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RESEARCH ARTICLE

Investigation of the efficiency and safety of half-dose and full-dose tissue plasminogen activator therapy in pulmonary embolism

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ABSTRACT

Investigation of the efficiency and safety of half-dose and full-dose tissue plasminogen activator therapy in pulmonary embolism

Introduction: The objective of this study was to investigate the impact of two different doses of alteplase, a thrombolytic therapy, specifically half-dose (50 mg) and full-dose (100 mg), on short-term (7 days) and long-term (1 year) mortality and morbidity in the treatment of pulmonary embolism (PE).

Materials and Methods: A retrospective cohort study was conducted at the Department of Chest Diseases of Erciyes University Faculty of Medicine Hospital from January 1, 2010 to October 31, 2021. The study enrolled patients diagnosed with PE who underwent treatment with either 50 mg or 100 mg of alteplase. In total, 58 patients participated, with 41 receiving a 50 mg dose of alteplase and 17 receiving a 100 mg dose of alteplase treatment.

Results: Of the patients, 62.1% (n= 36) were female, with a mean age of 63 ± 14.5 years. Mean length of hospital stay was 9.2 ± 7.4 days. Mortality rate of the patients who had PE and received half-dose treatment was 36.5%, and mortality rate of the patients who received full-dose treatment was 17.6%. Mean time to mortality for non-survivors was 126.1 ± 355.4 days. Of the 18 patients who did not survive, 44.4% (n= 8) died within the first seven days, 50% (n= 9) between days eight and 365, and 5.6% (n= 1) after 365 days. In-hospital mortality occurred in 25.9% of the patients (n= 15), with no statistically significant relationship found between mortality status, time to death, in-hospital mortality, vasopressor use, ventilation support requirement, cardiopulmonary resuscitation, and the dose of alteplase treatment (p> 0.05). The comparison of survival rates by the administered alteplase treatment dose revealed no significant relationship (p= 0.187). Notably, there was no in-hospital mortality among the patients under the age of 65 who received a full dose of alteplase treatment, and this result was statistically significant (p= 0.010).

Conclusion: Upon comprehensive evaluation of the data gathered from our study, short-term mortality was significant in favor of the group receiving full dose in patients under 65 years of age. However, it is worth noting that long-term mortality and bleeding rates were comparable in both groups.

Key words: Alteplase; half dose; pulmonary embolism; tissue plasminogen activator

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Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ÖZ

Pulmoner embolide yarı doz ve tam doz doku plazminojen aktivatör tedavisinin etkililiği ve güvenirliliğinin araştırılması

Giriş: Bu çalışmada, pulmoner emboli tedavisinde uygulanmış yarı doz (50 mg alteplaz) trombolitik tedaviyle tam doz trombolitik (100 mg alteplaz) tedavinin kısa dönemde (7 gün) ve uzun dönemde (1 yıl) mortalite ve morbiditeye olan etkisini araştırmayı amaçladık.

Materyal ve Metod: Çalışmamız retrospektif kohort bir çalışma olarak planlandı. 1 Ocak 2010 ve 31 Ekim 2021 tarihleri arasında Erciyes Üniversitesi Tıp Fakültesi Göğüs Hastalıkları Anabilim Dalında tedavi edilen hastalar çalışmaya dahil edildi. Çalışmada 50 mg alteplaz tedavisi uygulanan 41 hasta ve 100 mg alteplaz tedavisi kullanan 17 hasta olmak üzere toplam 58 hasta değerlendirildi.

Bulgular: Hastaların %62.1 (n= 36)'i kadın ve ortalama yaş 63 ± 14.5 yıl olarak saptandı. Hastaların ortalama yatış süreleri 9.2 ± 7.4 gün olarak saptandı. Pulmoner emboli tanısı almış ve yarı-doz tedavi alan hastaların mortalite oranı %36.5, tam doz tedavi alan hastaların mortalite oranı ise %17.6 olarak tespit edildi. Eksitus olan hastaların ortalama mortalite gün sayısı 126.1 ± 355.4 gün olarak tespit edildi. Eksitus olan 18 hastanın %44.4 (n= 8)'ünün ilk yedi gün içinde, %50 (n= 9)'sinin 8-365 gün arasında ve %5.6 (n= 1)'sinin ise 365 günden fazla bir süre içinde eksitus olduğu görüldü. Hastane yatışı sırasında eksitus olan hastaların oranı ise %25.9 (n= 15) idi. Hastaların mortalite durumları, mortalite gün sayıları, hastane içi mortalite durumu, vazopresör ihtiyacı ventilasyon desteği ihtiyacı ve kardiopulmoner resüsitasyon ihtiyacıyla alteplaz tedavi dozunun istatistiksel açıdan ilişkili olmadığı saptandı ($p > 0.05$). Uygulanan alteplaz tedavi dozuna göre iki grup sağkalım açısından karşılaştırıldığında tedavi dozu ile sağkalım arasında anlamlı bir ilişki olmadığı gözlemlendi ($p = 0.187$). Altmış beş yaş altı olan ve tam doz alteplaz tedavisi uygulanan hastalarda hastane mortalitesinin olmadığı görüldü ve bu durum istatistiksel açıdan anlamlı bulundu ($p = 0.010$).

Sonuç: Çalışmamız sonucunda elde edilen tüm veriler bütüncül olarak değerlendirildiğinde kısa dönem mortalitenin 65 yaş altı hastalarda tam doz alan grup lehine anlamlı çıktığı saptanmıştır. Bununla beraber uzun dönem mortalite ve kanama oranları her iki grupta benzer çıkmıştır.

Anahtar kelimeler: Alteplaz; doku plazminojen aktivatörü; pulmoner emboli; yarı doz

INTRODUCTION

Pulmonary embolism (PE) is a prevalent and potentially life-threatening condition, occurring in approximately 100 cases per 100,000 person-years worldwide (1,2). Thrombolysis is considered an effective intervention for massive PE, which represents the most lethal clinical presentation (3).

The natural convergence of all intravenous thrombolytic molecules within the lungs, an organ receiving the entire cardiac output, coupled with concerns regarding complications from standard recommended treatments, has prompted us to explore the possibility of reducing the current treatment dosage.

Emerging evidence suggests that the use of half-dose alteplase (50 mg) in PE treatment may mitigate the risk of bleeding (4-7). However, there remains limited data comparing treatment outcomes between full-dose and low-dose thrombolytic approaches in patients with acute PE (2). Furthermore, the utilization of thrombolytic therapy in individuals with intermediate-risk PE remains contentious, largely due to the absence of a clear demarcation between benefits and risks.

Considering these uncertainties and knowledge gaps, we conducted a single-center, retrospective cohort study aimed to evaluate the efficacy and safety of half-dose (50 mg) and full-dose (100 mg) alteplase in

the management of patients with acute PE admitted to the intensive care unit (ICU). Our primary objective was to compare the impact of half-dose (50 mg) and full-dose (100 mg) thrombolytic therapy (alteplase) on both short-term (seven-day) and long-term (one-year) mortality rates. Additionally, we sought to evaluate crucial clinical outcomes, including safety and the occurrence of major bleeding events.

MATERIALS and METHODS

The study was conducted as a retrospective cohort study. Patients diagnosed with PE and treated with either half-dose or full-dose alteplase at the Department of Chest Diseases of Erciyes University Faculty of Medicine Hospital between January 1, 2010 and October 31, 2021, were enrolled. The study protocol was reviewed and approved by the Ethics Committee of our institution (2021/811).

Patients over the age of 18 who received thrombolytic therapy (alteplase) as thrombolytic treatment when indicated at Erciyes University Faculty of Medicine Hospital were included in the study. Half-dose thrombolytic therapy was administered intravenously over two hours.

Patient data was accessed through patient files and the hospital information management system. In our study, the following data were recorded: Age, sex, comorbidities, mortality, major bleeding status, ward

and ICU admission data, hospital length of stay, need for vasopressors, need for ventilation support, and the status of cardiopulmonary resuscitation after alteplase administration.

Factors that were hypothesized to influence short- and long-term mortality in these patients were categorized into groups and subsequently compared to assess their impact on mortality outcomes. In addition, patients were divided into groups of over and under 65 years of age and compared for evaluation.

Statistical Analysis

Statistical analysis of the data was performed using the SPSS 25.0 software package. Categorical measurements were summarized as frequency and percentage. Numerical variables were presented as mean $\pm$ standard deviation, median, minimum, and maximum. The normality of the distribution of numerical variables was checked using the Shapiro-Wilk test. Since the variables did not show a normal distribution, comparisons were made using the Mann-Whitney U test. For the comparison of categorical variables, the

chi-square test or Fisher's exact test was used. Survival analysis was performed using the Kaplan-Meier (Log-rank) test. A statistical significance level (p value) of 0.05 was used for all tests.

RESULTS

Out of the total 58 patients assessed, computed tomography angiography diagnosed 96.6% (n= 56) of them, while perfusion/ventilation scintigraphy identified 3.4% (n= 2). Mean pulmonary artery pressure for the 36 patients whose pulmonary artery pressure was measured via echocardiography was 56.9 ± 21.4 mmHg. Patients treated for PE in our hospital had a mean length of stay of 9.2 ± 7.4 days.

Mean D-dimer values among the patients were 15523.3 ± 18606.3 ng/mL, and mean troponin values were 0.2 ± 0.9 ng/mL. In the scoring systems applied to assess PE patients, mean Pulmonary Embolism Severity Index (PESI) score was 184.1 ± 61 , mean PESI-2 score was 4.7 ± 0.7 , and the Simplified Pulmonary Embolism Severity Index (sPESI) score averaged 2.9 ± 1 (Table 1).

Table 1. Demographic data, imaging findings, laboratory results, and vital signs at admission

	Alteplase Therapy		p
	Half dose (50 mg) (n= 41)	Full dose (100 mg) (n= 17)	
Sex, n (%)			
Male	15 (36.6)	7 (41.2)	0.743
Female	26 (63.4)	10 (58.8)	
Age (years), median (min-max)	69 (24-89)	57 (39-85)	0.171
Groups by age 65, n (%)			
<65 years	16 (39)	12 (70.6)	0.029
≥ 65 years	25 (61)	5 (29.4)	
Groups by age 75, n (%)			
<75 years	29 (70.7)	15 (88.2)	0.195
≥ 75 years	12 (29.3)	2 (11.8)	
Presence of comorbidities, n (%)			
Lung disease	6 (14.6)	2 (11.8)	>0.999
Hypercholesterolemia	1 (2.4)	0 (0)	>0.999
Cardiovascular disease	9 (22)	5 (29.4)	0.737
Diabetes mellitus	8 (19.5)	2 (11.8)	0.707
Hypertension	24 (58.5)	5 (29.4)	0.043
ESC 2019 risk category, n (%)			
Intermediate-high	23 (56.1)	10 (58.8)	
High	18 (43.9)	7 (41.2)	

Table 1. Demographic data, imaging findings, laboratory results, and vital signs at admission (continue)

	Alteplase Therapy		p
	Half dose (50 mg) (n= 41)	Full dose (100 mg) (n= 17)	
Diagnostic technique, n (%)	(n= 41)	(n= 17)	
CT angiography	39 (95.1)	17 (100)	>0.999
Perfusion/ventilation scintigraphy	2 (4.9)	0 (0)	
CT angiography finding, n (%)	(n= 39)	(n= 17)	
Saddle embolism	3 (7.7)	0 (0)	0.709
Main pulmonary artery	19 (48.7)	9 (52.9)	
Lobar artery	15 (38.5)	7 (41.2)	
Segmental artery	2 (5.1)	1 (5.9)	
Pulmonary artery pressure (mmHg)*	(n= 26)	(n= 10)	
Median (min-max)	60 (20-100)	55 (25-75)	
Median length of stay, days (min-max)			
Emergency department	1 (1-1)	1 (1-2)	0.672
Ward	7 (1-23)	6 (1-11)	0.558
Intensive care unit	3 (1-27)	2 (1-18)	0.285
Hospital	8 (1-34)	9 (1-24)	0.952
Biochemistry			
Troponin (ng/mL)	0.066 (0.004-6.25)	0.108 (0.006-0.34)	0.636
D-dimer (ng/mL)	7950 (600-78000)	6440 (590-80000)	0.885
pH	7.43 (7.12-7.56)	7.43 (7.2-7.47)	0.595
Lactate (mmol/L)	1.61 (0.59-9.5)	1.7 (0.8-3.22)	0.343
pCO ₂ (mmHg)	31 (21-60)	34 (12-50)	0.160
pO ₂ (mmHg)	78 (17-165)	74 (55-128)	0.573
sO ₂ (%)	94 (17-98)	93 (60-98)	0.410
Vital signs			
Systolic blood pressure (mmHg)	96 (40-140)	95 (60-155)	0.776
Diastolic blood pressure (mmHg)	56 (30-87)	58 (40-84)	0.909
Heart rate/min	116 (73-140)	114 (70-128)	0.163
Severity scores			
PESI score	173 (88-279)	148 (86-235)	0.132
PESI-2 score	5 (3-5)	5 (3-5)	0.568
sPESI score	3 (0-4)	3 (1-5)	0.867

Min-max: Minimum-maximum, ESC: European Society of Cardiology, CT: Computed tomography, PESI: Pulmonary embolism severity index, sPESI: Simplified PESI.

The study revealed a mortality rate of 31.1% among the PE patients included in this study. Mortality rate of the patients who had PE and received half-dose treatment was 36.5%, and the mortality rate of patients who received full-dose treatment was 17.6%. Mean time to mortality for those who did not survive was 126.1 ± 355.4 days. Among the 18 patients who were deceased, 44.4% (n= 8) died within the initial seven days, 50% (n= 9) between days eight and 365,

and 5.6% (n= 1) within the first 365 days, underscoring the variability in the timing of these unfortunate events. Most of the deaths in the first seven days after thrombolytic therapy were due to prolonged systemic arterial hypotension, multiorgan failure, cardiogenic shock, etc. Only one patient died from cerebral hemorrhage. Additionally, there was an in-hospital mortality rate of 25.9% (n= 15).

Regarding clinical interventions, 36.2% (n= 21) of the patients required vasopressor therapy, 27.6% (n= 16) required ventilation support, and 25.9% (n= 15) underwent cardiopulmonary resuscitation (Table 2). Among the patients who received cardiopulmonary resuscitation, vasopressor therapy, and ventilation support, only one patient developed cardiac arrest in the emergency department immediately after imaging and received full-dose thrombolytic therapy simultaneously with cardiopulmonary resuscitation. Five patients received thrombolytic therapy while under vasopressor therapy. The other patients received cardiopulmonary resuscitation, ventilation support, and/or vasopressor support during their follow-up after thrombolytic therapy.

Figure 1 illustrates the Kaplan-Meier analysis results for the patients. The comparison of survival between the two groups based on the administered alteplase dose revealed no significant relationship between the treatment dose and survival ($p= 0.187$) (Figure 1).

Among the patients, the most frequently observed risk factors included a known prothrombotic condition in 63.8% (n= 37), concurrent deep vein thrombosis (DVT) in 50% (n= 29), and a history of immobilization in 29.3% (n= 17). Adverse events were noted in 29.3% of these cases. However, there was no statistically significant correlation between the presence of risk factors and the observed adverse events with the alteplase treatment dose ($p> 0.05$) (Table 3).

When the patients were stratified into two groups based on age, those under and over 65 years of age, it was found that there was no significant association between age and mortality status or mortality time ($p> 0.05$). Notably, there was no in-hospital mortality among patients under the age of 65 who received a full dose of alteplase therapy, with a statistically significant difference ($p= 0.010$). Additionally, no significant relationship was detected between the administered treatment doses and adverse events in patients under 65 years of age ($p> 0.05$) (Table 4).

Table 2. Comparison of patient mortality status and clinical treatments by administered alteplase dose

Parameters	Alteplase Therapy			p
	All patients (n= 58)	Half dose (50 mg) (n= 41)	Full dose (100 mg) (n= 17)	
Mortality status, n (%)				
Non-survivors	18 (31.1)	15 (36.6)	3 (17.6)	0.156
Survivors	40 (68.9)	26 (63.4)	14 (82.4)	
Mean time to mortality, days, median (min-max)	15 (1-1526)	15 (1-1526)	2 (1-140)	0.574
Groups by time to mortality, n (%)				
7 days	8 (44.4)	6 (40)	2 (66.7)	0.670
Between 8-365 days	9 (50)	8 (53.3)	1 (33.3)	
More than 365 days	1 (5.6)	1 (6.7)	0 (0)	
In-hospital mortality, n (%)				
No	43 (74.1)	28 (68.3)	15 (88.2)	0.188
Yes	15 (25.9)	13 (31.7)	2 (11.8)	
Requirement for vasopressor therapy, n (%)				
No	37 (63.8)	25 (61)	12 (70.6)	0.488
Yes	21 (36.2)	16 (39)	5 (29.4)	
Requirement for ventilation support, n (%)				
No	42 (72.4)	29 (70.7)	13 (76.5)	0.755
Yes	16 (27.6)	12 (29.3)	4 (23.5)	
Requirement cardiopulmonary resuscitation, n (%)				
No	43 (74.1)	29 (70.7)	14 (82.4)	0.514
Yes	15 (25.9)	12 (29.3)	3 (17.6)	

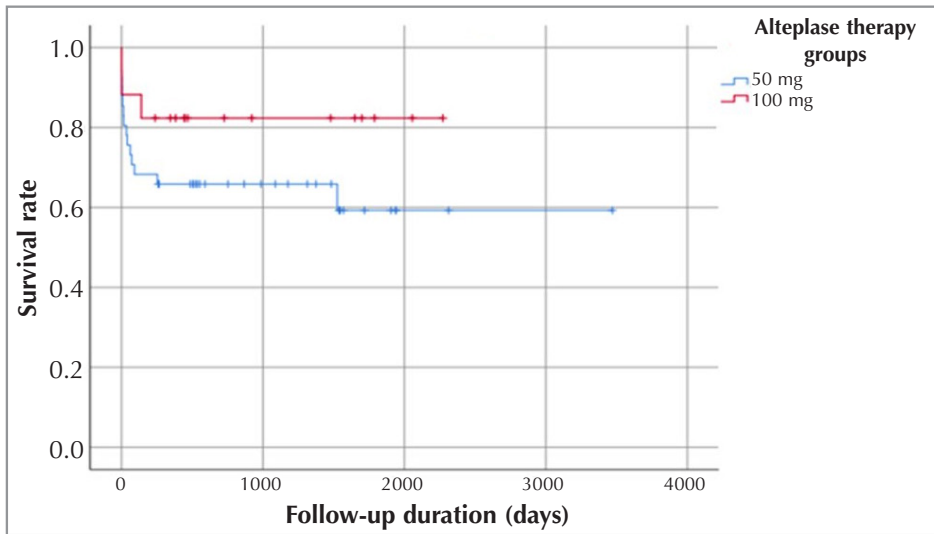


Figure 1. Kaplan-Meier survival analysis by alteplase therapy doses.

Table 3. Comparison of risk factors and adverse events by the administered dose of alteplase

Parameters	All patients (n= 58)	Alteplase Therapy		p
		Half dose (n= 41)	Full dose (n= 17)	
Presence of active cancer or a history of cancer, n (%)				
No	44 (75.9)	31 (75.6)	13 (76.5)	>0.999
Yes	14 (24.1)	10 (24.4)	4 (23.5)	
Unprovoked embolism, n (%)				
No	51 (87.9)	35 (85.4)	16 (94.1)	0.661
Yes	7 (12.1)	6 (14.6)	1 (5.9)	
Estrogen therapy, n (%)				
No	57 (98.3)	40 (97.6)	17 (100)	>0.999
Yes	1 (1.7)	1 (2.4)	0 (0)	
History of immobilization, n (%)				
No	41 (70.7)	28 (68.3)	13 (76.5)	0.753
Yes	17 (29.3)	13 (31.7)	4 (23.5)	
Known pro-thrombotic state, n (%)				
No	21 (36.2)	16 (39)	5 (29.4)	0.488
Yes	37 (63.8)	25 (61)	12 (70.6)	
Previous DVT history, n (%)				
No	51 (87.9)	34 (82.9)	17 (100)	0.093
Yes	7 (12.1)	7 (17.1)	0 (0)	
Concomitant DVT, n (%)				
No	29 (50)	20 (48.8)	9 (52.9)	0.773
Yes	29 (50)	21 (51.2)	8 (47.1)	
Recurrent pulmonary embolism, n (%)				
No	49 (84.5)	34 (82.9)	15 (88.2)	>0.999
Yes	9 (15.5)	7 (17.1)	2 (11.8)	

Table 3. Comparison of risk factors and adverse events by the administered dose of alteplase (continue)

Parameters	All patients (n= 58)	Alteplase Therapy		p
		Half dose (n= 41)	Full dose (n= 17)	
Adverse event, n (%)				
No	41 (71.9)	29 (72.5)	12 (70.6)	0.512
Exitus	9 (15.8)	7 (17.5)	2 (11.8)	
Acute blood loss anemia	5 (8.8)	3 (7.5)	2 (11.8)	
Hemothorax	1 (1.8)	1 (2.5)	0 (0)	
Cerebral hemorrhage	1 (1.8)	0 (0)	1 (5.9)	
Presence of adverse event, n (%)				
No	41 (70.7)	29 (70.7)	12 (70.6)	>0.999
Yes	17 (29.3)	12 (29.3)	5 (29.4)	

DVT: Deep vein thrombosis.

Table 4. Association between alteplase dosage and mortality, bleeding, and recurrence in patients aged 65 and under, and patients over 65 years of age

Parameters	65 Years of Age and Under		p	Over 65 Years of Age		p
	Half dose (50 mg) (n= 16)	Full dose (100 mg) (n= 12)		Half dose (50 mg) (n= 25)	Full dose (100 mg) (n= 5)	
Mortality status, n (%)						
Exitus	7 (43.8)	1 (8.3)	0.088	8 (32)	2 (40)	>0.999
Survived	9 (56.3)	11 (91.7)		17 (68)	3 (60)	
Time to mortality, days, median (min-max)	7 (1-40)	140	-	67 (1-1526)	2 (1-2)	0.089
Groups by mortality time, n (%)						
7 days	4 (57.1)	0 (0)	1.000	2 (25)	2 (100)	0.153
Between 8-365 days	3 (42.9)	1 (100)		5 (62.5)	0 (0)	
More than 365 days	0 (0)	0 (0)		1 (12.5)	0 (0)	
In-hospital mortality, n (%)						
No	9 (56.3)	12 (100)	0.010	19 (76)	3 (60)	0.589
Yes	7 (43.8)	0 (0)		6 (24)	2 (40)	
Recurrent PE, n (%)						
No	13 (81.3)	11 (91.7)	0.613	21 (84)	4 (80)	>0.999
Yes	3 (18.8)	1 (8.3)		4 (16)	1 (20)	
Adverse event, n (%)						
No	10 (62.5)	9 (75)	0.206	19 (79.2)	3 (60)	0.488
Exitus	4 (25)	0 (0)		3 (12.5)	2 (40)	
Acute blood loss anemia	2 (12.5)	2 (16.7)		1 (4.2)	0 (0)	
Hemothorax	0 (0)	0 (0)		1 (4.2)	0 (0)	
Cerebral hemorrhage	0 (0)	1 (8.3)		0 (0)	0 (0)	

Min-max: Minimum-maximum, PE: Pulmonary embolism.

DISCUSSION

This study analyzed patients from our hospital who had undergone thrombolytic (alteplase) treatment over the past 12 years. The study results revealed no significant differences between the groups receiving full-dose and half-dose treatment concerning mortality, bleeding, and recurrence. Nonetheless, it is noted to highlight that full-dose thrombolytic therapy exhibited a benefit in terms of in-hospital mortality among patients under the age of 65 even though long-term mortality rates remained similar. Hatipoglu, O. et al. have reported no significant difference in the time to in-hospital (early) and post-discharge (late) mortality in their study (8).

PE stands as a cardiovascular emergency with the potential for significant morbidity and mortality. Thrombolytic therapy is currently recommended for the management of massive pulmonary embolism, defined as acute PE with persistent hypotension and profound bradycardia. Thrombolytic therapy results in a swift improvement in early right ventricular dysfunction and a reduction in early mortality (9).

Among the most well-known thrombolytic drugs employed in the treatment of massive PTE are streptokinase, urokinase, and the recombinant tissue plasminogen activator alteplase (rt-PA). Alteplase, a second-generation fibrinolytic, is presently the most widely used thrombolytic agent due to its short infusion time of two hours and rapid onset of action (10). After a two-hour rt-PA infusion, an average reduction of 30% in pulmonary artery pressure and a 15% increase in cardiac index can be achieved. Notably, no significant difference has been found between first-generation thrombolytic drugs (such as streptokinase and urokinase) and rt-PA in terms of improving pulmonary perfusion at the end of the first 24 hours (11). However, it has been demonstrated that as thrombolytic effectiveness increases, bleeding complications decrease, especially with shorter infusion times (12). Hence, rt-PA is the preferred choice in contemporary practice.

The incidence of adverse events, such as major bleeding, tends to rise among patients receiving full-dose alteplase treatment (13). Consequently, alteplase treatment carries its own mortality risks due to these adverse events. Particularly, there are concerns regarding alteplase treatment in patients who are at risk of bleeding. There are studies conducting a comparison between half-dose and full-dose alteplase

treatments to assess their influence on adverse events and mortality outcomes (2). The concept of using half doses for the treatment of PE patients with alteplase was initially introduced in the 90s (4). Over the years, research intensity on half-dose alteplase treatment has progressively grown. The effectiveness of half-dose treatment is being explored not only in PE management but also in other conditions such as ischemic stroke and acute myocardial ischemia (14). Furthermore, meta-analyses specifically addressing this topic have emerged in the last decade. In a study conducted by Wang et al., which compared 118 PE patients receiving half and full dose alteplase treatment, it was concluded that treatment effectiveness was similar. The incidence of bleeding and mortality exhibited similar results in both treatment groups. Subgroup analysis revealed a higher bleeding incidence among the patients with a body weight below 65 kg and those treated with 100 mg alteplase (7). Sors et al. have investigated the effectiveness of low- and full-dose alteplase treatment in 53 PE patients and found no significant difference between the two groups in terms of treatment effectiveness and bleeding incidence (15). A large-scale cohort study by Kiser et al. has observed no significant difference in terms of mortality and bleeding between the full- and half-dose alteplase treatment groups (16). Hoang et al., in their cohort study involving 9 hospitals and 80 patients, have noted that similar treatment efficacy is achieved in patients treated with 50 mg alteplase as in those treated with 100 mg alteplase (17). Our study revealed a reduced hospital mortality rate among the patients who received the full dose of alteplase, while long-term mortality and bleeding outcomes were similar between the two groups. These results indicate a benefit of full-dose treatment regarding in-hospital mortality. Although there was no difference between the groups in terms of mortality risk, the comparison may not reflect the accuracy because the number of cases given full dose was small.

Given the existing body of literature, it becomes evident that there are limited studies that extensively examine patient characteristics based on alteplase treatment dosage. In a study by Kiser et al., akin to our research, the connection between patient demographic and clinical data and treatment dosages was investigated. Subdividing patients based on age, both over and under 65 years, and over and under 75 years, revealed no significant correlation between

the administered treatment dosage and age. Furthermore, there was no discernible relationship between sex and the doses of treatment administered (17). Previous research has indicated a higher incidence of massive embolism in women compared to men (18). Additionally, the occurrence of PE has been found to rise with age due to an increase in the frequency and number of comorbid conditions (19). Likewise, in our study, the proportion of female patients and individuals over the age of 65 was higher. However, sex did not emerge as a significant factor influencing treatment dosage decisions. Concerning age, it was noted that 50 mg alteplase treatment was more frequently chosen for patients over 65 years of age. In our study, it was demonstrated that the dosage of alteplase administered based on sex did not significantly affect mortality and bleeding outcomes, consistent with prior literature findings. Hospital mortality was notably lower in patients under the age of 65 who received full-dose alteplase treatment. Additionally, although not achieving statistical significance, mortality rates of the patients under 65 who received full-dose alteplase treatment were approximately four times lower than those who received half-dose alteplase treatment. However, it is important to note that large-scale randomized controlled studies are necessary to validate these results.

The presence of comorbidities increases the risk of PE, and studies have shown a link between PE and certain conditions such as renal failure and hypertension (20). In a study by Kiser et al., it has been noted that the choice of full-dose alteplase treatment is more common for patients with hypertension and chronic pulmonary heart disease, while half-dose alteplase treatment is favored for those with DVT (20). In our study, approximately half of the patients had a history of hypertension, and a 50 mg dose of alteplase was preferred in these individuals due to their elevated risk of bleeding. Patients in the half-dose group were generally older and had a higher prevalence of malignancy, which may have also influenced the decision regarding thrombolytic dosing. It is worth noting that treatment practices may vary among clinics worldwide.

The stratification of the patients in our study based on ESS risk groups showed that the treatment doses administered were similar, with no significant relationship in terms of bleeding and mortality rates. Moreover, more than half of the patients included in our study were in the intermediate-high-risk category,

indicating that contrary to guideline recommendations, thrombolytic therapy is also being used in our hospital for patients in this category. Similarly, PESI and sPESI scores were comparable among the treatment groups.

A study conducted by Kiser et al. has reported no significant association between the length of hospital stay and intensive care stay and the administered alteplase dose (16). Likewise, in our study, no correlation was observed between the length of stay and the alteplase treatment dose. Based on the obtained data, it is evident that the alteplase treatment dose does not significantly impact the length of the hospital stay.

Our results yielded no significant relationship between the use of vasopressor support, mechanical ventilation, and the dosage of alteplase administered. Previous research has suggested that employing a half-dose of alteplase may reduce the occurrence of side effects. However, our study revealed that the use of alteplase did not result in any discernible impact on side effects, the requirement for vasopressors, or mechanical ventilation.

A study conducted by Kiser et al. has also failed to establish a connection between the dose of alteplase administered and the recurrence of PE (16). Similarly, in our study, no correlation was observed between the dose of alteplase used and the recurrence of PE. It should be noted that a similar risk of recurrent PE as those treated with a full dose is faced by patients treated with a half-dose of alteplase, as suggested by these results.

It is important to acknowledge that our study has some limitations. Firstly, it is a single-center retrospective study, which may impact the generalizability of our results. Additionally, the number of patients receiving a full dose of thrombolytics in our study is relatively small.

Upon conducting a comprehensive analysis of all the data gathered from our study, a significant short-term mortality advantage was observed in favor of the group receiving the full dose among patients under 65 years of age. However, long-term mortality rates and bleeding incidents were found to be comparable in both groups. To validate our results, prospective randomized controlled studies on this topic are deemed necessary for the facilitation of the dissemination of our data within the scientific community.

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Ethical Committee Approval: This study was approved by Erciyes University Faculty of Medicine Clinical Research Committee (Decision no: 2021/811, Date: 22.12.2021).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: KK, NT

Analys/Interpretation: KK, NT

Data acquisition: BB, NAY, İG

Writing: BB, NAY

Clinical Revision: BB, NAY, İG

Final Approval: KK, İG, NT

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