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Using clinical parameters to determine the optimal dose of thrombolytic treatment in acute pulmonary thromboembolism

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Abstract:

BACKGROUND AND AIM: The objective of this study was to check if clinical parameters could help us determine the optimal dose of thrombolytic therapy for patients with acute pulmonary thromboembolism (PTE).

METHODS: This was a retrospective cohort study. The data were obtained through an examination of medical records and the use of an existing clinical database. A total of 367 individuals admitted to a tertiary care hospital between 2016 and 2019 and diagnosed with PTE were evaluated. The study includes people who had massive or submassive thromboembolism that required thrombolytic therapy. There were two rt-PA dosage groups (100 mg rt-PA and 50 mg rt-PA).

RESULTS: A total of 81 patients, 43 females and 38 males, were evaluated. Thirty-one of the patients were administered 100 mg rt-PA and 50 were administered 50 mg rt-PA. The mean age of patients in the 100 mg rt-PA group was 57±18 years, while it was 72±11 years in the 50 mg rt-PA group, with a statistically significant difference of $p<0.001$. In the malignancy 50 mg rt-PA group, the most frequent risk factors were deep vein thrombosis history 100 mg rt-PA ($p=0.54$ and $p=0.04$, respectively). Clinical findings at the time of application were similar in both groups except for systolic blood pressure. Systolic blood pressure was lower in the 50 mg rt-PA group ($p=0.03$). Especially the change of pulse up to the 60th minute was statistically significant in both 100 mg rt-PA and 50 mg rt-PA groups ($p=0.01$ and $p=0.002$, respectively). The change of saturation up to the 60th minute was statistically significant in the 50 mg rt-PA group ($p=0.003$).

CONCLUSIONS: While both 100 mg and 50 mg rt-PA are applied, meaningful activity on clinical parameters is in the first 60 min. In particular, the change in pulse and saturation may be more guiding in the follow-up of treatment effectiveness. The significant improvement of clinical parameters, especially pulse and saturation, in the first hour may suggest that lower dosage rt-PA and lower administration duration may be effective in acute PTE.

Keywords:

Clinical parameters, pulmonary thromboembolism, thrombolytic treatment

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Introduction

Pulmonary thromboembolism (PTE) is a frequent and potentially fatal illness. Mortality can reach 65%, especially in high-risk patients.[1] The vast majority of deaths occur within the first hour of patients presenting with shock; therefore, a rapid treatment approach is required for these patients to survive.[2–4]

Thrombolytic treatment is the primary choice in patients with high-risk (massive) PTE.[5] Today, it can also be applied in appropriate patients with medium risk (submassive) PTE.[3,6] The major restriction of thrombolytic therapy is the potential for hemorrhage, particularly in patients who are predisposed to bleeding. Recombinant tissue plasminogen activator is the most often utilized thrombolytic drug in the treatment of PTE (rt-PA). However, the bleeding risks of rt-PA are dose-dependent; thus, optimal dosing could enhance benefits while minimizing bleeding issues. The US Food and Drug Administration has approved intravenous rt-PA at a dose of 100 mg administered over 2 h, and it is also recommended by current guidelines.[2,5] Lower doses administration may be beneficial in those who are at high risk of bleeding.[5] Several studies have shown that lower doses of rt-PA are safe and effective in patients with massive and submassive PTE.[7–10] Recent meta-analyses support this hypothesis, revealing that lower dose rt-PA use was associated with fewer major bleeding events and the same efficacy as the 100 mg rt-PA dosing regimen.[11,12] However, current studies are related to rt-PA 50 mg and there are no adequate data on the lower dose rt-PA efficacy of PTE treatment to reduce hemorrhage risk and whether to use clinical parameters to evaluate this efficacy. The objective of this study was to see if clinical parameters could help us determine the optimal dose of thrombolytic therapy for patients with acute PTE.

Materials and Methods

This was a retrospective cohort study. The data were obtained through an examination of medical records and the use of an existing clinical database. All demographic, clinical, and laboratory findings, as well as treatment options and outcomes, were meticulously documented. The protocol for the study was approved by the institutional review board (B.30.2.ATA.0.01.00/61.09.21.06.61).

A total of 367 individuals admitted to a tertiary care hospital between 2016 and 2019 and diagnosed with PTE were evaluated. The study includes people who had massive or submassive thromboembolism that required thrombolytic therapy (n=84). Active bleeding patients were excluded from the study (n=3). The remaining cases (n=81), which included massive and submassive cases, were given either 50 mg (n=50) or 100 mg (n=31) thrombolytic treatment (recombinant tissue plasminogen activator) based on age and hemorrhage risk, with 50 mg treatment being given to those over the age of 65 years or having a relatively high risk of hemorrhage. During their first admission, we excluded patients who had any contraindication to receiving thrombolytic treatment, such as current bleeding.

All patients who had a high index of suspicion of PTE (major risk factors, clinical signs) had a chest X-ray, electrocardiogram, and echocardiographic assessment; those who had a strong clinical suspicion of PTE had computed tomography (CT) angiography using a 16-slice multidetector CT to confirm the diagnosis. Before, during, and after thrombolytic treatment, a clinical and laboratory assessment was performed, which included a physical exam, blood pressure, pulse rate, and oxygen saturation. Throughout the hospital stay, adverse outcomes such as PTE hemorrhage complications and mortality were recorded.

After confirming the diagnosis, the patients provided informed consent, and thrombolytic treatment was administered as either 100 mg rt-PA or 50 mg rt-PA, depending on the bleeding risk and age. The 100 mg dose of rt-PA was administered as a bolus of 10 mg alteplase followed by a 2-h infusion of 90 mg; the 50 mg dose was administered as a 2-h infusion.[13]

Massive (high-risk) PTE and submassive PTE are defined according to the PTE guidelines.[1,3] Major hemorrhage and minor hemorrhage are defined according to a previous study.[14]

Statistical analysis

SPSS for Windows version 17.0 was used for statistical analysis (SPSS, Inc., Chicago, IL, USA). The data were expressed as percentage, mean, and standard deviation. For comparisons of continuous variables between the 100 mg rt-PA and 50 mg rt-PA groups, we used the two-tailed Student's t-test, and for comparisons of nominal

variables, we used the Chi-squared test. To compare clinical parameters in each group, a paired t-test was used. If a p-value of 0.05 was observed, the findings were considered statistically significant.

Results

A total of 81 patients were assessed, with 43 females and 38 men. Thirty-one individuals received 100 mg rt-PA, whereas the other fifty received 50 mg rt-PA. Table 1 summarizes the baseline characteristics of the patient. The mean age of patients in the 100 mg rt-PA group was 57±18 years, while it was 72±11 years in the 50 mg rt-PA group, with a statistically significant difference of p<0.001. In the malignancy 50 mg rt-PA group, the most frequent risk factors were deep vein thrombosis history 100 mg rt-PA (p=0.54 and p=0.04, respectively). Clinical findings at the time of application were similar in both groups except for systolic blood pressure. The 50 mg rt-PA group had lower systolic blood pressure (p=0.03).

Rates of hemorrhage complications and hospital mortality are presented in Table 2. The 50 mg rt-PA group had a higher rate of major bleeding although it was not statistically significant (p=0.63). In either group, there was no statistically significant difference in minor hemorrhage or mortality (p=0.71 and p=1, respectively).

A comparison of clinical follow-up parameters of both treatment groups is shown in Table 3. Other follow-up parameters (pulse, diastolic blood pressure, and saturation) except systolic blood pressure (p=0.03) before treatment was started did not differ statistically in either group. It was observed that the difference in initial systolic blood pressure did not continue in the following minutes. There was no statistical significance when the differences in 15-min follow-ups were taken and compared.

A comparison of the follow-up parameters within each group is summarized in Table 4. In particular, the change of pulse up to the 60th minute was statistically significant in both 100 mg rt-PA and 50 mg rt-PA groups (p=0.01 and p=0.002, respectively). After the 60th minute, statistically significant differences were not observed in both pulse and other clinical follow-up parameters (systolic–diastolic blood pressure and saturation). The change of saturation up to the 60th minute was statistically significant in the 50 mg rt-PA group (p=0.003).

Table 1: Baseline characteristics of the cases (n=81)

Clinical features of groups	100 mg rt-PA (n=31)	50 mg rt-PA (n=50)	p
Demographics			
Mean age	57±18	72±11	**0.001**
Female, sex, %	42	60	0.16
Massive (high-risk) PTE, %	29	34	0.80
Submassive PTE, %	71	66	0.80
Risk factors, %			
Presence of malignancy	19	24	0.54
Previous history of DVT	30	11	**0.04**
Immobilization	18	22	0.45
Any recent surgery	12	17	0.45
Clinical findings (beginning)			
Heart rate (bpm)	104±17	107±21	0.56
Systolic pressure (mmHg)	119±25	110±18	**0.03**
Diasolic pressure (mmHg)	76±17	71±12	0.10
Saturation (SaO_2)	89±7	86±8	0.09
Echocardiography findings			
Acute cor pulmonale, %	100	100	1
Pulmonary arterial pressure (systolic, mmHg)	58±18	60±15	0.55
Paradox IVS, %	82	72	0.42
CT angiography findings, %			
Saddle embolism	23	13	0.35
Main pulmonary artery	81	74	0.57
Lober artery	98	88	0.12
Segmental artery	98	90	0.25

Data are presented as mean±SD or percentage unless otherwise stated. Statistically significant values are given in bold. PTE: Pulmonary thromboembolism, DVT: Deep vein thrombosis, IVS: Interventricular septum, CT: Computed tomography

Table 2: Frequency of mortality, major hemorrhage, and minor hemorrhage for each group

Outcomes	100 mg rt-PA (n=31)		50 mg rt-PA (n=50)		p
	n	%	n	%	
Hemorrhage					
Major	1	3	3	7	0.63
Minor	4	12	4	9	0.71
Mortality					
In hospital	2	6	3	7	1

The data were expressed as n (%). We used the Chi-squared test for comparisons

Discussion

Our study showed that while both 100 mg and 50 mg rt-PA were applied, the meaningful effectiveness on clinical parameters was in the first 60 min. In particular, the change in pulse and saturation may be more guiding in the follow-up of treatment effectiveness. In addition, although the 50 mg rt-PA group was relatively heavier, sig-

Table 3: Comparison of clinical follow-up parameters for each groups

Clinical parameters	100 mg rt-PA (n=31)	50 mg rt-PA (n=50)	p
Beginning			
Heart rate (bpm)	104±17	107±21	0.56
Systolic pressure (mmHg)	119±25	110±18	**0.03**
Diastolic pressure (mmHg)	76±17	71±12	0.10
Saturation	89±7	86±8	0.09
15 min			
Heart rate (bpm)	104±18	102±18	0.58
Systolic pressure (mmHg)	122±21	116±18	0.21
Diastolic pressure (mmHg)	78±17	73±11	0.11
Saturation	90±6	88±8	0.15
30 min			
Heart rate (bpm)	104±18	101±19	0.53
Systolic pressure (mmHg)	121±22	117±21	0.41
Diastolic pressure (mmHg)	76±15	74±12	0.47
Saturation	90±5	88±7	0.20
45 min			
Heart rate (bpm)	103±18	100±19	0.51
Systolic pressure (mmHg)	120±22	119±21	0.79
Diastolic pressure (mmHg)	73±13	72±12	0.69
Saturation	91±5	88±8	0.09
60 min			
Heart rate (bpm)	99±19	97±19	0.57
Systolic pressure (mmHg)	121±21	119±19	0.58
Diastolic pressure (mmHg)	77±15	73±13	0.13
Saturation	91±6	90±7	0.44
90 min			
Heart rate (bpm)	99±18	97±18	0.64
Systolic pressure (mmHg)	124±21	119±21	0.37
Diastolic pressure (mmHg)	80±14	73±13	0.04
Saturation	92±6	90±6	0.14
120 min			
Heart rate (bpm)	98±17	96±19	0.58
Systolic pressure (mmHg)	125±18	118±20	0.13
Diastolic pressure (mmHg)	77±14	72±12	0.08
Saturation	92±6	90±6	0.17

Data are presented as mean±SD unless otherwise stated. Statistically significant values are given in bold. Two-tailed Student's t-test was used for continuous variables between the groups

Table 4: Comparison of follow-up clinical parameters within each group

Clinical parameters	100mg rt-PA (n=31)	p	50 mg rt-PA (n=50)	p
Heart rate (bpm)				
15–60 min	104±18	0.01	102±18	**0.01**
	99±19		98±19	
30–60 min	104±18	0.02	101±19	**0.002**
	99±19		98±19	
45–60 min	103±18	0.01	100±19	**0.002**
	99±19		98±19	
60–90 min	99±19	0.27	98±19	0.66
	99±18		97±18	
90–120 min	99±18	0.05	97±18	0.91
	96±16		97±18	
Systolic pressure (mmHg)				
15–60 min	122±21	0.79	116±18	0.10
	121±21		119±19	
30–60 min	121±22	0.91	117±21	0.36
	121±21		119±19	
45–60 min	120±22	0.76	119±21	0.87
	121±21		119±19	
60–90 min	121±21	0.95	119±19	0.83
	124±21		119±21	
90–120 min	124±21	0.31	119±21	0.94
	126±19		119±20	
Diastolic pressure (mmHg)				
15–60 min	78±17	0.57	73±11	0.90
	77±15		73±13	
30–60 min	76±15	0.57	74±12	0.57
	77±15		73±13	
45–60 min	73±13	0.01	72±12	0.29
	77±15		73±13	
60–90 min	77±15	0.54	73±13	0.61
	80±14		73±13	
90–120 min	80±14	0.31	73±13	0.80
	79±15		73±11	
Saturation				
15–60 min	90±6	0.12	88±8	**0.005**
	91±6		90±7	
30–60 min	90±5	0.08	88±7	**0.002**
	91±6		90±7	
45–60 min	91±5	0.64	88±8	**0.003**
	91±6		90±7	
60–90 min	91±6	0.31	90±7	0.37
	92±6		90±6	
90–120 min	92±6	0.36	90±6	0.68
	91±5		89±6	

Data are presented as mean±SD unless otherwise stated. Statistically significant values are given in bold. A paired t-test was used to compare clinical parameters in each group

nificant efficacy in clinical parameters was observed in the first hour with the application of 25 mg rt-PA.

The primary goal of thrombolytic therapy in PTE is to prevent mortality. In massive PTE, mortality can increase to 65%. The thrombolytic treatment provides resuscitation of the thrombosis in a short time and acute cardiac decompression can be eliminated in PTE.[1] However, the risk of hemorrhage limits the application of thrombolytic therapy. Studies on applying lower dose alteplase to reduce this risk have shown that the low dose is as effective as the standard dose and the risk of bleeding is lower.[7–10,15] In their study, Zhang and his colleagues showed that 30 mg/2 h of alteplase application was effective and reliable in patients with submassive PTE. They also noted that low-dose thrombolytics do not increase the

risk of bleeding when comparing only patients who take anticoagulants.[15] In previous trials of patients receiving thrombolytic treatment for PTE, major bleeding rates ranged between 3.7% and 36%.[14,16,17] In our study, it was observed that the major hemorrhage rate was 3% in the 100 mg rt-PA group and 7% in the 50 mg rt-PA group. It is thought that the higher rate in the 50 mg rt-PA group may depend on patient selection. The effectiveness of thrombolytic treatment was evaluated through clinical parameters (blood pressure, pulse, saturation, number of breathings, and symptom weight), echocardiographic parameters (systolic pulmonary artery pressure, tricuspid annular plane systolic excursion, right ventricular/left ventricular ratio, etc.), and/or biochemical parameters such as troponin and brain natriuretic peptide.[15,18–20] In the PEITHO study,[18] they showed that changes in systolic blood pressure and respiratory rate were important in the clinical outcome. Güner and his colleagues[19] administered rt-PA in patients with moderate-risk PTE as low doses (25 mg) and slow infusions (6 h), showing statistically significant changes in blood pressure, pulse, respiratory count, and oxygen saturation. Ozcinar et al.[20] applied 21 mg rt-PA with an ultrasound-accelerated catheter-directed thrombolysis method and showed significant change in clinical parameters. On the other hand, in our study, both 100 mg rt-PA and 50 mg rt-PA groups found a statistically significant change in pulse and saturation in the first hour. In addition, although the 50 mg patient group is the riskier group, the significant improvement of clinical parameters here in the first hour suggests that it may be effective at 25 mg. However, prospective studies are needed.

Important limitations of our study are that it was a retrospective study, and it included a small number of cases. In addition, treatment efficacy was evaluated only by clinical parameters, and echocardiography and/or laboratory parameters were not evaluated. However, we believe that our study may guide prospective studies using clinical parameters of thrombolytic therapy dose.

In conclusion, while both 100 mg rt-PA and 50 mg rt-PA are applied, meaningful effectiveness on clinical parameters is in the first 60 min. In particular, the change in pulse and saturation may be more guiding in the follow-up of treatment effectiveness. The significant improvement of clinical parameters, especially pulse and saturation, in the first hour may suggest that lower dosage rt-PA and lower administration duration may be effective in acute PTE.

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by the Ataturk University Ethics Committee (No: B.30.2.ATA.0.01.00/61, Date: 30/09/2021).

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Authorship Contributions

Concept – E.Y.U., M.A.; Design – E.Y.U., M.A.; Supervision – E.Ç., Ö.A., B.K., E.Y.U.; Funding – E.Ç., Ö.A.; Materials – E.Ç., B.K.; Data collection &/or processing – E.Ç., B.K., Ö.A.; Analysis and/or interpretation – E.Y.U., M.A., B.K.; Literature search – E.Y.U., M.A., L.S.; Writing – E.Y.U., M.A., Ö.A.; Critical review – L.S., M.A.

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