021
Accepted: 5 July 2021

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How to cite this article:
Hamza Çıldır, Ersin Aksay, Emre Şancı, Başak Bayram, Neşe Çolak, Can Sevinç. Short-term effects of fibrinolytic therapy on the hemodynamic parameters of patients with intermediate- and high-risk pulmonary embolism. Clin Exp Emerg Med 2022;9(1):47-53. https://doi.org/10.15441/ceem.21.073

Capsule Summary

What is already known

There are limited data in the literature on the short-term effects of fibrinolytic therapy for different risk groups of pulmonary embolism.

What is new in the current study

Fibrinolytic therapy improved the blood pressures at the 4th hour of treatment in high-risk patients with pulmonary embolism. Oxygen saturation increased and pulse rate decreased in intermediate-risk patients.

INTRODUCTION

Pulmonary embolism (PE) is an important differential diagnosis in patients presenting to the emergency department (ED) with shortness of breath. It is one of the leading causes of sudden cardiac arrest and is responsible for 5% to 15% of all in-hospital deaths.[1] While PE-related mortality is approximately 25% to 30% for untreated patients, it decreases to 2% to 8% with treatment.[2-4]

The 2019 European Society of Cardiology (ESC) guidelines only recommends the use of fibrinolytic therapy for hemodynamically unstable patients and those with intermediate-risk PE with clinical deterioration. At present, its use is controversial because previous guidelines (2008 and 2014 ESC PE guidelines) stated that the effect of fibrinolytic therapy on mortality in patients with intermediate-risk PE was uncertain.[1,5]

This study aimed to compare the vital signs at baseline and 4 hours after fibrinolytic therapy (primary outcome) and evaluated the complications of fibrinolytic therapy (secondary outcome) in patients with intermediate- and high-risk PE.

METHODS

This retrospective cohort study included patients aged over 18 years who had been diagnosed with PE and had received fibrinolytic therapy in the ED between January 2010 and August 2018. Patient records were screened, and clinical data were retrieved using the hospital information management system. Vital signs, imaging results, fibrinolytic drug type and dosage, treatment-related complications, and the management of complications were examined. The use of fibrinolytic therapy despite contraindications, risk factors that may increase the incidence of bleeding, and the frequency of bleeding were also evaluated.

Patients with a systolic blood pressure below 90 mmHg at the time of admission, systolic blood pressure decrease of more than 40 mmHg during follow-up, and cardiac arrest at admission or on follow-up were classified into the high-risk group. Patients with acute right ventricular failure on echocardiography or those with a positive troponin test (> 0.06 ng/mL) despite the absence of the high-risk criteria were classified into the intermediate-risk group. This study was approved by the institutional ethics committee of the Faculty of Medicine, Dokuz Eylul University (No. 2018/24-28). Due to the retrospective nature of the study, informed consent could not be obtained from the participants.

Analysis

Data was recorded using the IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA). The normality of the data was evaluated using the Kolmogorov-Smirnov test. Normally distributed data are presented as means and standard deviations, and nonparametric data are presented as medians and interquartile ranges. Between-group comparisons of numerical variables were performed using the Mann-Whitney U-test. Differences between the rates of categorical variables were analyzed using the chi-square test. Variables were reported at the 95% confidence interval (CI) level, and $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Of the 79 patients included in this study, 31 (39.2%) were male, and the mean age was 69.3 ± 16.2 years. Forty-three (54.4%) of the patients had at least one risk factor for PE. Seventy (88.6%) were diagnosed based on computed tomography (CT) angiography findings, while nine (11.4%) were diagnosed based on high clinical suspicion and echocardiographic findings. Sixty-five patients (92.8%) showed main pulmonary artery occlusion on CT, while five patients (7.2%) showed segmental or subsegmental pulmonary artery occlusion.

The mean pulmonary embolism severity index of the patients was 136.3 ± 52.2 (95% CI, 124.6–148.0). Four (5.7%), 10 (14.3%),

eight (11.4%), 11 (17.7%), and 37 (52.9%) patients had a pulmonary embolism severity index of I, II, III, IV, and V, respectively.

Primary outcome: efficacy of fibrinolytic therapy at 4 hours after treatment

Thirty-four patients (43%) were classified into the high-risk group. Twenty of them had low blood pressure on ED admission, two had low blood pressure at follow-up, and twelve had cardiac arrest at admission or follow-up. Forty-five patients (57%) were classified into the intermediate-risk group due to signs of right ventricular loading (echocardiographic findings or positive troponin test), although their vital signs were stable.

The systolic and diastolic blood pressures and the oxygen saturation of all patients at 4 hours after fibrinolytic therapy were higher than those at the initiation of fibrinolytic therapy (102 mmHg vs. 111 mmHg, P=0.008; 67 mmHg vs. 73 mmHg, P=0.025; 94% vs. 96%, P=0.006), while, the pulse rate decreased (105 beats/min vs. 90.5 beats/min, P<0.001). In the high-risk group, the systolic and diastolic blood pressures at 4 hours after treatment were higher than the pretreatment blood pressures (80 mmHg vs. 99 mmHg, P=0.029; 49 mmHg vs. 67 mmHg, P=0.011, respectively). In the intermediate-risk group, the pulse rate was lower (104 beats/min vs. 91 beats/min, P<0.001), and the oxygen saturation was higher (94% vs. 96%, P=0.004) than the pretreatment values at 4 hours after treatment. The comparisons of the patients' vital signs are shown in Table 1.

Secondary outcome: bleeding complications

Bleeding complications associated with fibrinolytic therapy developed in 17 patients (21.5%). The clinical features of these patients are shown in Table 2. Five of them underwent blood product transfusion, one required endotracheal intubation and mechanical ventilation, and one underwent splenectomy. Six of them (35.3%) died within 30 days of admission. There were no statistically significant between-group differences in sex, age, hypotension on admission, mean platelet level, international normalized ratio (INR) level, fibrinolytic dose, and bleeding frequency (Table 3). The clinical characteristics of the four patients who underwent fibrinolytic therapy despite having contraindications are shown in Table 4.

Other findings

The electrocardiography findings of 73.4% of patients (n=58) were available; the three most common findings were sinus tachycardia (27.6%), T-wave inversion in V1–V4 (24.1%) and atrial fibrillation (22.4%). The troponin I (TnI) level of 75 patients was available; it was above the threshold in 72% of them. Thirty-four patients had undergone repeat TnI level measurements; and 85.3% of them had a second TnI level above the threshold. The TnI level was measured for the third time in 17 patients, and 58.8% of them had TnI levels above the threshold.

Among the 73 patients (92.4%) who had undergone echocardiography, 68.5% had a D-shaped left ventricle; 38.4% had increased systolic pulmonary artery pressure (>25 mmHg); 12.3% had McConnell findings; and 9.6% had normal findings. All seven patients with normal echocardiography findings showed main pulmonary artery occlusion on CT angiography; among them, six patients had hypotension and one had CT angiography findings of right ventricular loading (right-to-left ventricular ratio <0.9) and treatment-resistant hypoxemia.

Seventy-seven patients (97.4%) received alteplase and two (2.5%) received streptokinase. Patients receiving alteplase were administered eight different regimens, with the most common regimen being a 2-hour infusion of 100 mg of alteplase (63.6%). In 72.7% of patients, 100 mg, in 27.3% of patients, 50 mg, and in 1.3% of patients, 85 mg alteplase were administered. The two patients treated with streptokinase received 250,000 IU within 30 minutes of admission, followed by infusion of 100,000 IU/hr for 23.5 hours. Most of the patients (62%) received fibrinolytic therapy within 12 hours of ED admission; 12.7% and 25.3% received it at 12–24 hours of ED admission and after 24 hours of

Table 1. Vital signs of the patients at admission, before treatment, and at 4 hours after fibrinolytic therapy

Variable	Before treatment	4 Hours after treatment	P-value
All patients			
SBP (mmHg)	102 (85–120)	111 (101–131)	0.008
DBP (mmHg)	67 (54–76)	73 (64–85)	0.025
Respiratory rate (min)	24 (20–26)	22 (20–24)	0.516
Pulse (min)	105 (87–120)	90.5 (81–106)	0.005
SpO_2 (%)	94 (91–96)	96 (94–98)	0.006
High-risk patients[a]			
SBP (mmHg)	80 (69–86)	99 (86–134)	0.029
DBP (mmHg)	49 (40–57)	67 (57–95)	0.011
Respiratory rate (min)	24 (20–28)	24 (21–28)	0.854
Pulse (min)	107 (80–123)	94 (73–107)	0.077
SpO_2 (%)	94 (88–96)	96 (94–98)	0.888
Intermediate-risk patients			
SBP (mmHg)	113 (100–126)	112 (105–130)	0.600
DBP (mmHg)	71 (66–88)	75 (68–85)	0.153
Respiratory rate (min)	22 (20–24)	22 (20–24)	0.111
Pulse (min)	104 (88–119)	91 (81–105)	<0.001
SpO_2 (%)	94 (91–97)	96 (93–98)	0.004

Values are presented as number or median (interquartile range).
SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, oxygen saturation.
[a]Patients with SBP <90 or ≥40 mmHg decrease from initial value.

Table 2. Clinical characteristics of the patients with complications associated with fibrinolytic therapy

Age (yr)	Sex	Severity	Fibrinolytic dose (mg)	Application regime	Complication	Treatments for complications	Outcome
71	Female	Intermediate	100	2 Hours infusion	Gingival bleeding	-	Discharged
47	Male	Intermediate	100	2 Hours infusion	Epistaxis	Nasal tamponade	Death
57	Male	Intermediate	100	2 Hours infusion	Subconjunctival bleeding	-	Discharged
94	Female	High	50	1 Hour infusion	Hemoptysis+airway obstruction+bleeding at the intravenous site	Replacement of three units fresh frozen plasma+ mechanical ventilation	Death
34	Male	High	100	2 Hours infusion	Epistaxis	Nasal tamponade	ICU admission, death
73	Female	High	50	2 Hours infusion	Epidural hematoma	Anti-epileptic drug	Discharged
50	Male	Intermediate	100	2 Hours infusion	Bleeding from the previous coronary angiography intervention site	Compression	Discharged
85	Female	High	100	2 Hours infusion	Bleeding at the intravenous site	-	Discharged
73	Male	Intermediate	100	2 Hours infusion	Epistaxis	-	Discharged
79	Female	High	50	Bolus	Splenic hematoma+ intraabdominal bleeding	Replacement of two units of erythrocyte suspensions+ splenectomy	ICU admission, discharged
47	Male	Intermediate	100	Bolus+2 hours infusion	Subconjunctival bleeding+ gingival bleeding	-	Discharged
86	Female	High	85	Bolus+1.5 hours infusion	Conjunctival bleeding+ hematoma around the femoral catheter	-	ICU admission, death
85	Male	High	100	2 Hours infusion	Bleeding at the intravenous intervention site+ subcutaneous hematoma	-	Discharged
74	Male	Intermediate	100	2 Hours infusion	GI bleeding	Replacement of three units of erythrocyte suspensions	ICU admission, death
92	Female	High	(Streptokinase) 2.600.000 units	Bolus+24 hours infusion	Intramuscular hematoma on the right thigh	Replacement of five units of erythrocyte suspensions	ICU admission, discharged
72	Female	Intermediate	100	2 Hours infusion	Vaginal bleeding	-	ICU admission, death
77	Male	Intermediate	50	2 Hours infusion	GI bleeding	Replacement of one unit of erythrocyte suspensions	Death

ICU, intensive care unit; GI, gastrointestinal.

Table 3. Complication rates according to factors associated with increased bleeding risk

Variable		Without complications (n=62)	With complications (n=17)	P-value
Sex	Male	22	9	0.192
	Female	40	8	
Risk	High	26	8	0.705
	Intermediate	36	9	
Platelet count (mm^3)		214,500 (160,000–272,500)	219,000 (149,000–237,000)	0.575
Initial INR value[a]		1.14 (1.08–1.27)	1.16 (1.09–1.35)	0.620
Dose of alteplase	Half	16 (80)	4 (20)	1.000
	Full	45 (78.9)	12 (21.1)	

Values are presented as number, median (interquartile range), or number (%).
INR, international normalized ratio.
[a]INR levels were analyzed over 69 patients whose results were available.

ED admission, respectively.

Thirty-one (39.2%) of the patients included in the study died within 30 days of admission, including 12 of 22 (54.5%) who were hypotensive at admission and 10 of 45 (22.2%) who were normotensive at admission (P=0.008). Of the 12 patients who received fibrinolytic therapy during cardiac arrest, seven did not respond to initial cardiopulmonary resuscitation, two died in the hospital after successful resuscitation, and three recovered and were discharged from the hospital.

DISCUSSION

To the best of our knowledge, the short-term effects of fibrinolytic therapy on the hemodynamic parameters of patients with high- and intermediate-risk PE have not been fully studied. We investigated the effect of intravenous fibrinolytic therapy on vital signs at 4 hours after treatment and bleeding complications in patients with high- and intermediate-risk PE. As this was a retrospective study, we evaluated several different fibrinolytic agents with different administration regimens.

Four hours after fibrinolytic therapy, the pulse rate decreased

Table 4. Clinical features of the patients who received fibrinolytic therapy despite having contraindications

Age (yr)	Sex	Contraindication reason	Application reason	Complication	Outcome
73	Female	High energy trauma (5 days ago)	Hemodynamic unstability	Epidural hematoma	Discharged
50	Male	Coronary angiography (1 day ago)	RV loading findings+filling defect in the main pulmonary arteries on CT	Subcutaneous hematoma around the femoral artery	Discharged
72	Female	Adrenal malinancy+brain metastasis	Hemodynamic unstability	-	Death
81	Female	Gastrointestinal bleeding (15 days ago)	Cardiac arrest during follow-up	-	Death

RV, right ventricle; CT, computed tomography.

and oxygen saturation increased in patients with intermediate-risk PE and the systolic and diastolic blood pressures improved in patients with high-risk PE. Complications developed in 21% of the patients with PE receiving fibrinolytic therapy. Among them, five patients underwent blood product replacement, one required endotracheal intubation and mechanical ventilation, and one underwent splenectomy.

The 2019 ESC PE guidelines recommend the use of fibrinolytic therapy only in patients with unstable vital signs.[6] The mean pretreatment systolic and diastolic blood pressures of the patients in the intermediate-risk group were 113 and 71 mmHg, respectively. As these blood pressure values are normal, we did not expect these patients to show any improvement at 4 hours after treatment. Nevertheless, they showed a decrease in pulse rate and an increase in oxygen saturation at 4 hours after treatment. However, due to the retrospective nature of the study, we could not determine whether this improvement was due to fibrinolytic therapy or oxygen therapy.

A meta-analysis by Chatterjee et al.[7] showed that the incidence of major bleeding was 18% in patients receiving fibrinolytic therapy. Of the 2,115 patients included in the meta-analysis, 1,499 had intermediate-risk PE. Similarly, we found that fibrinolytic therapy was associated with bleeding complications, although it did not provide a significant improvement in the blood pressures of patients with intermediate-risk PR in the short-term. Here, nine of the 17 patients with complications were in the intermediate-risk group. These data support the recommendation of not providing fibrinolytic therapy to patients with intermediate-risk PE.

In the Pulmonary Thromboembolism Diagnosis and Treatment Reconciliation Report published by the Turkish Thoracic Society in 2015,[4] the recommended dose of alteplase is 100 mg, administered as an infusion over 2 hours. However, only 63.6% of the patients in our study had received this dose. This may be because 12 patients received a bolus dose of 50 mg of alteplase during cardiac arrest or because low doses of fibrinolytics were administered to patients at high-risk for bleeding complications. Our study included both patients receiving 50 mg of alteplase and those receiving 100 mg of alteplase, resulting in heterogeneous data and difficulty in interpreting the results. However, our study presents real world data because in clinical practice, the regimen of fibrinolytic therapy might vary depending on the patients' age and current clinical condition and the physicians' preference.

In our study, the 30-day mortality rates of patients with high-risk PE, intermediate-risk PE, and cardiac arrest were 54.5%, 22.2%, and 75%, respectively. The International Cooperative Pulmonary Embolism Registry (ICOPER) study reported mortality rates of 58.3% and 15.1% in unstable and stable patients, respectively.[8] Stein et al.[9] reported an in-hospital mortality rate of 37% in patients with PE with unstable hemodynamics who received fibrinolytic therapy. These differences in the mortality rates between studies indicates a need for further exploration, especially in the early stages of the treatment.

Table 5 shows the rates of bleeding complications reported in previous studies.[8,10-14] The ICOPER study reported that major bleeding occurred in 21.7% of patients receiving fibrinolytic therapy.[8] Here, the bleeding rate was 21.5%, and the incidence of bleeding requiring serious intervention was 8.8%. The submassive and massive PE treatment with ultrasound accelerated thrombolysis therapy and ultrasound accelerated thrombolysis of PE studies on low-dose alteplase therapy with the EkoSonic endovascular system reported bleeding complication rates of 10% and 6.8%, respectively.[10,11] Patients with systemic fibrinolysis are expected to have higher rates of bleeding than those with selective fibrinolysis. Intracranial bleeding is one of the most undesirable complications of fibrinolytic therapy. Here, only one patient (1.3%) had intracranial bleeding; the rate of intracranial bleeding was 3% in the ICOPER study,[8] 5% in the study by Fiumara et al.[12] 2% in the study by Kanter et al.[15] and 1.4% in the study by Geller et al.[14]

In our study, there was no difference in factors such as sex, age, INR and platelet levels at admission, and fibrinolytic dose, which may be risk factors for fibrinolytic-related bleeding, between patients with and without bleeding. Kiser et al.[16] found no difference in the rates of cerebral hemorrhage, bleeding that caused anemia, and other adverse events related to fibrinolytic therapy between PE patients who received full dose and half dose alteplase.

Additionally, four patients in this study had received fibrinolytic therapy despite it being contraindicated. Although two of these

Table 5. Complication rates of fibrinolytics reported in previous studies

Variable	Current study	ICOPER[8]	Zuin et al.[13]	Fiumara et al.[12]	SEATTLE II[10]	ULTIMA[11]	Geller et al.[14]
No. of patients	79	2,454	76	104	150	59	1,915
Study type	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Prospective	Prospective	Prospective
Population	Fibrinolytic administrated PE patients (mostly alteplase)	All PE patients	Fibrinolytic administrated PE patients (alteplase)	Fibrinolytic administrated PE patients (alteplase)	Fibrinolytic administrated with EKOS (alteplase)	RV loading and PE Fibrinolytic administrated with EKOS+heparinized (alteplase) (n = 30)	Systemic and catheter-directed fibrinolytic administrated (no. of patients given systemic fibrinolytic, 1,283)
Bleeding complication (%)	21.5	24.7[a]	9.2	39	10	5.1	10.7
Bleeding type (%)	Mucosal bleeding (8.9) Bleeding from vascular access (6.3) GI bleeding (2.5) Intraabdominal bleeding (1.3) Vaginal bleeding (1.3) Hemoptysis (1.3) Intracranial bleeding (1.3)	Major bleeding (21.7) Intracranial bleeding (3) Bleeding that requires transfusion (11.5) < 10% decrease in packed-cell volume during initial hospital stay (12.8)	Major bleeding (3.9) Minor bleeding (5.3)	Major bleeding (19.0) Unknown (8.6) GI bleeding (5.7) Retroperitoneal (2.9) Intracranial (1) Splenic hemorrhage (1) Minor bleeding (20) Subcutaneous bleeding (18) Hematuria (16) GI bleeding (2) Mucosal bleeding (2) Hemoptysis (2) Retroperitoneal bleeding (1)	Subcutaneous bleeding (5.3) Hemoptysis (1.3) Mucosal bleeding (0.7) Hematuria (0.7) Anemia (2)	Hemoptysis (3.4) Subcutaneous bleeding (1.7)	GI bleeding (4.2) Intracranial bleeding (1.4) Hemoptysis (1.1)

ICOPER, International Cooperative Pulmonary Embolism Registry; SEATTLE II, submassive and massive pulmonary embolism treatment with ultrasound accelerated thrombolysis therapy trial; ULTIMA, ultrasound accelerated thrombolysis of pulmonary embolism trial; PE, pulmonary embolism; EKOS, ekosonic endovascular system; RV, right ventricle; GI, gastrointestinal.

[a]Bleeding was observed in 75 of 304 patients received fibrinolytic.

patients developed bleeding complications (subdural hematoma and groin hematoma), they were discharged without sequelae.

This study has several limitations. Oxygen therapy or vasopressor medication use, which could affect vital signs, were not evaluated. Vital signs were evaluated only at 4 hours after treatment; however, fibrinolytic therapy may affect vital signs even after this time (e.g., at 12 or 24 hours after treatment). The retrospective and single-center nature of the study are also limitations.

In summary, the systolic and diastolic blood pressures of patients with high-risk PE and the pulse rate and oxygen saturation of patients with intermediate-risk PE were significantly improved at 4 hours after fibrinolytic therapy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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