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Optional therapeutic management of intermediate-risk pulmonary embolism patients

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Abstract

Background: Few studies have evaluated the thrombolytic treatment in patients with intermediate-high risk pulmonary embolism, making this study more valuable.
Material and methods: It was a prospective, non-randomized, open-label, single-center study. Eligible patients at the age of 18 or older with an acute pulmonary embolism (PE) confirmed by CT pulmonary angiography with onset until 14 day and signs of right ventricular (RV) overload on echocardiography took part in the study. Pulmonary Arterial CT Obstruction Index Rate (PACTOIR) was used to define the localization and the expansion zone of thromboembolism. This study included 18 patients with intermediate risk and acute submassive pulmonary thromboembolism. In thrombolysis (TT) group (n=9) were used 50 mg of tissue-plasminogen activator (t-PA) administered in infusion as 0.4 mg/h for 2 hours. In the standard anticoagulation group, unfractioned heparin (UFH) was administered as a bolus of 70 units/kg or a maximum of 5000 units, followed by continuous infusion at an initial rate of 16 units/kg or a maximum of 1000 units/h.
Results: The mean age for TT group was 69 vs 63 for the UFH group. PACTOIR was 100% in 3 patients in the half-dose rt-PA group and in 2 patients in the UFH group. RV/LV diameter ratio decreased from baseline to 48 h post-procedure (1.55 vs. 1.13; mean difference, -0.42; $p < 0.0001$). Mean pulmonary artery systolic pressure was 55 mm Hg in both groups ($p < 0.05$), with 53 [43–60] in TT group vs. 41.5 [37–45] mmHg in UFH group, $P<0.05$. Also, RV/LV ratio and systolic PAP decreased significantly in both groups. Severe bleeding with a need in red blood cell transfusion was seen in 0.11% (1 patient) in the TT group vs 0 in UFH group. The hospitalization length of stay was significantly shorter in the TT group (3.8±1.8, $p < 0.05$). The rate of secondary endpoints was significantly higher in the UFH group with a high rate of pulmonary hypertension (0 vs. 19%, p=0.003).
Conclusions: Half-dose thrombolytic therapy in patients diagnosed with submassive pulmonary embolism significantly reduced death and hemodynamic decompensation in the first 7 days compared to anticoagulant therapy only. With all that being said, it can be concluded that patients with high-intermediate risk PE could benefit from reduced-dose TT.
Key words: pulmonary embolism, intermediate risk, submassive pulmonary embolism.

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Introduction

Acute pulmonary embolism (PE) is a life-threatening disease that usually is a serious complication of venous thromboembolism [1]. Life risk stratification in PE (high risk, intermediate risk, and low risk) is based on clinical presentation and on markers of myocardial dysfunction and/or injury.

In hospitalized patients there is significant mortality rate, with 3-8 % in intermediate risk (a submassive PE) and 25-52% in patients with high-risk pulmonary embolism (massive PE) [2-4]. Patients who survive PE, after hospital discharge, they may develop chronic thromboembolic pulmonary hypertension with functional impairment [5-7].

Thrombolytic therapy is an established treatment option for patients with high-risk pulmonary embolism [8, 9]. However, the use of thrombolytic therapy in patients with intermediate-risk pulmonary embolism is controversial because of the lack of sufficient information about its benefits and risks [2, 9-13]. This group of patients requires special interest because the in-hospital mortality can reach up to 30% [14, 15].

In the PEITHO trial was observed an increased incidence of hemorrhagic stroke and major non-intracranial bleeding, in the thrombolytic group [16]. The aim of this trial was to determine the controversial issue in intermediate-risk pulmonary embolism. Unfortunately, the question of the applicability of thrombolysis in submassive PE was not established.

Most of the evidence supporting the use of thrombolytic therapy for intermediate-risk pulmonary embolism

focuses on minimizing the treatment and helping to return at normal functional status with reduced risk of residual pulmonary hypertension. Three-year follow-up data from the PEITHO study showed no long-term mortality benefit or difference in the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) in either group [2, 5, 10, 11]. The clinical benefits of thrombolytic therapy are less significant than the one of high-risk PE, as 2% and 6% risk of cerebral hemorrhage and major bleeding respectively is higher than in another group [10]. Knowing that the pulmonary vasculature receives the majority of any intravenous thrombolytic dose, it has been suggested that lower-dose thrombolytics may provide sufficient efficacy while reducing the risk of major bleeding [5, 17-20]. This hypothesis is supported by recent evidence suggesting that the use of half the usual dose of alteplase in pulmonary embolism may be effective, with a reduced risk of bleeding [5, 18, 19]. In order to study the usefulness of thrombolysis in PE with high intermediate risk (submassive), was compared treatment approach with half-dose thrombolysis and monotherapy with unfractionated heparin (UFH).

The aim of the study is to evaluate the efficacy and safety of half-dose alteplase versus UFH alone (standard therapy) for the treatment of intermediate-risk acute PE.

Material and methods

Study design

It was a prospective, non-randomized, open-label, single-center study conducted between January 2020 and December 2022. The study included 18 patients diagnosed with submassive acute pulmonary thromboembolism (with intermediate thromboembolic risk). The patients included in the thrombolysis group received half-dose of tissue plasminogen activator (rt-PA) – alteplase. All patients in this group presented a written consent for this procedure. The standard therapy group included patients who refused thrombolysis with acute PE at intermediate risk with similar clinical profile. They received unfractionated heparin according to the scheme. Finally, 9 patients were taken into the half-dose rt-PA group and 9 patients into the UFH group.

Studied population

Inclusion criteria:

– Age 18 or older.

– Acute PE confirmed by pulmonary CT angiography (CTPA) with early onset (maximum 14 days old PE)

– Signs of RV overload: Confirmed pulmonary hypertension (pressure in the pulmonary artery above 40 mm Hg) on echocardiography (ECHOCG) and/or expansion of the right ventricular cavity (end-diastolic diameter of the right ventricle > 30 mm); deviation of the interventricular septum; hypokinesis of the right ventricular free wall; LV/RV ratio ≥ 0.9 mm on CTPA or ECHOCG.

Exclusion criteria:

– Hypotension (Systolic blood pressure <90 mm Hg) or shock.

– Known risk of bleeding.

– Ischemic stroke <3 months.

– The presence of uncontrolled hypertension (Systolic >180 mm Hg and/or diastolic >110 mm Hg).

– Known hypersensitivity to thrombolytic therapy or UFH (including previous HIT).

– Known coagulopathy and vitamin K antagonist treatment, ACOD or platelet count below 100000/mm^3.

– Recent major surgery (<1 week).

Treatment scheme

For the half-dose thrombolysis group: 50 mg of rt-PA was infused for 2 hours, checking the activated partial thromboplastin time (APTT) immediately and after 4 hours. When APTT became less than twice the control value, the UFH therapy was initiated during at least next 24 hours.

In the standard anticoagulation group, UFH was administered as a bolus of 70 units/kg or a maximum of 5000 units, followed by continuous infusion at an initial rate of 16 units/kg or a maximum of 1000 units/h. Every 6 hours the APTT was evaluated, adjusting the dose based on the result received (the target being 60 to 70 s). In rare situations, when the APTT became <50 s, an intermittent mini-bolus of UFH (16 units/kg or maximum 1000 units) of UFH was associated along with a dose adjustment (2 units/kg/h infusion). In case of a longer APTT, more than 80 s, UFH was stopped for 30 to 60 minutes and the dose was adjusted.

All patients continued treatment with warfarin and enoxaparin simultaneously, as standard coagulation scheme requires. When target INR was achieved (>2.0) and was maintained for at least 24 hours, the UFH or enoxaparin was suspended. The treatment with warfarin or DOAC was continued for at least 3 months.

Efficacy

The treatment efficacy was the primary outcome assessed in this study. It is defined as the lack of need in vasopressors, secondary thrombolysis, assisted ventilation, or cardiopulmonary resuscitation, occurring within the first 24 hours after administration of alteplase [3]. Secondary efficacy outcomes included in-hospital mortality, readmission for pulmonary embolism, ICU length of stay, length of hospital stay, and total hospital costs. Safety outcomes were considered major bleeding: a documented cerebral hemorrhage, gastrointestinal bleeding, acute anemia with blood loss, including the need to transfuse red blood cell mass, or aminocaproic acid/ tranexamic acid after the alteplase infusing.

Hemodynamic decompensation (or collapse) was defined as sustained hypotension (i. e., Systolic blood pressure <90 mmHg) that involves the need of initiation of vasopressors/inotropes within 48 hours of ICU admission. Vasopressors/inotropes included norepinephrine, phenylephrine, vasopressin, epinephrine, dopamine, dobutamine and milrinone, including drop in Systolic blood pressure of at least 40 mm Hg in 15 min with signs of end-organ hypoperfusion (cold extremities or low urine output <30 ml /hour) or mental confusion.

In this prospective study were evaluated patients' sociodemographic characteristics, such as age, sex, symptoms, risk factors, vital signs, electrocardiography results and blood gas values, D-dimer and cardiac biomarker (troponin and NT proBNP). The cut-off value for D-dimer was taken as 500 μg/L for those under 50 years age and × 10 μg/L for those over 50 years [21]. The cut-off value for troponin was 0.14 μg/mL [22].

The pretreatment risk assessment test as pulmonary embolism severity index was used to determine the intermediate-low and intermediate-high risk groups. The HASBLED score calculated patients' bleeding risk (hypertension, abnormal kidney or liver function, stroke, bleeding, labile international normalized ratio, age >85 years, using drugs and/or alcohol): 0 = low risk, 1 to 2 = moderate risk, >2 = high risk [23].

As diagnostic tools were used the chest radiography, perfusion scintigraphy, compression ultrasonography of the lower extremities, echocardiography and CTPA. The gold standard – CTPA showed partial or complete vessel occlusion by locating the filling defect in the lobar and segmental branches of the right and left main pulmonary arteries. Pulmonary Arterial Obstruction CT Index (PACTOI) and Pulmonary Arterial Obstruction CT Index Rate (PACTOIR) were calculated using these data [24]. After studying related articles, PACTOI and PACTOIR were calculated:

$$\mathbf{PACTOI=n\times d}$$

$$\mathbf{PACTOIR=PACTOI\times 100/maximum\ total\ score}$$

where **n** is the number of segmental branches in the distal field (1–20) and **d** is the degree of obstruction: 0 (none), 1 (partial), and 2 (complete).

Transthoracic echocardiography (TTE) was performed within the first 2 hours of hospital admission, before t-PA administration, and was repeated at 12–24 hours. The pressure in AD was assessed and classified as 10, 15, and 18 mmHg for mild, moderate, and severe right atrial enlargement, respectively. Systolic pulmonary artery pressure (SPAP) was calculated using the velocity of the tricuspid valve regurgitation jet according to the modified Bernoulli equation [25, 26].

In the simplified Bernoulli equation for measuring pulmonary artery Systolic pressure (PASP), tricuspid regurgitation jet flow and right atrial pressure were used, with systolic PAP calculated using the following formula:

$$\mathbf{PASP = [4\times(tricuspid\ regurgitation\ jet)^2] + AD\ pressure}$$

An M-mode cursor was placed over the lateral tricuspid annulus to measure the longitudinal motion of the annulus at peak systole in the typical apical 4-chamber view. This information was used to determine the systolic excursion of the tricuspid annular plane. The Simpson method was used to determine the left ventricular ejection fraction [27]. A cardiologist not involved in the treatment scheme interpreted the echocardiographic results. Pulmonary hypertension was defined as systolic PAP with a value superior of 40 mmHg. A RV-to-left ventricular (RV/LV) ratio > 0.9 was considered to indicate RV hypertrophy [25-26]. A retrospective analysis was done on the recorded images taken at the time of diagnosis and after TT or heparin. Methods for measuring the RV/LV ratio were developed according to previous definitions [28-30].

Control CTPA and echocardiography were performed to examine residual and/or chronic organized thrombus in the pulmonary arteries and pulmonary hypertension at 6 months.

Follow-up

After discharge, patients were contacted and underwent reexaminations at 3 months. At recall patients underwent ETT and CT investigations to assess systolic PAP, RV size and functional capacity. The follow-up was made retrospectively by review of medical records or by phone call (confirmation of medical record events) and an assessment of any clinical event.

Statistics

The data obtained from the study were analyzed in the SPSS V.15.0 program. While data were evaluated, continuous variables were expressed as mean ± SD, median, and lowest–highest values, and census data were expressed as numbers and percentages. In statistical analysis, the conformity of continuous variables to normal distribution was assessed with the "Kolmogorov-Smirnov Test". When the continuous variables obtained in the study did not follow the normal distribution, they were given the highest and lowest values with the median values, instead of the mean and SD. The Mann-Whitney U test was used in groups that did not follow normal distribution in comparing of arithmetic means of continuous variables. The Pearson $\chi 2$ test was used to compare categorical data. A p-value of 0.05 was accepted as the limit of statistical significance.

Results

The study included eighteen patients. The mean age of half-dose thrombolysis group was 69 years, which was comparable to the age of those in the UFH group, which was 63 years. Five of them (55%) were females and 4 (45%) were males. Patients over 75 years of age constituted 33% (n=6) of all patients. Chronic lung disease was present in 2 (11%) patients and chronic heart disease in 4 (22%). Patients with a body mass index over 30 constituted 33% of all. Four patients (22%) were smokers.

Dyspnea was observed in almost all patients (94.5%), while the second most common symptom was chest pain, which was present in 55% of patients in the half-dose thrombolytic group and 67% in the UFH. A smaller proportion of patients experienced tachypnea (37.3%), syncope (12%) and chest pain (9.6%). Although 14.4% of patients were on antiplatelet therapy, the HASBLED score was 1 in 53% of patients. No patient had a score greater than 2. Arterial pressure was decreased in 2 (11%) patients without any hemodynamic decompensation. The rate of hypotension was significantly higher in the TT group than in the UFH (4 (44%) vs. 2 (22%), p=0.07). Symptoms presented in two groups had a similar range (tab. 1).

Table 1. Clinical characteristics of studied patients in both groups

	TT (n=9)	UFH (n=9)	P value
Age	69±14	63±16	0.085
Gender, n (%)			0.107
Masculin	5 (55)	3 (33)	
Feminin	4 (45)	6 (67)	
SBP (mm Hg)	126±23	124±17	0.9
DBP (mm Hg)	77±13	80±11	0.758
Breathing (per minute)	26±2.9	24±3.2	0.6
Oxygen level in breathing air	88±4.8	91±4.8	0.19
Pa O_2 (mm Hg)	62±5.8	70±6.2	0.32
Troponins (g/mL)	2.60±0.4	2.48±0.4	0.685
NT – proBNP	986±120	783±230	0.78
Risk factors, n (%)			
Imobilisation	3 (33)	2 (22)	0.338
Malignancy	2 (22)	1 (11)	0.560
Previous DVT	2 (22)	1 (11)	0.564
Previous PE	1 (11)	1 (11)	1.000
BMI (kg/m^2)	28 (25.73–32.0)	26.95 (25.32–29.9)	0.365
Obesity (BMI >30 kg/m^2)	2 (22)	1 (11)	0.329
Arterial hypertention	6 (66)	5 (55)	0.518
Diabetus mellitus	2 (22.0)	3 (33.3)	0.247
COPD	2 (22)	0	0.335
Surgical procedure (in the last 45 days)	1 (11)	2 (22)	0.787
Trauma (in the last 45 days)	1 (11)	0 (0)	0.358
Clinical presentation, n (%)			
Dyspnea	8 (89)	9 (100)	0.909
Thoracic pain	5 (55)	6 (67)	0.476
Cough	3 (33)	4 (44)	0.480
Hemoptysis	3 (33)	3 (33)	1.000
Syncope	1 (11.1)	0 (0)	0.9
Onset (days)	3.6	4.86	0.09
HASBLED score			
1	5 (56)	4 (44.8)	0.746
2	4 (44)	5 (55.2)	0.588
PESI score	112 (108–121)	111.5 (105–120)	0.565
PESI class			
3	3 (33.3)	5 (55.5)	0.488
4	6 (66.6)	4 (44.4)	

Note: BMI, body mass index; DBP, diastolic blood pressure; DVT, deep vein thrombosis; PaO2, partial pressure of arterial oxygen; rt-PA, tissue-type plasminogen activator; SBP, Systolic blood pressure; NT – proBNP, N-terminal pro–B-type natriuretic peptide; PE, pulmonary embolism; PESI, pulmonary embolism severity index; COPD, chronic obstructive pulmonary disease. There was no statistical difference between the two groups in ECG and chest X-ray results.

Immobilization, trauma, hospitalization, malignancy and known history of VTE (DVT and/or PE) were predisposing factors in the studied groups (tab. 1). The influence of hormonal therapy, oral contraceptive drugs, hormone replacement treatments during menopause and hormonal drugs used for malignant diseases were evaluated. Only one person had VTE during hormonal therapy in breast cancer.

In this study, pulmonary CT angiography (CTPA) and echocardiography (ECHOCG) were used as the main diagnostic method. However, ECHOCG and perfusion scintigraphy were used to diagnose a high probability PE in 3 patients in which a high level of creatinine was found. The PACTOIR index on CTPA was 75% in both groups. PACTOIR was 100% in 3 patients in the half-dose rt-PA group and in 2 patients in the UFH group. The same index was not significantly different between the two groups (p=0.505). The mean RV/LV ratio on CTPA was 1.2 in both groups. As the location of the embolic thrombus, the main pulmonary artery was more frequently found in the TT group, although there was no statistically significant (44.4 vs. 11.1%, p=0.095). The CTPA findings are summarized in tab. 2, and the CTPA images of 3 cases are shown in figures 1 and 2.

Echocardiography revealed ventricular septal displacement in 15 patients (8 patients (88%) in the half-dose rt-PA group and 7 patients (77%) in the UFH group. Pulmonary arterial pressure had a mean of 55 mm Hg in both groups. Right ventricular enlargement or RV hypokinesis was detected in all patients in the half-dose rt-PA group (100%) and in 8 (88%) patients in the UFH group. There was no significant difference in echocardiographic parameters in both groups except systolic PAP. When the TT and UFH groups were compared in terms of systolic PAP, the TT group had a higher prevalence of elevated PAP (53 [43–60] vs. 41.5 [37–45] mmHg, P<0.05). Imaging data are summarized in tab. 2.

Table 2. Results of imaging investigations (CTPA and ECHOCG) in 18 patients with submassive PE (intermediate risk)

	TT n=9 (%)	UFH n=9 (%)	P valoare
PACTOIR	73 (12.5–100)	75 (25–100)	0.505
RV/LV	1.2 (1.0–1.7)	1.2 (0.9–2.0)	0.888
Pleural effusion	2 (25)	1 (14.2)	0.176
Hampton's sign	2(25)	1 (14.2)	0.127
Diffuse hypoperfusion	3 (37.5)	2 (28.4)	0.491
Embolus localization			
Bilateral	6 (75)	6 (85.7)	0.243
Bilateral basal	1 (12,5)	1 (14.3)	0.615
Main AP	1 (12.5)	0 (0)	0.95
ECHOCG features			
LVEF (%)	60 (58–60)		0.509
RV/LV	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
Systolic PAP (mmHg)	53 (43–60)	41.5 (37–45)	<0.05

Note: UFH, unfractioned heparin; PACTOIR, pulmonary Arterial Obstruction CT Index Rate;
CTPA, computed tomography pulmonary angiogram; LV, left ventricle; RV, right ventricle; Systolic PAP, pulmonary artery systolic pressure; TT, thrombolytic therapy; TAPSE, tricuspid annular plane systolic excursion.

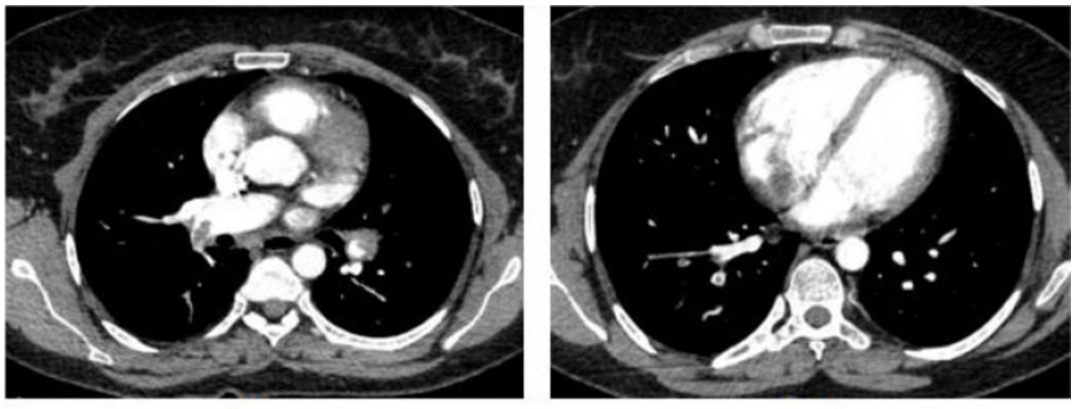

Fig. 1. This is a patient in the UFH group who was immobilized due to surgery and had bilateral total pulmonary artery occlusion (A) with a right-left ventricular ratio of 1.07 (B) on pulmonary CT angiography.
Pulse rate, respiratory rate, blood pressure, sPESI, and PASP on echocardiography at presentation were 121 per minute, 24 per minute, 120/70 mm Hg, 2, and 65 mm Hg, respectively. Half rt-PA escalation dose was used due to hemodynamic decompensation and severe dyspnea. He had mild dyspnea at 6 months with a PASP of 55 mmHg on echocardiography. UFH, unfractioned heparine; CT, computed tomography; sPESI, simplified pulmonary embolism severity index; PASP, pulmonary artery systolic pressure; rt-PA, tissue plasminogen activator.

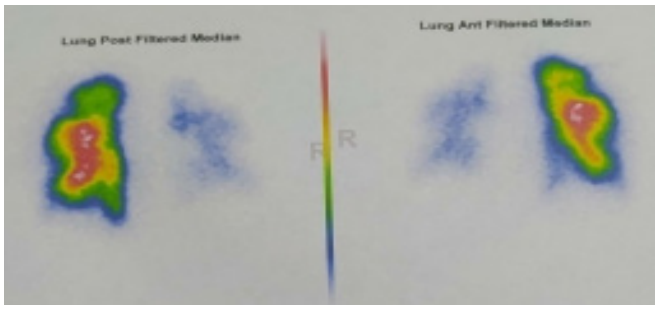

Fig. 2. Perfusion scintigraphy shows in a patient persistent filling defects of the pulmonary arterial bed

Efficacy and safety results

A summarized data of pre– and post-treatment echocardiographic and clinical parameters for both groups is specified in table 3. Oxygen saturation in arterial blood and TAPSE increased in the post-TT period, while heart rate, RV/LV ratio and systolic PAP decreased significantly in both groups (tab. 3). Low-dose TT has been used successfully in all patients. The number of hypotension significantly decreased after TT (22 vs. 0%, P<0.5), but 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 shown in tab. 4. The proportion of primary outcomes at 3 months 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 (11.1 vs. 33.3%, p=0.05). The rate of secondary endpoints was significantly higher in the UFH group (Table 4). The prevalence of pulmonary hypertension was significantly higher in the UFH group (0 vs. 19%, p=0.003). Although all-cause mortality (0 vs. 11.1%, p=0.253) and recurrent PE (0 vs. 11.1%, p=0.253) were not significantly different, they were numerically higher in the group with UFH at 3-month follow-up.

Table 3. Comparison of pre– and post-treatment echocardiographic and clinical parameters according to treatment strategy

	TT group			UFH group		
	Initial level	At 3 months	p	Initial level	At 3 months	p
HR (beats/min)	111 (109–118)	80 (77.5–86)	<0.05	110.5 (109–117)	80 (75–82.5)	<0.05
O_2 saturation	87 (86–88)	96 (95–96)	<0.05	87 (85.75–88)	94 (92–95)	<0.05
High respiratory rate, n (%)	4 (44.4)	0	<0.01	3 (33.3)	1 (11.1)	0.013
Hypotension, n (%)	2(22.0)	0	<0.05	1 (11.1)	1 (11.1)	0.825
RV/LV	1.2 (1.0–1.2)	0.66 (0.63–0.70)	<0.05	1.1 (1.0–1.2)	0.71 (0.65–0.84)	<0.05
Systolic PAP (mmHg)	53 (43–60)	24 (23–25)	<0.05	41.5 (37–45)	32 (29.5–37.25)	<0.05
TAPSE (mm)	16 (15–17)	24 (21.5–25)	<0.05	16 (15–17.1)	20.5 (19–24)	<0.05

Note: HR, heart rate; LV, left ventricle; RV, right ventricle; systolic PAP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TT, thrombolytic therapy; UFH, unfractionated heparin.

Table 4. Three-month clinical outcomes in both groups

Parameters	TT group (n=9), n (%)	UFH group (n=9), n (%)	p
Primary end-point	1 (11.1)	3 (33.3)	0.06
All cause mortality	0	0	1.00
Hemodynamic decompensation	1	3 (33.3)	0.059
Severe blood loss	1 (11,1)	0	0.54
Secondary end-point	0	1 (11.1)	0.16
PE recurrence	0	1 (11.1)	0.553
Pulmonary hypertension (Systolic PAP ≥40 mmHg at ECHOCG)	1(11,1)	4 (44.4)	0.39
Moderate blood loss	1 (11,1)	1(11.1)	0.494
Minor blood loss	3 (33.3)	2 (22.2)	0.615
Mean hospital lenght of stay in IT department (days)	3.8±1.8	5.2±1.2	0,05
Total lenght of stay (days)	7.4±2.1	8.8±2.9	0.05
Hospitalization cost	13237±2341	13421±1673	0.06

Note: TT, thrombolytic therapy; UFH, unfractionated hepatin; PE, pulmonary embolism; PAP, pulmonary artery pressure; ICU, intensive care unit; ECHOCG, echocardioglaphy

There was 1 patient with relatively severe bleeding in the TT group (massive subcutaneous ecchymosis at the jugular puncture site that was associated with a decrease in hemoglobin by 40 units and required the transfusion of 1 bag of erythrocyte mass) (tab. 4). Moderate hemorrhages – persistent epistaxis and menorrhagia were presented in 1 patient from both research groups; menor hemorrahges as slight ecchymoses and gingival hemorrhages, episodic epistaxis, profuse mensis, hemorrhoidal bleeding were presented in 3 patients from the TT group and 2 patients from the UFH group.

The hospitalization length of stay was significantly shorter in the TT group both in the ICU and in the recovery department. The costs presented a different structure, without significant changes in both groups. In the TT group it was lower due to the reduction in the duration of hospitalization, but at least without significant difference because of increased cost of thrombolysis agent and laboratory tests perceived more frequently.

There was no in-hospital mortality from any cause or serious hemorrhagic complications requiring additional medical implications in both research arms.

To conclude, half-dose thrombolytic therapy in patients diagnosed with submassive PE (intermediate risk) significantly reduced death and hemodynamic decompensation in the first 7 days compared to anticoagulant therapy only. There was no significant difference in both treatment groups regarding bleeding complications and none of the patients had serious hemorrhagic complications. The obtained results show the benefit of the use of low-dose rt-PA in cases of normotensive PE with right ventricular dysfunction diagnosed on echocardiography and/or high right-to-left ventricular ratio on CTPA, especially in cases with PACTOIR and/or high PASP on echocardiography associated with biomarkers (elevated troponin and/or NT-proBNP). Thus, patients with high-intermediate risk PE could benefit from reduced-dose TT with higher minor bleeding complications compared to general low-intermediate-risk group.

Importance and practical meaning of the research

What is already known about this topic?

– Patients in the intermediate-risk group are more controversial for thrombolytic therapy.

– Although thrombolytic drugs have been used as a life-saving agent in massive pulmonary embolism in high-risk group with persistent hypotension, they have not been used in the non-massive (low-risk) group due to the high frequency of fatal intracranial hemorrhage.

– In the PEITHO trial, was observed a higher incidence of stroke and major non-intracranial bleeding in the thrombolytic group, with controversial issue for intermediate-risk pulmonary embolism.

– The use of thrombolysis in PE with intermediate risk was not sufficiently studied in the PEITHO trial.

What are the new findings?

– The main objectives in the treatment of patients with pulmonary thromboembolism are the prevention of mortality without causing bleeding in the acute situation, the prevention of recurrence and the development of pulmonary hypertension as long-term outcomes.

– The present study aimed to answer the same question (clinical use and applicability of reduced doses thrombolytics in PE patients with intermediate risk), comparing half-dose thrombolytics with standard anticoagulation.

– This study revealed that half-dose tissue plasminogen activator (rt-PA) prevents death or hemodynamic decompensation in the first 7 days in patients with submassive PE without increasing major bleeding complications.

How might these results change the course of further research or clinical practice (practical applicability)?

– Pulmonary embolism at intermediate risk treated by half-dose thrombolytic therapy reduced patient's death or hemodynamic decompensation in the first 7 days compared with anticoagulant therapy only.

– There was no significant difference in both treatment groups regarding bleeding complications and none of the patients had intracranial bleeding.

These results support the use of low-dose rt-PA in cases of normotensive PE with right ventricular dysfunction and/or a high right ventricular to left ventricular ratio on pulmonary CT angiogram. Moreover, it showed the benefit for patients with a high CT index for pulmonary artery obstruction and/or very high pulmonary artery Systolic pressure on echocardiography, in association with markers of myocardial injury and positive cardiac overload.

Discussion

This research revealed the benefit of half-dose rt-PA that supposingly prevents death/hemodynamic decompensation within the first 7 days in intermediate-risk PE patients without increasing the rate of bleeding complications. The given this study is one of the few prospective

studies that have compared half-dose rt-PA and unfractioned heparin [31]. In this study, the two therapies had similar effects on PE recurrence and development of pulmonary hypertension at 3 months. The main objectives in the treatment of patients with pulmonary thromboembolism are the prevention of mortality without causing bleeding in the acute situation, the prevention of recurrence and the development of pulmonary hypertension as long-term outcomes. This study met the first objective, with no deaths in either group. Moreover, both therapies also showed similar effects on thromboembolic event recurrence and development of pulmonary hypertension, compared with previous studies [32, 33].

Efficacy of thrombolytic therapy

Although the efficacy of thrombolytics is indisputable in massive (high life-risk) PE, the management of intermediate-risk PE remains controversial. As the risk of mortality being very high due to acute hemodynamic deterioration in massive pulmonary thromboembolism, clinicians need to make decisions based only on their clinical judgment. A trial comparing thrombolytic therapy with heparin in patients with massive PE was stopped early because all patients in the heparin group died [34]. Based on the evidence, thrombolytic therapy has been accepted as standard treatment in this specific group [14, 29]. Thrombolytic therapy leads to a more rapid improvement in the pulmonary circulation, reducing pulmonary obstruction, pulmonary arterial pressure, pulmonary vascular resistance, with reduction of right ventricular failure in patients with massive PE compared with unfractionated heparin (UFH) alone [34-37]. The earlier starts treatment, the greater is the benefit. However, thrombolytic therapy may still be used only in patients with the beginning of symptoms no more than 14 days before [38]. Normotensive patients with PE may be at increased risk of early death if they have right ventricular dysfunction or myocardial injury secondary to acute pressure overload [39, 40]. However, clinical guidelines do not recommend the routine use of thrombolytics in cases of intermediate-risk PE due to insufficient research data. Rescue thrombolytic therapy is, instead, recommended for patients with hemodynamic deterioration under anticoagulant treatment [14, 29].

There are some randomized clinical trials showing the efficacy of thrombolytic therapy in submassive PE, but with controversial results regarding bleeding, especially ICH. The Management Strategies and Prognosis of Pulmonary Embolism-3 (MAPPET-3) study investigated the use of heparin in addition to 100 mg rt-PA in 118 patients with 138 who received heparin plus placebo [23]. The primary end-point was met, with in-hospital mortality or clinical deterioration significantly higher in the heparin/placebo group (p=0.006) and the 30-day survival and event-free being higher in the rt-PA plus heparin group (p= 0.005). The bleeding rate was higher in rt-PA group, without any fatal bleeding or ICH. The randomized, double-blind, PEITHO9 study was a pivotal trial in acute PE comparing full-dose tenecteplase plus heparin with heparin plus placebo in 1006 intermediate-risk PE patients. The primary end-point (death from any cause, hemodynamic decompensation or collapse within 7 days of randomization) occurred in 13 of 506 (2.6%) patients in the thrombolytic group compared with 28 of 449 (5.6%) patients in the placebo group (p. =0.02). Intracranial hemorrhage occurred in 10 (2%) patients from the tenecteplase group and in only 1 (0.2%) patient from the placebo group. Similar to the current study, this one revealed that thrombolytic therapy prevents hemodynamic decompensation. Although, there was observed an increased risk of major hemorrhage and stroke, this data is different from the data of the given research. The PEITHO trial influenced guidelines' recommendations, in which it is not recommended to use as routine thrombolytic therapy for intermediate-risk PE cases, although there are some small trials that have shown no difference in bleeding complications between groups with full-dose thrombolytics and heparin alone [18, 41, 42].

High rates of ICH in the PEITHO trial led researchers to start new studies, lowering the usual dose of thrombolytics to achieve positive result with minor complications. Although guidelines recommended rt-PA 100 mg in 2-hour infusion in high-risk PE treatment, there aren't defined clearly optimal doses in specific situations. Even there is no strong evidence, in the "real world", many clinicians choose to use lower doses rt-PA, being cautious because of major bleeding. Lower doses of thrombolytics may be of particular interest in the elderly, body mass less than 65 kg and pregnant women, as well as those with relative contraindications [43]. The currently standard dose of rt-PA is based on experience and studies in cardiology [44]. However, if it is considered that the lungs receive the entire cardiac output compared to the coronary arteries which receive only a fraction of it, reducing the dose of thrombolytics in the treatment of PE could be a logical approach.

A randomized trial of 118 patients with high or intermediate-risk PE established that using half-dose rt-PA resulted in fewer bleeding complications than full-dose rt-PA. Moreover, it had similar effects on improving right ventricular diameter at echocardiography, as well as the reduction of perfusion defects and obstruction of the pulmonary arteries in CTPA [32].

Subsequently, a prospective, randomized trial on intermediate-risk pulmonary embolism treated by thrombolysis (MOPETT) compared low-dose rt-PA versus UFH or enoxaparin in 121 cases [31]. The all-cause mortality was similar in both groups and the progression of pulmonary hypertension was statistically decreased in the low-dose thrombolytic group. During the 12-month follow-up, pulmonary hypertension and recurrent PE developed in 1 (11%) patient in the low-dose thrombolytic group and in 3 (33%) in the heparin-only group. However, no major or minor bleeding reported in either group was specifically described, being an unusual fact in a study in which 61 patients received systemic thrombolysis.

Other study comparing half-dose (50 mg/2 h) and full-dose (100 mg/2 h) rt-PA treatment strategies in massive (high-risk) pulmonary thromboembolism, showed efficacy and hemodynamic stability in both groups, although in

the low-dose group had been fewer bleeding complications in patients with body mass less than 65 kg [32]. Recurrent pulmonary thromboembolism was described in none of the studied groups. Therefore, according to this study, when the half-dose was compared with the full-dose, in pulmonary thromboembolism, the similar efficacy of the half-dose regimen provided more protection in terms of bleeding complications (in separate patient groups) [32]. Half-dose alteplase is used as an initial treatment strategy versus full-dose alteplase in approximately 19% of ICU patients with acute pulmonary embolism, being used more often from 2010 to 2014. Full-dose alteplase therapy is preferred by clinicians in high-risk pulmonary embolism patients. Less than a quarter of patients in the half-dose group received vasopressors at the time of thrombolysis. In addition, at the time of alteplase administration, patients treated with half-dose therapy were less likely to receive mechanical ventilation and less frequently evaluated by cardiac functional tests. However, patients receiving half-dose alteplase were more likely to receive positive outcome and additional care in the management of acute pulmonary embolism.

Zhang et. al. compared low-dose thrombolytic therapy (30 mg/rt-PA) and LMWH treatment in patients diagnosed with intermediate-risk pulmonary thromboembolism [33]. It was observed that in contrast with the LMWH group, there was a significant decrease in blood pressure and an important decrease in symptom intensity in the rt-PA group. After 90 days, there were no differences in mortality, recurrent VTE and major bleeding between groups. However, in the rt-PA group, there was increased minor bleeding and reduced hemodynamic decompensation. As a conclusion to this study, low-dose thrombolytic treatment could be recommended as a protective and effective treatment for patients diagnosed with intermediate-risk pulmonary thromboembolism [33].

According to the guidelines of the European Society of Cardiology/European Respiratory Society (ESC/ERS)[29] risk stratification is done by evaluating the pulmonary embolism severity index (PESI) (or the simplified pulmonary embolism severity index (sPESI)), a right ventricular function on echocardiography and cardiac troponin testing after a diagnosis of PE has been confirmed. The intermediate-risk group is further divided into intermediate-high and intermediate-low risk groups. There was mentioned a small difference in hemodynamic decompensation according to the classification of intermediate-high and intermediate-low risk, observing a more frequent need for treatment update among patients in the intermediate-high risk group (3 vs 1 patient). Four patients in the intermediate-low risk group presented a faster compensation and a shorter length of hospitalization.

Several studies have shown that low-dose thrombolytics decrease systolic PAP during the first week of treatment [45]. However, no difference in systolic PAP on echocardiography was observed in low-dose thrombolytics compared with long-term heparin anticoagulation alone, except in the MOPETT trial [37]. In the MOPETT trial, systolic PAP measurements on dynamic echocardiography after 28 months were statistically higher in patients receiving anticoagulant therapy alone compared with half-dose rt-PA therapy [31]. However, chronic thromboembolic pulmonary hypertension was not confirmed with right heart catheterization in either study. Of the 16 patients who developed long-term pulmonary hypertension, 11 were in the intermediate-high risk group and 5 in the medium-low risk group according to the ESC/ERS4 guidelines. In this study, 1 patient from the TT group and 4 from the UFH at 3 months had presented with PH, and at 12 months of follow-up only 2 of the 4 still had systolic PAP above 40 mmHG.

It should be noted that according to the results of the conducted study, hemodynamic decompensation and pulmonary hypertension can develop in both subgroups of PE with intermediate risk.

Adverse events

In the PEITHO trial, extracranial and intracranial bleeding complications were significantly higher in the tenecteplase group compared with the placebo plus anticoagulant group [16]. In another study that compared tenecteplase plus UFH with placebo plus UFH groups, there was no difference in major bleeding complications, whereas minor bleeding was more frequent in tenecteplase patients [41]. In the MAPPET [2, 3] trial, no significant difference in bleeding complications was found between rt-PA plus UFH and placebo plus UFH treatment. In the meta-analysis made by Nakamura et al., the risk of major bleeding and ICH was found to be more frequent in the thrombolytic group, but it was not statistically significant [46]. In the MOPETT trial, no significant bleeding was observed in any of the patients receiving half-dose rt-PA plus anticoagulant and anticoagulant alone [31]. In a systematic review by Zhang et al., it was observed that bleeding complications were reduced in half-dose thrombolytic treatment compared with full-dose [45]. In the given study, there was no statistically significant difference between the half-dose rt-PA group and the UFH group in terms of bleeding complications (p=0.254), but minor bleeding was more frequent among patients with thrombolysis. No ICH was observed in this study. Increasing age and comorbidities have been shown to be associated with a higher risk of bleeding complications in full-dose thrombolytic trials [16, 45]. Using half-dose rt-PA, we observed no difference in bleeding complication including ICH between patients who were older than 75 years or younger. The obtained findings, combined with those of another controlled trial of thrombolysis in submassive PE, support the use of half-dose rt-PA instead of UFH/LMWH in the prevention of hemodynamic decompensation and the use of secondary thrombolytic therapy [31].

Clinical trials in progress

The PEITHO-3 trial is a global randomized, placebo-controlled, double-blind, multicenter trial with long-term follow-up (ClinicalTrials.gov Identifier: NCT04430569) [47]. Researchers are studying the safety and efficacy of low-dose alteplase therapy with conventional heparin an-

ticoagulation. However, they give a weight-adjusted dose of 0.6 mg/kg, up to a total of 50 mg over 15 minutes. If PEITHO-3's theory proves to be correct International clinical practice guidelines would revise their recommendations to include reperfusion and, in particular, low-dose systemic thrombolysis as first-line treatment in intermediate-risk PE. If the hypothesis is rejected, catheter-directed treatment may become the only option to improve prognosis of intermediate-high-risk PE patients.

Study limits

– This is a single-center study, this being the reason of a small number of patients to study. It limits from obtaining statistically stronger results, especially regarding the mortality rate.

– This study group included some different values, such as respiratory rate, oxygen saturation, and partial pressure of arterial oxygen (PaO2), indicating that the low-dose thrombolytic group has more severe cases, although there was no difference between groups regarding risk classification. Although it is believed this difference to be coincidental, this unintentional situation increases the credibility of the study.

– Another limitation was a non-blinded approach, as physicians responsible for the treatment and follow-up of the patients were aware what treatment each patient had in acute phase. However, very strict criteria were defined for hemodynamic decompensation and for further escalation of treatment to thrombolysis.

– Decision making in case of using thrombolysis is variable because of the bleeding risk fear. It is easy to associate patient's mean HAS-BLED score in the TT group with the precaution use of systemic alteplase.

– A limited or delayed access to CTPA is an important factor influencing the safe use of thrombolytic therapy and the enrollment of patients to the study. At the same time, the lack of other imagistic tools, such as ventilation/perfusion scintigraphy does not allow the enrollment of patients with contraindications to the contrast injection.

– Delayed addressability at a specialized medical institution in the acute PE (more often over 14 days), limits the enrollment of patients to the thrombolysis group, and reduces the results of complete thrombus lysis regardless to the treatment's options.

In conclusion, more studies of high methodological quality are needed to assess safety and cost effectiveness of thrombolytic therapy in intermediate-risk pulmonary embolism.

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