ORIGINAL ARTICLE

Low-dose thrombolytic therapy versus unfractionated heparin in patients with intermediate-high risk pulmonary embolism

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ABSTRACT

BACKGROUND: Patients with intermediate-high risk pulmonary embolism (PE) who have acute right ventricular dysfunction and myocardial injury without overt hemodynamic compromise may be candidates for thrombolytic therapy (TT). In this study, we aimed to compare the clinical outcomes of low-dose prolonged TT and unfractionated heparin (UFH) in intermediate-high risk PE patients.

METHODS: This study enrolled 83 (female: 45 [54.2%], mean age: 70.07±10.7 years) retrospectively evaluated patients with the diagnosis of acute PE who were treated with low-dose and slow-infusion of TT or UFH. The primary outcomes of the study were defined as a combination of death from any cause and hemodynamic decompensation, and severe or life-threatening bleeding. Secondary endpoints were recurrent PE, pulmonary hypertension, and moderate bleeding.

RESULTS: The initial management strategy of intermediate-high risk PE was TT in 41 (49.4%) patients and UFH in 42 (50.6%) cases. Low-dose prolonged TT was successful in all patients. While the frequency of hypotension decreased significantly after TT (22 vs. 0%, P<0.001), it did not decrease after UFH (2.4 vs. 7.1%, p=0.625). The proportion of hemodynamic decompensation was significantly lower in the TT group (0 vs. 11.9%, p=0.029). The rate of secondary endpoints was significantly higher in the UFH group (2.4 vs. 19%, P=0.016). Moreover, the prevalence of pulmonary hypertension was significantly higher in UFH group (0 vs. 19%, p=0.003).

CONCLUSION: Prolonged TT regimen with low dose, slow infusion of tissue plasminogen activator was found to be associated with a lower risk of hemodynamic decompensation and pulmonary hypertension in patients with acute intermediate-high-risk PE compared to UFH.

Keywords: Bleeding; death; heparin; pulmonary embolism; thrombolytic therapy.

INTRODUCTION

Acute pulmonary embolism (PE) is a life-threatening disease that usually occurs as a serious complication of venous thromboembolism.[1] Mortality rates of PE vary widely, but approximately 10% of all patients with acute PE die within 3 months of diagnosis.[1] Acute right ventricular (RV) pressure overload at the time of diagnosis is one of the most important determinants of the severity and early clinical outcomes of PE. Patients with acute RV dysfunction and myocardial injury without overt hemodynamic impairment may be at intermediate-high risk for an adverse early outcome.[2,3] In-hospital mortality can reach up to 30%, especially in the patient population presenting with hemodynamic deterioration. Therefore, careful care should be given to this patient group.[3] In

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the PE International Thrombolysis (PEITHO) study,[4] aimed at resolving the controversial issue in intermediate-risk PE cases, a higher incidence of stroke and major non-intracranial hemorrhage was observed in the full-dose thrombolytic therapy (TT) group. Unfortunately the question whether or not to lyse in intermediate-high PE was not solved in this trial. Systemic TT is increasingly being applied in intermediate-high-risk PE cases.[5-12] In addition, alternative intravenous TT strategies have been proposed to provide efficacy with less bleeding. However, it remains unclear which of the different systemic TT strategies described in the literature is more effective and safe than heparin. However, recent major cardiovascular guidelines still recommend anticoagulation therapy for patients with intermediate-high-risk PE.[2] Previously, we have reported that a prolonged TT regimen with low-dose and slow-infusion of tissue plasminogen activator (t-PA) was associated with lower complication rates without compromising effectiveness in patients with acute intermediate-high risk PE.[8] There are no clinical studies in the literature regarding the efficacy and safety of the low-dose slow infusion of t-PA compared to anticoagulation only in this patient population. This study aimed to compare the clinical results of low-dose, slow infusion of t-PA with unfractionated heparin (UFH) only.

MATERIALS AND METHODS

Study Population

This observational retrospective study enrolled a total of 83 patients (female: 45 [54.2%], mean age: 70.07±10.7 years) who were diagnosed with intermediate-high risk PE between January 2011 and January 2023 in Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital. The study protocol was approved by the institutional ethics committee in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and all patients provided written informed consent. Potential study participants were the patients who had compatible computed tomography (CT) findings and clinical symptoms and indications suggestive of PE. A minimum of two new signs and symptoms, including chest pain, tachypnea (respiratory rate >20 breaths/min), tachycardia (resting heart rate >100 beats/min), dyspnea, and oxygen desaturation (oxygen partial pressure <95%), was necessary for patients to be eligible for inclusion. A contraindication to TT or severe thrombocytopenia (platelet count <50.000/mm^3), significant risk of bleeding, systemic arterial systolic blood pressure <90 or >200 mm Hg, and a PESI score of >4 or 3 were among the exclusion criteria. The HAS-BLED score was used to determine the patients' bleeding risk (hypertension, abnormal renal function or liver function, stroke, bleeding, labile international normalized ratio (excluded as all patients not on warfarin before inclusion), elderly >85 years old, and drugs and alcohol): 0 = low risk, 1 to 2 = moderate risk, >2 = high risk.[13] Using the HAS-BLED score, patients were clinically risk-stratified for eligibility for escalation of therapy to low-dose systemic TT in accordance with accepted clinical guidelines.[13] Bleeding problems were categorized according to the GUSTO classification as severe or life-threatening if they were intracerebral or caused considerable hemodynamic compromise that required treatment. The need for a transfusion was the criterion for moderate bleeding. Other types of bleeding that did not require transfusion or cause hemodynamic worsening were referred to as minor bleeding.[14]

Imaging Tools

Transthoracic echocardiography (TTE) was carried out within 2 h of hospital admission, before the administration of t-PA, and was repeated every 6–12 h. The right atrial pressure was assessed as 10, 15, and 18 mmHg for mild, moderate, and severe right atrial enlargement, respectively. Systolic pulmonary artery pressure (SPAP) was calculated using the tricuspid valve regurgitation jet velocity in line with the modified Bernoulli equation.[15,16] An M-mode cursor was placed across the lateral tricuspid annulus to measure the amount of longitudinal motion of the annulus at peak systole in the typical apical 4-chamber view. This information was used to determine the tricuspid annular plane systolic excursion. Biplane Simpson's approach was used to determine the patients' left ventricular ejection fractions.[17] A cardiologist who was not aware of the patients' treatment plans interpreted the echocardiographic results. Pulmonary hypertension was defined as SPAP with a dichotomous value of 40 mmHg. A RV-to-left ventricular ratio (RV/LV) of >0.9 was considered to indicate RV hypertrophy.[15,16] A 320-slice helical CT scanner (Toshiba Medical Systems Corp., Tokyo, Japan) with angiographic contrast material (Omnipaque 350; GE Healthcare, Chicago, IL, USA) was used to take images both before and after the treatment. A retrospective analysis was done on the recorded images taken at the time of diagnosis and after the TT or heparin. The methods for measuring the RV/LV ratio were developed in accordance with the prior definitions.[2,3,18]

Treatment Strategy of İntermediate-high Risk Pulmonary Embolism

In the TT group, t-PA was the only agent used for TT. The dose of t-PA was half of the standard dose (100 mg) commonly used for the treatment of PE, which we defined as "safe dose" thrombolysis. The low dose, slow infusion of t-PA regimen was initiated with 2 consecutive episodes (25 mg t-PA/6 h), followed by systemic UFH therapy for at least 24 h. The route, duration, and preparation of t-PA were made in accordance with previous publications.[19] For the anticoagulation group, a 70 units/kg or maximum 5.000 unit bolus of UFH was given to the anticoagulation group, followed by an initial infusion rate of 16 units/kg or a maximum of 1.000 units/h. Every 6 h, the desired aPTT of 60 to 70 s was evaluated, and the infusion rate was modified accordingly. An intermittent mini-bolus (16 units/kg or a maximum of 1.000 units) of UFH was given along with a dose adjustment (2 units/kg/h in-

crease in infusion rate) when an aPTT of <50 s was detected. UFH was stopped for 30 to 60 min and the dose was adjusted (2 units/kg/h decrease in infusion rate) when an aPTT of >80 s was recorded.

Table 1. Baseline demographic, clinical and laboratory characteristics of the study population

Parameters	Low dose TT group (n=41), n (%)	UFH group (n=42), n (%)	p
Age (years)	70.8±10.2	69.4±11.2	0.541
Gender (female)	22 (53.7)	23 (54.8)	0.920
BMI (kg/m2)	28 (25.73–32.0)	26.95 (25.32–29.9)	0.365
Hypertension	30 (73.2)	28 (66.7)	0.518
Diabetus mellitus	9 (22.0)	14 (33.3)	0.247
COPD	8 (19.5)	12 (28.6)	0.335
Surgical history			
Arthroplasty	3 (7.3)	0	0.116
Femur fixation	1 (2.4)	3 (7.1)	0.317
Gastrectomy	0	1 (2.4)	0.506
Hysterectomy	1 (2.4)	0	0.494
Antiplatelet use	6 (14.6)	6 (14.3)	0.964
Prior DVT	23 (56.1)	23 (54.8)	0.903
Malignancy	2 (4.9)	1 (2.4)	0.491
Clinical presentation			
Dyspnea	41 (100.0)	42 (100.0)	
Tachypnea	16 (39.0)	15 (35.7)	0.755
Syncope	5 (12.2)	5 (11.9)	0.615
Chest pain	4 (9.8)	4 (9.5)	0.630
Troponin (ng/mL)	1.379±0.587	1.251±0.430	0.259
HASBLED score			
1	21 (51.2)	23 (54.8)	0.746
2	20 (48.8)	18 (42.9)	0.588
Hypotension	9 (22.0)	1 (2.4)	0.007
Heart rate (bpm)	111 (109–117)	110.5 (109–117)	0.497
O2 saturation	87 (86–88)	87 (86–88)	0.952
PTE location			
Bilateral	31 (75.6)	36 (85.7)	0.243
Saddle	5 (12.2)	5 (11.9)	0.615
MPA	5 (12.2)	1 (2.4)	0.095
LVEF (%)	60 (58–60)	60 (58–62)	0.509
RV/LV ratio	1.2 (1.0–1.2)	1.13 (1.0–1.2)	0.625
TAPSE (cm)	1.6 (1.5–1.7)	1.6 (1.5–1.7)	0.585
SPAP (mmHg)	53 (43–60)	41.5 (37–45)	<0.001
PESI score	112 (108–121)	111.5 (105–120)	0.565
PESI class			
3	9 (22.0)	12 (28.6)	0.488
4	32 (78.0)	30 (71.4)	

Continuous variables with normal distribution were expressed as mean±SD and continuous variables without normal distribution were expressed as median (25th–75th percentiles). BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, DVT: Deep vein thrombosis, LV: Left ventricle, LVEF: Left ventricular ejection fraction, MPA: Main pulmonary artery, PESI: Pulmonary embolism severity index, PTE: Pulmonary thromboembolism, RV: Right ventricle, SPAP: Systolic pulmonary artery pressure, SD: Standard deviation, TT: Thrombolytic therapy, UFH: Unfractioned heparin, TAPSE: Tricuspid annular plane systolic excursion.

When the TT group had finished receiving 50 mg of t-PA (12th h), UFH treatment was started. Warfarin was then administered concurrently in the UFH and TT groups. In cases where the international normalized ratio was 2.0 or greater for at least 24 h, heparin was stopped after a minimum of 5 days. A minimum of 3 months of treatment were administered.

Clinical Follow-up

Following the index treatment, the patients underwent examinations at 1 and 3 months. After therapy, all patients underwent TTE and CT scans to evaluate SPAP, RV size, and functionality. At the time of death or discharge, in-hospital complications were noted. Through a check of medical records or a phone call (confirmation of events from medical records), the follow-up information of 3 months was gathered retrospectively. In addition, each clinical visit included a thorough assessment of any clinical event development. Through the Turkish national death indices, the information regarding the follow-up vital status of every patient was also verified.

End-points of the Study

The primary outcomes of the study were defined as a combination of death from any cause and hemodynamic decompensation, and severe or life-threatening bleeding. Secondary endpoints were recurrent PE, pulmonary hypertension, and moderate bleeding.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp. Armonk, NY, USA). The normality distribution of continuous variables was tested with the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean ± standard deviation while continuous variables without normal distribution were expressed as median (25th–75th percentiles). Categorical variables were expressed as frequencies and percentages. Continuous variables were compared using Student's t-test or the Mann–Whitney U test when applicable. Chi-square, Fisher's or McNemar exact test was used for the comparison of categorical variables as appropriate. A two-sided $P < 0.05$ was considered statistically significant. The cumulative incidence of primary endpoints was calculated with Kaplan–Meier survival test. The effect of treatment strategy on the development of death, hemodynamic decompensation, and severe or life-threatening bleeding was investigated using the log-rank test. A two-sided $P<0.05$ was considered statistically significant.

RESULTS

The study population comprised 83 retrospectively evaluated patients (female: 45, mean age: 70.07±10.7 years) with the diagnosis of acute PE who were treated with low dose, slow infusion of t-PA or UFH. The initial management strategy of intermediate-high risk PE was TT in 41 (49.4%) patients and UFH in 42 (50.6%) cases.

The demographic data of the study patients are summarized in Table 1. The clinical manifestations included dyspnea (100%), tachypnea (37.3%), syncope (12%), and chest pain (9.6%). Although 14.4% of the patients were on antiplatelet therapy, the HASBLED score was 1 in 53% of the patients. No patient had score more than 2. The mean arterial blood pressure was low in 10 (12%) patients without any hemodynamic decompensation. The rate of hypotension was significantly higher in the TT group than in UFH (4 vs. 22%, p=0.007). Considering the embolic formation localization in the pulmonary artery, the main pulmonary artery localization was numerically higher in the TT group, although it was not statistically significant (12.2 vs. 2.4%, p=0.095). There was no significant difference in echocardiographic parameters in both groups, except for SPAP. When the TT and UFH groups were compared in terms of SPAP, the TT group had a higher preva-

Table 2. Comparison of pre- and post-treatment echocardiographic and clinical parameters according to treatment strategy

	TT group			UFH group		
	Baseline	3rd month	p	Baseline	3rd month	p
Heart rate (bpm)	111 (109–118)	80 (77.5–86)	<0.001	110.5 (109–117)	80 (75–82.5)	<0.001
O^2 saturation	87 (86–88)	96 (95–96)	<0.001	87 (85.75–88)	94 (92–95)	<0.001
Tachypnea, n (%)	16 (39.0)	0	<0.001	15 (35.7)	4 (9.5)	0.013
Hypotension, n (%)	9 (22.0)	0	<0.001	1 (2.4)	3 (7.1)	0.625
RV/LV ratio	1.2 (1.0–1.2)	0.66 (0.63–0.70)	<0.001	1.1 (1.0–1.2)	0.71 (0.65–0.84)	<0.001
SPAP (mmHg)	53 (43–60)	24 (23–25)	<0.001	41.5 (37–45)	32 (29.5–37.25)	<0.001
TAPSE (mm)	16 (15–17)	24 (21.5–25)	<0.001	16 (15–17.1)	20.5 (19–24)	<0.001

LV: Left ventricle; RV: Right ventricle; SPAP: Systolic pulmonary artery pressure; TAPSE: Tricuspid annular plane systolic excursion; TT: Thrombolytic therapy; UFH: Unfractioned heparin.

Table 3. The list of 3-month clinical outcomes in the study groups

Parameters	TT group (n=41), n (%)	UFH group (n=42), n (%)	p
Primary endpoint	1 (2.4)	5 (11.9)	0.106
All-cause death	0	2 (4.8)	0.253
Hemodynamic decompensation	0	5 (11.9)	0.029
Severe or life-threatening bleeding	1 (2.4)	0	0.494
Secondary endpoint	1 (2.4)	8 (19.0)	0.016
Recurrent PE	0	2 (4.8)	0.253
Pulmonary hypertension (≥40 mmHg on echocardiography)	0	8 (19.0)	0.003
Moderate bleeding	1 (2.4)	0	0.494
Minor bleeding	5 (12.2)	5 (11.9)	0.615

TT: Thrombolytic therapy; UFH: Unfractioned heparin; PE: Pulmonary embolism.

lence of SPAP (53 [43–60] vs. 41.5 [37–45] mmHg, P<0.001).

A comparison of pre- and post-treatment echocardiographic and clinical parameters according to treatment strategy is summarized in Table 2. Arterial oxygen saturation and TAPSE were increased while heart rate, RV/LV ratio, and SPAP decreased significantly after TT and UFH (Table 2). Low-dose prolonged TT was successful in all patients. While the frequency of hypotension decreased significantly after TT (22 vs. 0%, P<0.001), it did not decrease after UFH (2.4 vs. 7.1%, p=0.625).

The rates of primary and secondary outcomes in the first 3 months are presented in Table 3. The proportion of 3-month primary endpoints was not different between the two groups (2.4 vs. 11.9%, p=0.106). However, hemodynamic decompensation was significantly lower in the TT group (0 vs. 11.9%, p=0.029). The rate of secondary endpoints was significantly higher in UFH group (2.4 vs. 19%, p=0.016) (Table 3). Moreover, the prevalence of pulmonary was significantly higher in UFH group (0 vs. 19%, p=0.003). Although the rates of all-cause death (0 vs. 4.8%, p=0.253) and recurrent PE (0 vs. 4.8%, p=0.253) were not significantly different, they were numerically higher in the UFH group at the 3-month follow-up.

There were two patients with severe and moderate bleeding (Table 3). Both patients were in the TT group. Intracranial bleeding developed in 1 of 2 patients with clinically significant bleeding and gastrointestinal bleeding in the other.

A Kaplan–Meier analysis revealed that short-term cumulative primary end-points free survival ratio was not found to be significantly decreased in patients with intermediate-high risk PE (p=0.104) (Fig. 1).

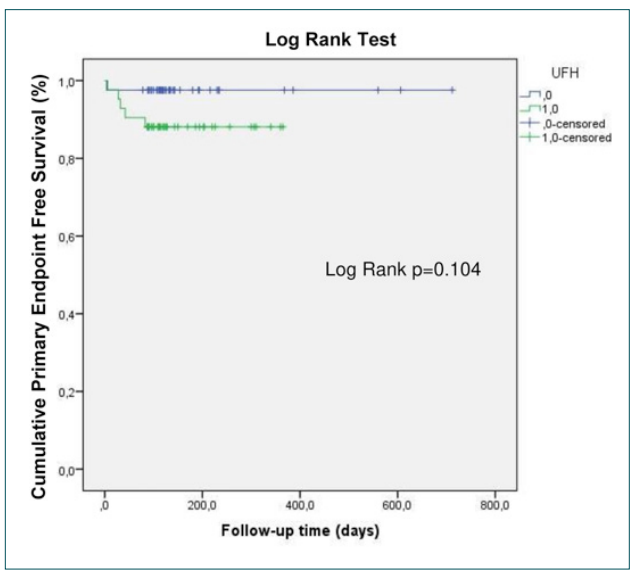

Figure 1. Kaplan–Meier survival analysis indicates that short-term cumulative primary end-points free survival ratio was not found to be significantly decreased in patients with intermediate-high risk pulmonary embolism. UFH: Unfractionated heparin.

DISCUSSION

The principal finding of the present investigation is that the low dose slow infusion TT regimen prevents hemodynamic decompensation and pulmonary hypertension in the first 3 months in patients with intermediate-high risk PE without increasing hemorrhagic complications. To the best of our knowledge, this is the first study comparing low-dose slow infusion TT regimen, and UFH in patients with intermediate-high risk PE.

Rational of Thrombolytic Strategy

Prior studies have demonstrated that TT may have hemodynamic and clinical advantages in the treatment of patients with massive and some submassive PE patients.[2,4,11,12, 14, 20-22] TT is a "double-edged sword;" its therapeutic effect has been demonstrated in the seemingly integral "cost" of bleeding complications related to the induction of a systemic lytic state.[2,3] Even though there is a chance of serious bleeding (including intracranial bleeding) due to the nature of t-PA, it is employed as an approved therapeutic treatment in patients with PE that results in hemodynamic deterioration.[2] Nonetheless, accelerated systemic TT (100 mg t-PA in 2h)

in intermediate-high risk PE reduces the incidence of hemodynamic impairment, but the benefit of mortality has not been proven yet and is associated with a 10% risk of major bleeding. The major cardiovascular guidelines regarding the management of PE do not recommend full-dose systemic TT for submassive PE.[2] To limit bleeding consequences without compromising effectiveness, a variety of novel methods have been devised.[4,12,20,21,23-27] Previously, Kucher et al. randomly assigned 61 patients with submassive PE to receive heparin treatment or catheter-directed thrombolysis, and they reported no deaths or severe bleeding.[25] Besides, the larger prospective nonrandomized SEATTLE 2 trial that included 150 patients with massive and submassive PE and showed clinical benefit without intracranial bleeding was unable to confirm this encouraging finding.[26] The trial was still associated with an 11.4% GUSTO moderate bleeding rate, 20% of which were related to access site complications. Based on the assumption that all venous return and right cardiac output wash the pulmonary circulation, non-invasive "low-dose" systemic TT (50 mg t-PA) has been promoted, with a lower dosage and avoidance of "invasive" vascular access can maintain increased thrombolytic efficacy with less bleeding. This method, which has only been tested on a small number of patients, has been shown to significantly reduce major bleeding issues while producing outstanding clinical outcomes.[7,8,11,12] In 2013, Sharifi et al. reported that low-dose TT (a 10-mg bolus by an intravenous push within 1 minute followed by infusion of the remaining (40 mg within 2 h) achieved excellent clinical results with a striking absence of bleeding in patients with moderate PE.[11] In addition, similar to a previous trial on systemic TT, Rothschild et al.[12] demonstrated hazards of 30-day fatality (4.4%) related to the treatment of half-dose systemic TT against acute submassive PE. Based on these promising results, we have recently reported that a prolonged TT regimen with low-dose and slow-infusion of t-PA was associated with lower complication rates without compromising effectiveness in patients with acute intermediate-high risk PE.[8] In 2021, Yilmaz et al. have showed considerable elimination of severe bleeding and excellent clinical results utilizing a half-dose TT approach (50 mg/2 h) in a prospective study.[7]

Hemodynamic Status and Pulmonary Hypertension

A recent study compared UFH alone in 76 patients with acute intermediate-risk PE to further reducing the dose of t-PA to 30 mg.[28] It has been demonstrated that even a dose reduction of this size can lower SPAP from 52 mm Hg to 34.8 in the low-dose group (p<0.01) and from 53.4 mm Hg to 48.5 mm Hg in the UFH group (p=0.11). Despite the fact that there were no occurrences of hemodynamic decompensation in the thrombolytic group compared to three in the UFH group, 30 mg rt-PA was not worse than the UFH group in terms of death and hemodynamic decompensation. Moreover, a recently published prospective study compared the hemodynamic status of low molecular weight heparin (LMWH) and half-dose TT.[7] Although there was no significant difference between low-dose TT and LMWH groups in terms of short-term mortality (3 vs. 10%, p=0.358), hemodynamic decomposition was significantly higher in the LMWH group. In our results revealed that a a strong correlation between treatment strategy and hemodynamic decompensation in intermediate-high risk PE patients (0 vs. 11.9%, p=0.029).

Numerous investigations have demonstrated that low-dose TT reduces SPAP during the 1st week of therapy.[29] With the exception of the MOPETT trial, however, there was no change in SPAP on echocardiography between low-dose TT and heparin anticoagulation over the long term.[11] SPAP values on follow-up echocardiography at the 28th month in the MOPETT trial were statistically higher in patients receiving anticoagulant-only medication than those receiving half-dose t-PA therapy.[11] Similarly, Yilmaz et al. have recently reported that there was no difference between TT and LMWH treatment strategies in terms of pulmonary hypertension outcome (24 vs. 18%, p=0.778).[7] However, the current study showed that the low-dose slow-infusion TT regimen has a lower incidence of pulmonary hypertension and there is a stark correlation between treatment choice and the presence of pulmonary hypertension.

To date, several clinical studies, including randomized clinical trials, have failed to provide a mortality benefit of the low-dose TT regimen in patients with intermediate-high risk PE.[5-7,11,12] In our study, similar to the literature, no significant difference was observed when low-dose slow-infusion TT regimen and UFH treatment were compared in terms of short-term mortality.

Bleeding

Extracranial and cerebral hemorrhage issues were substantially more common in the tenecteplase group than in the placebo plus anticoagulant group in the PEITHO trial.[4] There was no noticeable difference in the incidence of bleeding problems between the rt-PA plus UFH and placebo plus UFH treatments in the MAPPET-3 trial.[30] The risk of major bleeding and intracranial bleeding was shown to be higher in the thrombolytic group in the meta-analysis by Nakamura et al.[31] although this difference was not statistically significant. In the MOPETT trial,[11] no patients who received half-dose t-PA plus anticoagulant or anticoagulation alone experienced substantial bleeding. Hemorrhagic complications were shown to be less prevalent in the half-dose thrombolytic treatment compared to the full dose in a systematic study by Zhang et al.[29] In our study, there was no statistically significant difference in the rate of bleeding complications between the low-dose slow infusion TT regimen and UFH treatment (2.4 vs. 0%, P=0.494). However, severe-life-threatening (n=1) and moderate bleeding (n=1) were seen in the TT group, but not in the UFH group. However, bleeding complications did not cause death. In addition, no intracranial bleeding finding was found in our study. This might be connected to the slow infusion and low-dose thrombolytic treatment.

Ongoing Major Trial

The PEITHO-3 study is a randomized, placebo-controlled, double-blind, multicenter, global trial with long-term follow-up (ClinicalTrials.gov Identifier:NCT04430569).[32] The researchers contrast the safety and effectiveness of reduced-dose alteplase therapy with that of conventional heparin anticoagulation. However, they give a weight-adapted dose of 0.6 mg/kg, up to a total of 50 mg over 15 min. International clinical practice guidelines will probably revise their recommendations to include reperfusion and, in particular, reduced-dose systemic thrombolysis as first-line treatments in this risk class if PEITHO-3's theory is found to be accurate. If the hypothesis is rejected, catheter-directed treatment may become the only option for improving the prognosis of patients with intermediate–high-risk PE.

Limitations of the Study

The limitations that apply to this study's methodology need to be emphasized. First of all, patients were included in the current study who were given the low dose, slow infusion of the TT regimen based on management decisions made by several clinical multidisciplinary teams. Second, there was a small patient population in this retrospective study. Thirdly, it needs to be highlighted that the clinical team's judgments on the TT method are significantly influenced by the risk of bleeding. Finally, the pretty low average HAS-BLED score in the current case series underlines this clinically sensible decision; yet, despite their minimal risk, this systemic TT method was still linked with minor bleeding issues.

Conclusion

A prolonged TT regimen with low dose, slow infusion of t-PA was found to be associated with a lower risk of hemodynamic decompensation and pulmonary hypertension in patients with acute intermediate-high-risk PE compared to standard anticoagulation therapy. These findings show that extending the duration of administration of TT may increase safety without compromising effectiveness. However, larger series of randomized controlled trials are needed to consider this regimen as an acceptable treatment modality.

Ethics Committee Approval: This study was approved by the Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Research Ethics Committee (Date: 15.02.2023, Decision No: 2023-13

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Conflict of Interest: None declared.

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REFERENCES

1. Laporte S, Mismetti P, Decousus H, Uresandi F, Otero R, Lobo JL, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: Findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation 2008;117:1711–6. [CrossRef]
2. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41:543–603. [CrossRef]
3. Piazza G. Advanced management of intermediate-and high-risk pulmonary embolism: JACC focus seminar. J Am Coll Cardiol 2020;76:2117–27. [CrossRef]
4. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402–11. [CrossRef]
5. Layman SN, Guidry TJ, Gillion AR. Low-dose alteplase for the treatment of submassive pulmonary embolism: A case series. J Pharm Pract 2019;33:708–11. [CrossRef]
6. Lozier JN, Elinoff JM, Suffredini AF, Rosing DR, Sidenko S, Sherry RM, et al. Low-dose, short course alteplase treatment of submassive pulmonary embolism: A case series from the National Institutes of Health Clinical Center. Blood Coagul Fibrinolysis 2018;29:701–7. [CrossRef]
7. Yilmaz ES, Uzun O. Low-dose thrombolysis for submassive pulmonary embolism. J Investig Med 2021;69:1439–46. [CrossRef]
8. Güner A, Kalçik M, Aykan AÇ, Gürsoy MO, Kalkan AK, Astarcioğlu MA, et al. Clinical safety and efficacy of thrombolytic therapy with low-dose prolonged infusion of tissue type plasminogen activator in patients with intermediate-high risk pulmonary embolism. Blood Coagul Fibrinolysis 2020;31:536–42. [CrossRef]
9. Güner A, Kahraman S, Ertürk M. Does fibrinolytic strategy of pulmonary embolism international thrombolysis (PEITHO)-3 trial need more strong evidence? Thromb Haemost 2022;122:2050–1. [CrossRef]
10. Güner A, Güner EG, Karakurt S, Kalçık M. Efficacy and safety of low-dose systemic fibrinolytic therapy for acute submassive pulmonary embolism. JACC Cardiovasc Interv 2021;14:809. [CrossRef]
11. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M, "MOPETT" Investigators. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" trial). Am J Cardiol 2013;111:273–7. [CrossRef]
12. Rothschild DP, Goldstein JA, Bowers TR. Low-dose systemic thrombolytic therapy for treatment of submassive pulmonary embolism: Clinical efficacy but attendant hemorrhagic risks. Catheter Cardiovasc Interv 2019;93:506–10. [CrossRef]
13. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. Chest 2010;138:1093–100. [CrossRef]
14. GUSTO İnvestigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673–82. [CrossRef]
15. Feigenbaum H, Armstrong WF, Ryan T. Hemodynamics. In: Feigenbaum's Echocardiography. Philadelphia, PA: Lippincott Williams and Wilkins; 2005. p. 231.
16. Noordegraaf AV, Chin KM, Haddad F, Hassoun PM, Hemnes AR, Hopkins SR, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: An update. Eur Respir J 2019;53:1801900. [CrossRef]
17. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G,

et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: An expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2017;18:1301–10. [CrossRef]

18. Schoepf UJ, Kucher N, Kipfmueller F, Quiroz R, Costello P, Goldhaber SZ. Right ventricular enlargement on chest computed tomography: A predictor of early death in acute pulmonary embolism. Circulation 2004;110:3276–80. [CrossRef]
19. Guner A, Kalcik M, Gursoy MO, Gunduz S, Ozkan M. How to perform and manage low-dose and slow/ultra-slow tissue type plasminogen activator infusion regimens in patients with prosthetic valve thrombosis. J Thromb Thrombolysis 2018;46:399–402. [CrossRef]
20. Wang C, Zhai Z, Yang Y, Wu Q, Cheng Z, Liang L, et al. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: A randomized, multicenter, controlled trial. Chest 2010;137:254–62. [CrossRef]
21. Zhao T, Ni J, Hu X, Wang Y, Du X. The efficacy and safety of intermittent low-dose urokinase thrombolysis for the treatment of senile acute intermediate-high-risk pulmonary embolism: A pilot trial. Clin Appl Thromb Hemost 2018;24:1067–72. [CrossRef]
22. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W, Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002;347:1143–50. [CrossRef]
23. Kaymaz C, Akbal OY, Tanboga IH, Hakgor A, Yilmaz F, Ozturk S, et al. Ultrasound-assisted catheter-directed thrombolysis in high-risk and intermediate-high-risk pulmonary embolism: A meta-analysis. Curr Vasc Pharmacol 2018;16:179–89. [CrossRef]
24. Kaymaz C, Öztürk S, Akbal Ö, Tanboğa IH, Yılmaz F, Poçi N, et al. Ultrasound-assisted catheter-directed thrombolysis in high-risk and intermediate-high-risk pulmonary embolism: Results from a single-center cohort. Angiology 2017;68:433–40. [CrossRef]
25. Kucher N, Boekstegers P, Müller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014;129:479–86. [CrossRef]
26. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: The SEATTLE II study. JACC Cardiovasc Interv 2015;8:1382–92. [CrossRef]
27. Kaymaz C, Akbal OY, Hakgor A, Tokgoz HC, Karagoz A, Tanboga IH, et al. A five-year, single-centre experience on ultrasound-assisted, catheter-directed thrombolysis in patients with pulmonary embolism at high risk and intermediate to high risk. EuroIntervention 2018;14:1136–43. [CrossRef]
28. Zhang LY, Gao BA, Jin Z, Xiang GM, Gong Z, Zhang TT, et al. Clinical efficacy of low dose recombinant tissue-type plasminogen activator for the treatment of acute intermediate-risk pulmonary embolism. Saudi Med J 2018;39:1090–5. [CrossRef]
29. Zhang Z, Zhai ZG, Liang LR, Liu FF, Yang YH, Wang C. Lower dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: A systematic review and meta-analysis. Thromb Res 2014;133:357–63. [CrossRef]
30. Becattini C, Agnelli G, Salvi A, Grifoni S, Pancaldi LG, Enea I, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res 2010;125:e82–6. [CrossRef]
31. Nakamura S, Takano H, Kubota Y, Shimizu W. Impact of the efficacy of thrombolytic therapy on the mortality of patients with acute submassive pulmonary embolism: A meta-analysis. J Thromb Haemost 2014;12:1086–95. [CrossRef]
32. Sanchez O, Charles-Nelson A, Ageno W, Barco S, Binder H, Chatellier G, et al. Reduced-dose intravenous thrombolysis for acute intermediate-high-risk pulmonary embolism: Rationale and design of the pulmonary embolism international thrombolysis (PEITHO)-3 trial. Thromb Haemost 2022;122:857–66. [CrossRef]

ORİJİNAL ÇALIŞMA - *ÖZ*

Orta yüksek riskli pulmoner emboli hastalarında düşük doz trombolitik tedaviye karşı fraksiyone olmayan heparin

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AMAÇ: Akut sağ ventrikül disfonksiyonu ve belirgin hemodinamik bozulma olmaksızın miyokardiyal hasarı olan orta-yüksek riskli pulmoner emboli (PE) hastaları trombolitik tedavi (TT) için aday olabilir. Bu çalışmada orta-yüksek riskli PE hastalarında düşük doz uzamış TT ve fraksiyone olmayan heparinin (FOH) klinik sonuçlarını karşılaştırmayı amaçladık.

GEREÇ VE YÖNTEM: Bu çalışmaya 83 [kadın: 45 (%54.2), ortalama yaş: 70.07±10.7 yıl] dahil edilen akut PE tanılı, düşük doz ve yavaş infüzyon TT veya FOH ile tedavi edilen hasta retrospektif olarak değerlendirildi. Çalışmanın birincil sonuçları, herhangi bir nedenden ölüm ve hemodinamik dekompansasyon ve şiddetli veya yaşamı tehdit eden kanama kombinasyonu olarak tanımlandı. İkincil son noktalar, tekrarlayan PE, pulmoner hipertansiyon ve orta derecede kanama idi.

BULGULAR: Orta-yüksek riskli PE'nin başlangıç tedavi stratejisi 41 (%49.4) hastada TT ve 42 (%50.6) hastada FOH idi. Düşük doz uzamış TT tüm hastalarda başarılı oldu. Hipotansiyon sıklığı TT sonrası anlamlı olarak azalırken (%22'ye karşı %0, p<0.001), FOH tedavi sonrası azalmadı (%2.4'e karşı %7.1, p=0.625). Hemodinamik dekompansasyon oranı TT grubunda anlamlı olarak daha düşüktü (%0'a karşı %11.9, p=0.029). İkincil son nokta oranı FOH grubunda anlamlı olarak daha yüksekti (%2.4'e karşı %19, p=0.016). Ayrıca pulmoner hipertansiyon prevalansı FOH grubunda anlamlı olarak yüksekti (%0'a karşı %19, p=0.003).

TARTIŞMA: Düşük doz, yavaş t-PA infüzyonu ile uzun süreli TT rejiminin, akut orta-yüksek riskli PE'li hastalarda FOH'ye kıyasla daha düşük hemodinamik dekompansasyon ve pulmoner hipertansiyon riski ile ilişkili olduğu bulundu.

Anahtar sözcükler: Trombolitik tedavi; pulmoner emboli; heparin; kanama; ölüm.

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