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Evaluation of patients diagnosed with intermediate -high risk pulmonary thromboembolism

Sedat Çiçek, Fatih Üzer, Tülay Özdemir

Department of Chest Diseases, Faculty of Medicine, Akdeniz University, Antalya, Türkiye

ABSTRACT

Aims: In this study we aimed to share our treatment approach in patients with intermediate -high risk pulmonary embolism (PE).

Methods: This is a single center retrospective observational study. Patients diagnosed with PE at Akdeniz University Hospital between January 1, 2015, and January 1, 2021, were retrospectively analyzed. Patients whose diagnosis of PE was confirmed by computed tomography angiography (CTA) or perfusion/ventilation scintigraphy were considered to have PE. Patients with intermediate-high risk were included in the study. Patients with a diagnosis of low-risk, low-intermediate risk, high-risk PE, patients younger than 18 years of age, and pregnant were excluded from the study.

Results: A total of 150 patients, 64 (42.7%) male and 86 (57.3%) female, with a mean age of 62.2±16.2 years, who met the criteria of these patients were included. 22.7% (34) of the patients received thrombolytic therapy. While 67.7% (23) of the patients who received thrombolytic therapy received half-dose (50mg rt-PA) thrombolytic therapy, 32.3% (11) received full-dose (100 mg rt-PA) thrombolytic therapy. Major hemorrhage (3 intracranial hemorrhages, 1 femoral hemorrhage) was detected in 11.7% (4) of the patients who received thrombolytic therapy.

Conclusion: No significant effect of thrombolytic therapy or full or half dose on mortality was found in the intermediate -high risk group.

Keywords: Pulmonary embolism, thrombolytic, intermediate-high risk

INTRODUCTION

Pulmonary thromboembolism (PE) is a common cause of cardiovascular mortality nowadays, with an increasing incidence and decreasing mortality rate. It usually occurs as a complication of deep vein thrombosis (DVT).[1] In PE, a series of pathophysiological events are triggered by the placement of the thrombus in the lungs. The number and diameter of occluded vessels, the size of the embolism, the patient's cardiopulmonary reserve, reflex vasoconstriction due to pulmonary artery dilatation, inflammatory mediators, serotonin released from platelets, thromboxane, and vasoconstriction due to fibrinogen degradation product fibrinopeptid B trigger a series of pathophysiological events in PE. These pathophysiological events present three different tables to us in the clinic; massive (high risk), sub-massive (intermediate risk), and non-massive (low risk). In the guideline published by the European Society of Cardiology (ESC) in 2019, the intermediate-risk group is divided into high-intermediate risk and low-intermediate risk.[1] High-risk PE has acute right ventricular failure accompanied by hypotension, shock, or cardiopulmonary arrest. Patients with syncope, severe hypoxemia, cardiac arrest, or who are undergoing cardiopulmonary resuscitation should be evaluated for high-risk PE. In patients with intermediate -risk PE, there are signs of right ventricular dysfunction (dilatation and hypokinesia) detected on echocardiography despite normal systemic blood pressure. In low-risk PE, systemic blood pressure and right ventricular functions are found to be normal. This classification is important in terms of complicated clinical course, mortality risk, and determination of treatment approach.

According to the prognostic assessment strategy, patients who are hemodynamically unstable due to shock or hypotension go directly into the high-risk group. When PE is proven, direct reperfusion therapy is administered. Further risk assessment should be performed after diagnosis in patients without hypotension or shock. Low and intermediate-risk patients are identified with PESI or sPESI tests. Patients with PESI Class I-II or sPESI=0 are considered low risk, and patients with PESI Class III-IV or sPESI ≥ 1 are considered intermediate risk. Among intermediate -risk patients, those with right ventricular dysfunction and positive cardiac biomarkers are in the high-risk group. It is recommended that this group, which has a

Corresponding Author: Fatih Üzer, uzerfatih@gmail.com

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intermediate-high risk for an early poor prognosis, be closely monitored under anticoagulants, and rescue reperfusion therapy should be applied when signs of hemodynamic impairment are detected. We do not have sufficient studies on the effect of full-dose or half-dose thrombolytic therapy on mortality and morbidity in the intermediate -high-risk group. In the largest study on this subject, it was stated that the application of thrombolytic therapy in the intermediate -high risk group prevented hemodynamic decompensation but increased intracranial hemorrhage.[2] Clinicians may hesitate to apply full-dose thrombolytic therapy due to the fear of major bleeding risk and seek alternative treatments to reduce bleeding risk.[3] Our study was carried out to share our treatment approach with intermediate -high risk PE patients who have question marks in terms of treatment.

METHODS

This study was approved by the Ethics Committee of the Akdeniz University School of Medicine (Date: 09.11.2022, Decision No: KAEK-665). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This is a single center retrospective observational study. Patients diagnosed with PE at Akdeniz University Hospital between January 1, 2015, and January 1, 2021, were retrospectively analyzed. I26, I26.0, and I26.9 ICD codes were scanned from the hospital automation system, and patients who were examined for PE were identified. Patients whose diagnosis of PE was confirmed by computed tomography angiography (CTA) or perfusion/ventilation scintigraphy were considered to have PE. Patients with intermediate-high risk (PESI (Pulmonary Embolism Severity Index) Class III-IV or sPESI (simplified PESI) ≥1 according to the 2019 European Society of Cardiology Guidelines and those with positive right ventricular dysfunction and cardiac biomarkers) were included in the study.[1] Patients with a diagnosis of low-risk, low-intermediate risk, high-risk PE, patients younger than 18 years of age, and pregnant were excluded from the study.

Symptoms, sociodemographic data, comorbidities, and radiological findings leading to the diagnosis of PE were recorded in the data form. Echocardiographic findings performed in the emergency room or as soon as possible after hospitalization were noted. The unit where the patients were hospitalized (chest disease service or intensive care), the treatments they received for pulmonary embolism, the number of days they spent in the hospital, and their in-hospital mortality were examined. Thrombolytic treatment was administered as a full dose (100 mg/2 hour TPA) or half dose (50 mg/2 hour TPA).

Statistical Analysis

Statistical analyzes of the data were run using the SPSS 19.0 program. Categorical variables were defined as frequency and percentage, and continuous variables as mean and standard deviation. The conformity of the data to the normal distributions was evaluated with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare the medians of the paired groups that did not fit the normal distribution, and the chi-square significance test was used for the analysis of categorical variables. The relationship of continuous variables with each other was evaluated with the Spearman Correlation test. The statistical significance level was accepted as 0.05 in the study.

RESULTS

A total of 13100 patients were examined with a preliminary diagnosis of PE at Akdeniz University during the study. A total of 150 patients, 64 (42.7%) male and 86 (57.3%) female, with a mean age of 62.2±16.2 years, who met the criteria of these patients were included. 22.7% (34) of the patients received thrombolytic therapy. While 67.7% (23) of the patients who received thrombolytic therapy received half-dose (50 mg rt-PA) thrombolytic therapy, 32.3% (11) received full-dose (100 mg rt-PA) thrombolytic therapy. Major hemorrhage (3 intracranial hemorrhages, 1 femoral hemorrhage) was observed in 11.7% (4) of the patients who received thrombolytic therapy. The most common comorbid disease was hypertension (n=43, 28.7%), while 21.3% (32) of the patients had a history of malignancy. The basic characteristics of the patients are given in Table 1.

Table 1. General features of the patients

Feature	n (%)
Gender	
Female	86 (57.3)
Male	64 42.7)
Treatment	
Thrombolytic	34 (22.7)
LMWH	116 (77.3)
Comorbidity	
Hypertension	43 (28.7)
Diabetes mellitus	33 (22.0)
Coronary artery disease	10 (6.7)
Malignancy	32 (21.3)
Chronic lung disease	16 (10.7)
Atrial fibrillation	6 (4.0)
PE risk factor +	46 (30.7)
Immobilization	9 (6.0)
PE history	6 (4.0)
Symptom	
Shortness of breath	82 (54.7)
Chest Pain	30 (20.0)
Syncope	32 (21.3)
Other	6 (4.0)
Mortality	
30 day	28 (18.7)
Need for intensive care	
Need for intensive care	71 (47.3)

PE: pulmonary embolism, LMWH: low molecular weight heparin

Right heart cavities were found to be wide in all of the patients who received thrombolytic therapy, and the mean pulmonary artery pressure (PAP) was 57.7±10.1 in these patients. Transthoracic echocardiography (TTE) findings of patients receiving thrombolytic therapy before and after thrombolytic therapy are given in Table 2.

Table 2. Echocardiography findings

	Pre- treatment		Pos-treatment	
	Half-dose thrombolytic	Full-dose thrombolytic	Half-dose thrombolytic	Full-dose thrombolytic
Right gap width	23 (100)	11 (100)	2 (11.1)	1 (14.3)
D-septum	9 (39.1)	9 (81.8)	n.d.	n.d.
PAP	57.7±10.1	n.d.	39.5±12.8	38.7±8.5
TV velocity	3.5±0.3	3.6±0.4	2.6±0.5	2.6±0.4

PAP: pulmonary artery pressure, TV: Tricuspid regurgitation, n.d.: no data

When the full thrombolytic treatment dose (100 mg tPA) and half dose (50 mg tPA) were compared, the probability of D-septum before the treatment was found to be statistically significantly higher in the group that received the full dose of thrombolytics (p:0.030). There was no statistically significant difference between the groups in terms of other clinical and prognostic factors. The comparison of patients receiving full-dose thrombolytic therapy with patients receiving half-dose thrombolytic therapy is given in **Table 3**. According to the results of logistic regression test, after controlling the age and gender of the patients, taking thrombolytic therapy was not found to be a factor in increasing the chance of survival within 30 days (p=0.82). Thrombolytic therapy had no significant effect on TTE findings in subjects with wide right cavities at the beginning of treatment (p=0.24). When the patients who received thrombolytic (full dose+half dose) treatment compared with low molecular weight heparin (LMWH), the incidence of D-septum (p: 0.006) and intensive care unit admission rate (p <0.001) were significantly higher in the group receiving thrombolytic therapy. Moreover, the duration of hospitalization in the intensive care unit (p<0.001) was higher in the group receiving LMWH. A detailed comparison of patients receiving LMWH and patients receiving thrombolytic therapy is given in **Table 4**.

DISCUSSION

In this study, in which we investigated the efficacy of thrombolytic therapy in patients with intermediate-high risk pulmonary embolism, no statistically significant difference was found in the mortality, length of stay in the intensive care unit, and cardiac decompensation effects of full-dose and half-dose r-tPA administration. When the patients who received LMWH treatment and those who received thrombolytic treatment were compared, it was found that the group that received thrombolytic treatment had a higher rate of hospitalization in the intensive care unit, while the group that received LMWH treatment stayed in the intensive care unit longer.

Hospital mortality due to PE has been reported at 7%, and hemodynamically unstable patients at 33%.[4] Systemic thrombolytic therapy has been shown to prevent hemodynamic collapse and reduce mortality due to progressive right heart failure in patients with moderate to high risk.[5] In the PEITHO study,[2] systemic fibrinolytic therapy was shown to prevent cardiac collapse compared with LMWH. However, an increased risk of intracranial hemorrhage has been demonstrated. In addition, in the TOPCOAT study,[6] in which systemic thrombolytic treatment and LMWH treatment were compared in patients with sub-massive PE, it was found that thrombolytic

Table 3. Comparison of full dose and half dose of thrombolytic therapy

		Half-dose (n=23)	Full-dose (n=11)	p
Gender n(%)	Female	12 (52.2)	7 (63.6)	0.715
Age (mean±ss)		60.7±16.7	64.1±12.9	0.553
Comorbidity n(%)	+	21 (91.3)	9 (81.8)	0.580
PE risk factor n(%)	+	5 (21.7)	4 (36.4)	0.425
Echocardiography (pre treatment)	Right Width n(%)	23 (100)	11 (100)	1.000
	D-septum n(%)	9 (39.1)	9 (81.8)	0.030
	PAP (mean ±ss)	57.7±10.1	-	n.d.
	Tricuspid insufficiency velocity (mean±ss)	3.5±0.3	3.6±0.4	n.d.
Intensive care unite n(%)		20 (87.0)	10 (90.9)	1.000
Major bleeding		1 (4.4)	2 (18.2)	n.d.
Mortality n(%)		4 (17.4)	2 (18.2)	n.d.
Echocardiography (post- treatment)	Right gap width n (%)	2 (11.1)	1 (14.3)	n.d.
	PAP (mean ±ss)	39.5±12.8	38.7±8.5	0.945
	Tricuspid insufficiency velocity (mean±ss)	2.6±0.5	2.6±0.4	0.872
Intensive care hospital stay/day (mean±ss)		2.8 ±2.4	2.6±1.4	0.795

i.d: insufficient data, PAP: pulmonary artery pressure

Table 4. Comparison of low molecular weight heparin and systemic thrombolytic therapies

		LMWH (n=116)	Thrombolytic (n=34)	p
Gender n(%)	Female	67 (57.8)	19 (55.9)	0.847
Age (mean ±ss)		62.3±16.5	61.8±15.4	0.866
Comorbidity n(%)	+	104 (89.7)	30 (88.2)	0.760
PE risk factor n(%)	+	37 (31.9)	9 (26.5)	0.673
Echocardiography (pre treatment)	Right width n(%)	108 (93.1)	34 (100)	0.199
	D-septum n(%)	30 (25.9)	18 (52.9)	0.006
	PAP (mean ±ss)	51.6±23.5	57.7±10.1	0.588
	Tricuspid insufficiency velocity (mean±ss)	3.3±0.6	3.5±0.3	0.384
Troponin n(%)	Positive	107 (92.2)	34(100)	0.210
Intensive care hospitalization n(%)		41 (35.3)	30 (88.2)	<0.001
Mortality n(%)		22 (19.1)	6 (17.6)	1.000
Echocardiography (post- treatment)	Right gap width	17 (21.3)	3 (12.0)	0.391
	D-septum	8 (10.0)	0	-
	PAP (mean±ss)	42.4±14.1	39.3±11.6	0.323
	Tricuspid insufficiency velocity (mean±ss)	2.7±0.5	2.6±0.4	0.316
Intensive care hospital stay/day (mean±ss)		6.2 ±4.0	2.8±2.1	<0.001

PAP: pulmonary artery pressure

treatment had a positive effect on 3-month cardiac outcomes, reduced dyspnea, but its effect on mortality was not different from LMWH treatment. In our study, 22.7% of the patients diagnosed with intermediate-high risk PE were treated with thrombolytic therapy. Early mortality was found to be 18.7%. Compared with LMWH, the effect of thrombolytic therapy on 30-day mortality was not different from the LMWH-treated group, but the duration of stay in the ICU was higher in the LMWH-treated group.

The role of full-dose thrombolytic therapy in high-risk patients has been well defined in many studies and emphasized in many guidelines. However, there is insufficient evidence for half-dose thrombolytic therapy.[7] In the study by Kiser et al.[8] 50 mg r-tPA treatment was compared with 100 mg r-tPA treatment, and 50 mg r-tPA was associated with treatment escalation, but no significant difference was found between treatments in terms of mortality and major bleeding risk. In another study comparing full-dose and half-dose thrombolytic therapy given with the aid of ultrasound-guided catheter in sub-massive and massive PE, it was shown that half-dose therapy improved right ventricular functions, decreased pulmonary artery pressure, and did not cause intracranial bleeding.[3] In our study, although we did not have enough patients to evaluate mortality and major bleeding between doses, no statistically significant difference was found between the treatment doses in the time spent in the intensive care unit.

If the patients diagnosed with PE are in the high-risk group, it is recommended to be monitored in the intensive care unit. It is recommended to decide where to follow the patients in the intermediate-high risk group according to the patient's clinic. It has been stated that if the patient has hypotension, tachycardia, tachypnea, and increased oxygen demand, intensive care monitoring may be necessary.[9] In our study, 47.3% of the patients were monitored in the intensive care unit. As LMWH and patients who were started on thrombolytic therapy were compared, the patients having thrombolytic therapy were admitted to the intensive care unit at a higher rate, and the full dose or half dose of thrombolytic therapy did not affect the length of stay in the intensive care unit.

Our study has some limitations. These can be regarded as the small number of patients, the single-center study, and the absence of monitoring echocardiograms of all patients after treatment.

CONCLUSION

No significant effect of thrombolytic therapy or full or half dose on mortality and long-term TTE findings was found in the intermediate -high risk group. In addition, no significant difference was found between the treatments in terms of major side effects.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Ethics Committee of the Akdeniz University School of Medicine (Date: 09.11.2022, Decision No: KAEK-665).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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