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

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The patients with intermediate-high risk pulmonary embolism who have acute right ventricular (RV) dysfunction and myocardial injury without overt hemodynamic compromise may be candidates for thrombolytic therapy. Alternative low-dose thrombolytic therapy strategies with prolonged infusion may further decrease the complication rates as its efficacy and safety have been previously proven in the management of prosthetic valve thrombosis. In this study, we aimed to investigate the clinical outcomes of low-dose prolonged thrombolytic therapy regimen in intermediate-high risk pulmonary embolism patients. This study enrolled 16 retrospectively evaluated patients (female 9, mean age: 70.9 ± 13.5 years) with the diagnosis of acute pulmonary embolism who were treated with low-dose and slow-infusion of tissue-type plasminogen activator (t-PA). All patients underwent transthoracic echocardiography and computed tomography scan for assessment of thrombolytic therapy success. Low-dose prolonged thrombolytic therapy was successful in all patients. The mean t-PA dose used was 48.4 ± 6.3 mg. There was residual segmental thrombus in nine (56.3%) patients after thrombolytic therapy. The arterial oxygen saturation and tricuspid annular plane systolic excursion increased after thrombolytic therapy whereas heart rate, RV to left ventricular (LV) ratio, systolic pulmonary artery pressure, and the frequencies of hypotension and tachypnea significantly decreased. There was no cerebrovascular accident or major bleeding requiring transfusion. There were two minor bleedings (12.5%) including hemoptysis and epistaxis. Thrombolytic therapy in these intermediate-high risk pulmonary embolism patients was associated with excellent clinical outcomes and survival to discharge (100%) without any 60-day mortality. Prolonged thrombolytic therapy regimen with low-dose and slow-infusion of t-PA may be associated with lower complication rates without comprimising effectiveness in patients with acute intermediate-high risk pulmonary embolism. *Blood Coagul Fibrinolysis* 31:536–542

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Introduction

Acute pulmonary embolism is a life-threatening disorder which usually presents as a severe complication of venous thromboembolism [1]. The pulmonary embolism is globally the third most frequent acute cardiovascular syndrome behind myocardial infarction (MI) and stroke [2]. In epidemiological studies, annual incidence rates for pulmonary embolism range from 39 to 115 per 100 000 population [2–4]. Cross-sectional data show that the incidence of pulmonary embolism is almost eight times higher in individuals aged more than 80 years than those in the 5th decade of life [3]. Fatality rates of pulmonary embolism vary widely, but approximately 10% of all patients with acute pulmonary embolism die within 3 months after the diagnosis [1]. Acute RV pressure overload at diagnosis is an important determinant of the severity and early clinical outcomes of pulmonary embolism. High-risk pulmonary embolism is characterized by overt hemodynamic instability and warrants immediate advanced therapy, including consideration of fibrinolysis [4]. In contrast, for patients presenting without systemic hypotension or hemodynamic deterioration, standard anticoagulation is generally considered as an adequate treatment. However, patients who have acute RV dysfunction and myocardial injury without overt hemodynamic impairment may be at intermediate-high risk for an adverse early outcome [4,5]. These patients may also be a candidate for early reperfusion thrombolytic therapy. In the last 2 decades, thrombolytic therapy has been increasingly performed in cases with

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intermediate-high risk pulmonary embolism [6–14]. However, recent major cardiovascular guidelines still recommend anticoagulation therapy for patients with intermediate-high risk pulmonary embolism [4,5].

Alternative thrombolytic therapy strategies have been proposed to provide efficacy with less bleeding. Although various catheter-directed treatments have been reported in patients with pulmonary embolism [15–19], only one of these, a novel ultrasound-assisted thrombolysis technology, was tested in a randomized clinical trial [17]. 'Invasive' catheter-directed lytic intervention (direct pulmonary artery infusion of Alteplase 10–51 mg) appears clinically beneficial and is reported to have largely eliminated intracranial hemorrhage, but is still associated with 7.8–10% major bleeding rates [14–19]. Previously, 'low-dose' thrombolytic therapy has been discussed as a potential option for the treatment of intermediate-high risk pulmonary embolism [20].

Since the lungs are the only organ receiving 100% of the cardiac output (CO), theoretically, the thrombolytic therapy agent is 100% available, regardless of which venous route is used for administration [6]. Based on this hypothesis, low dose, slow infusion of tissue-type plasminogen activator (t-PA) regimen may potentially be equally effective as full-dose, while reducing the risk of major bleeding complications. The efficacy and safety have been previously proven in the treatment of prosthetic valve thrombosis [21,22]; therefore, we have considered that this regimen may also be effective and safe in patients with intermediate-high risk pulmonary embolism. This retrospective analysis included the clinical outcomes of the low dose, slow infusion of t-PA regimen in these patients.

Material and methods

Between January 2013 and January 2020, low-dose slow infusion thrombolytic therapy has been performed in different tertiary centers (mostly Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital) for patients with intermediate-high risk pulmonary embolism. The diagnosis of acute pulmonary embolism and the definition of the intermediate-high risk pulmonary embolism were based on the criteria as recommended by the European Society of Cardiology/European Respiratory Society 2019 pulmonary embolism Guidelines [4]. In addition, pulmonary embolism severity index (PESI) score was calculated for each patient in accordance with the literature [23]. All patients provided written informed consent, and the institutional ethics committee approved the study protocol in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

The patients who had clinical signs and symptoms suggestive of pulmonary embolism and compatible computed tomography (CT) findings constituted potential candidates for the study. To be eligible for enrollment, the patients were required to have a minimum of two new signs and symptoms consisting of chest pain, tachypnea (respiratory rate >20 bpm), tachycardia [heart rate (HR) at rest over 100 bpm], dyspnea, oxygen desaturation (oxygen partial pressure <95%). The exclusion criteria included an onset of symptoms more than 14 days; systemic arterial SBP less than 90 or more than 200 mm Hg; PESI score more than 4 or less than 3; a contraindication to thrombolytic therapy or severe thrombocytopenia (platelet count <50 000/μl), and high risk of bleeding. The bleeding risk of the patients was made in accordance with the HAS-BLED scoring [hypertension, abnormal renal function or liver function, stroke, bleeding, labile international normalized ratio (excluded as all patients not on warfarin prior to inclusion), elderly more than 85 years old, and drugs and alcohol]: 0 = low risk, 1–2 = moderate risk, more than 2 = high risk [24].

Transthoracic echocardiography (TTE) was performed within 2 h after admission to the hospitals and before administration of t-PA and was repeated at 6–12-h intervals. Systolic pulmonary artery pressure (SPAP) was calculated from the tricuspid valve regurgitation jet velocity in accordance with the modified Bernoulli equation and the right atrial pressure was estimated as 10, 15, and 18 mmHg for mild, moderate, and severe right atrial enlargement, respectively [25,26]. Tricuspid annular plane systolic excursion (TAPSE) was acquired by placing an M-mode cursor through the lateral tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole in the standard apical four-chamber view. LV ejection fractions (LVEF) of the patients were calculated by using biplane Simpson's method [27]. Interpretation of the echocardiographic findings was performed by a cardiologist who was unaware of the patients' treatment assignments. A dichotomous value of SPAP of 40 mmHg was used to define pulmonary hypertension. RV enlargement was defined as a RV : LV ratio of more than 0.9 [25,26].

Images were acquired before and after the thrombolytic therapy using a 64 and 320-slice helical CT scanner (Toshiba Medical Systems Corp., Tokyo, Japan) with angiographic contrast material (Omnipaque 350; GE Healthcare, Chicago, Illinois, USA). The stored images recorded at the time of diagnosis and following the thrombolytic therapy were retrospectively evaluated. The methods of evaluating the RV : LV ratio were made in accordance with the previous definitions [4,5,28].

In the current study, t-PA was the only agent used for thrombolytic therapy. The dose of t-PA was half of the standard dose (100 mg) commonly used for the treatment of pulmonary embolism, which we defined as 'safe dose' thrombolysis. The route, duration and preparation of t-PA were made in accordance with previous publications [23,29]. Patients were clinically risk-stratified for

appropriateness for escalation of care to low-dose systemic thrombolytic therapy according to standard clinical criteria via the HAS-BLED score [24]. Bleeding complications were made according to the GUSTO classification as follows: if intracerebral or resulting in significant hemodynamic compromise requiring treatment, they were classified as severe or life-threatening. Moderate bleeding was defined by the need for transfusion. Minor bleeding referred to other bleeding, not requiring transfusion or causing hemodynamic deterioration [30]. The low dose, slow infusion of t-PA regimen was initiated with two consecutive episodes (25 mg t-PA/6 h), followed by systemic heparin therapy for at least 24 h. All patients underwent TTE and CT scan after thrombolytic therapy for assessment of SPAP, RV size and functions. Successful thrombolytic therapy was defined due to improvement in SPAP and RV functions assessed by TTE, RV : LV ratio and plasminogen activator obstruction severity in CT images. The endpoints were success of thrombolytic therapy, nonfatal major complications including intracranial hemorrhage and other bleedings requiring transfusion, and all-cause mortality up to 60 days following thrombolytic therapy. Nonfatal minor complications included bleedings without need for transfusion.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp. Armonk, New York, USA). Normality distribution of continuous variables was tested with the Kolmogorov–Smirnov test. Continuous variables with normal distribution were expressed as mean ± SD while continuous variables without normal distribution were expressed as median (25–75th 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 or Fisher exact test was used for comparison of categorical variables as appropriate. A two-sided *P* value of less than 0.05 was considered as significant.

Results

The study population comprised 16 retrospectively evaluated patients (female 9, mean age: 70.9 ± 13.5 years) with the diagnosis of acute pulmonary embolism who were treated with low dose, slow infusion of t-PA regimen. The demographic data of the study patients are summarized in Table 1. The clinical manifestations included dyspnea (100%), tachypnea (31.3%), syncope (12.5%), palpitation (50%), and chest pain (6.3%). Although 12.5% of the patients were on antiplatelet therapy, the average HAS-BLED score was quite low [1.0 (1.0–2.0)] and no patient had score more than 2. The mean arterial blood pressure was low in four (25%) patients without any hemodynamic decompensation. The mean HR was 111.4 ± 4.8 bpm and mean arterial oxygen saturation was 87.1 ± 1.9%. The systolic function of the LV was normal in all patients with a mean LVEF of 59.8 ± 3.3%. CT angiography revealed thrombi in both pulmonary arteries in 75% of the cases. This substantial clot burden was associated with striking RV dilation (RV : LV ratio: 1.14 ± 0.12). Decreased TAPSE (1.61 ± 0.19 cm) and increased SPAP (57.1 ± 12.9 mmHg) mmHg) were indicative of severe RV strain. The mean PESI score was 112.6 ± 10.3 in the study population and PESI class was three in three (18.8%) and four in 13 (81.2%) patients (Table 1).

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

Parameters	Values
Age (years)	70.9 ± 13.5
Sex (female), *n* (%)	9 (56.3)
BMI (kg/m^2)	28.9 ± 5.7
Hypertension, *n* (%)	12 (75)
Diabetes mellitus, *n* (%)	2 (12.5)
COPD, *n* (%)	4 (25)
Surgical history, *n* (%)	3 (18.8)
Antiplatelet use, *n* (%)	2 (12.5)
Prior DVT, *n* (%)	9 (56.3)
Malignancy, *n* (%)	0
Clinical presentation, *n* (%)	
Dyspnea	16 (100)
Tachypnea	5 (31.3)
Syncope	2 (12.5)
Palpitation	8 (50)
Chest pain	1 (6.3)
HAS-BLED score, *n* (%)	
1	9 (56.3)
2	7 (43.8)
Hypotension, *n* (%)	4 (25)
Heart rate (bpm)	111.4 ± 4.8
O_2 saturation (%)	87.1 ± 1.9
PTE location, *n* (%)	
Bilateral	12 (75)
Saddle	2 (12.5)
MPA	2 (12.5)
LVEF (%)	59.8 ± 3.3
RV/LV ratio	1.14 ± 0.12
TAPSE (cm)	1.61 ± 0.19
SPAP (mmHg)	57.1 ± 12.9
PESI score	112.6 ± 10.3
PESI class, *n* (%)	
3	3 (18.8)
4	13 (81.2)

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; TAPSE, tricuspid annular plane systolic excursion [continuous variables with normal distribution were expressed as mean ± SD and continuous variables without normal distribution were expressed as median (25–75th percentiles)].

Low-dose prolonged thrombolytic therapy was successful in all patients. The frequency of hypotension and tachypnea were significantly decreased after thrombolytic therapy. Arterial oxygen saturation and TAPSE were increased while HR, RV : LV ratio, SPAP, troponin, and brain natriuretic peptide levels decreased significantly after thrombolytic therapy (Table 2). Thrombolytic therapy was performed in two sessions of t-PA infusions (25 mg each) in 15 (93.7%) patients. One patient expressed an early resolution of symptoms after one

Table 2 Comparison of clinical, laboratory, and echocardiographic parameters before and after thrombolytic therapy

Parameters	Before TT	After TT	*P* value
Hypotension, *n* (%)	4 (25)	0	0.033
Heart rate (bpm)	111.4 ± 4.8	79.9 ± 7.1	<0.001
Tachypnea, *n* (%)	14 (87.5)	2 (13)	<0.001
O_2 saturation (%)	87.1 ± 1.9	95.3 ± 0.9	<0.001
RV : LV ratio	1.14 ± 0.12	0.68 ± 0.07	<0.001
TAPSE (cm)	1.61 ± 0.19	2.24 ± 0.28	<0.001
SPAP (mmHg)	57.1 ± 12.9	26.3 ± 4.9	<0.001
Troponin (ng/ml)	2.6 (0.3–7.5)	0.35 (0.20-.0.52)	<0.001
BNP (pg/ml)	434.6 (226.4–743.8)	112.2 (52.3–198.7)	<0.001

BNP, brain natriuretic peptide; LV, left ventricle; RV, right ventricle; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion [continuous variables with normal distribution were expressed as mean ± SD and continuous variables without normal distribution were expressed as median (25–75th percentiles)]; TT, thrombolytic therapy.

Table 3 Outcomes of low dose thrombolytic therapy

Parameters	Values
Number of TT sessions, *n* (%)	
1	1 (6.3)
2	15 (93.7)
t-PA dose (mg)	48.4 ± 6.3
Residual segmental thrombus, *n* (%)	9 (56.3)
Minor bleeding, *n* (%)	2 (12.5)
Moderate bleeding, *n* (%)	0 (0)
Severe or life-threatening bleeding, *n* (%)	0 (0)
Cerebrovascular accident, *n* (%)	0 (0)
Hemodynamic decompensation, *n* (%)	0 (0)
Survival to discharge, *n* (%)	16 (100)
60-Day mortality, *n* (%)	0 (0)

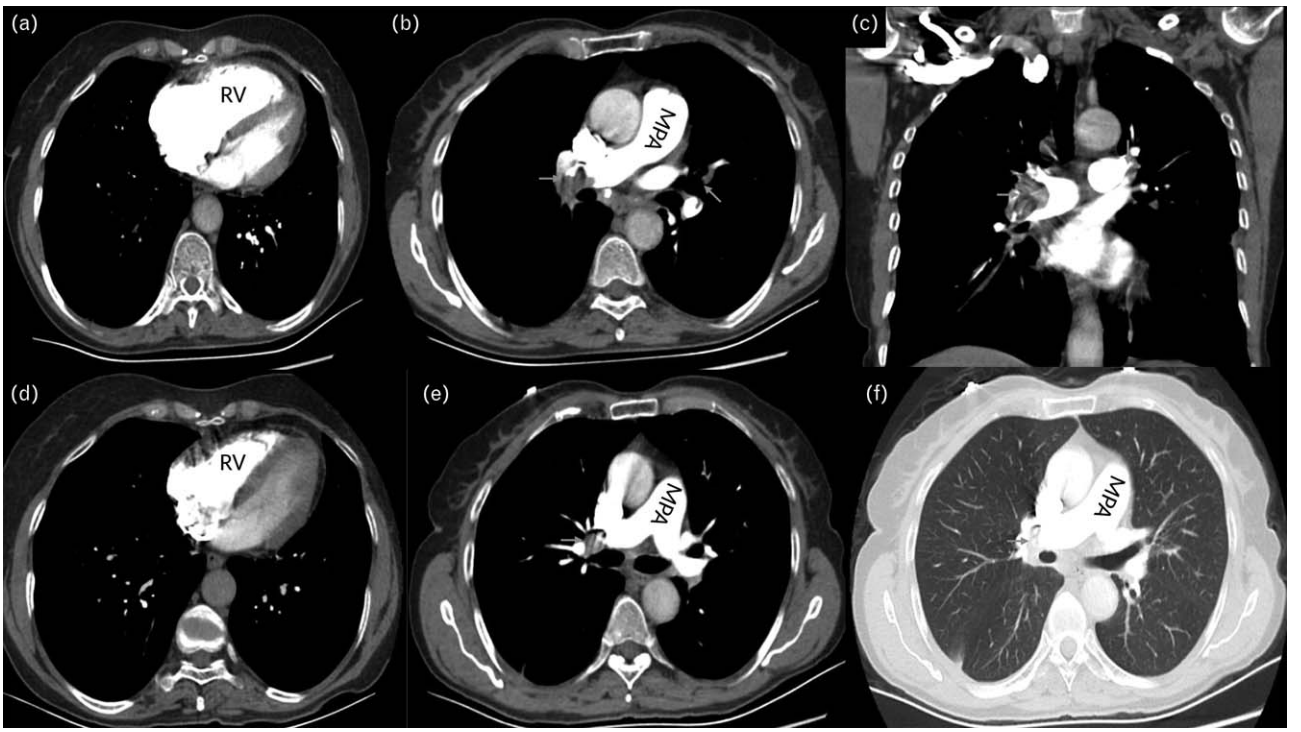
t-PA, tissue-type plasminogen activator; TT, thrombolytic therapy.

session (25 mg) of t-PA infusion. Thrombolytic therapy was withheld in this patient after complete thrombus resolution was confirmed with CT scan. The mean t-PA dose used was 48.4 ± 6.3 mg. There was residual segmental thrombus in nine (56.3%) patients after thrombolytic therapy (Fig. 1). There was no cerebrovascular accident or moderate/severe bleeding requiring transfusion. There were two minor bleedings (12.5%) including hemoptysis and epistaxis in two cases. Thrombolytic therapy in these intermediate-high risk pulmonary embolism patients was associated with excellent clinical outcomes with low rates of further hemodynamic deterioration, excellent survival to discharge (100%) without any 60-day mortality (Table 3). The demographic and clinical characteristics of the participants are presented in Table 4.

Discussion

In the current study, we have focused on the safety and efficacy of thrombolytic therapy with low dose, slow

Fig. 1



Computed tomography (axial view) of a patient with pulmonary thromboembolism revealing markedly dilatation of right ventricular (a) and thrombus (red arrows) in right and left pulmonary arteries in axial (b) and coronal views (c). Computed tomography of the same patient after thrombolytic therapy with 50 mg tissue-type plasminogen activator infusion revealing normal right ventricular size (d) and decreased thrombus burden (e and f). MPA, main pulmonary artery; RV, right ventricle; t-PA, tissue-type plasminogen activator; TT, thrombolytic therapy.

Table 4 Demographic and clinical characteristics of the participants

No	Age	Sex	Presentation	DVT	PESI class	PESI score	PTE location	RV : LV ratio	t-PA dose (mg)	TT success	Bleeding	60-Day mortality
1	56	Female	Dyspnea, tachypnea	−	4	106	Bilateral	1.2	50	+	−	−
2	74	Female	Dyspnea, palpitation	+	4	114	Bilateral	1.0	50	+	−	−
3	82	Female	Dyspnea, tachypnea	+	4	112	Saddle	1.15	50	+	−	−
4	48	Female	Dyspnea, tachypnea	+	3	88	Bilateral	1.3	50	+	−	−
5	74	Male	Syncope, dyspnea	+	4	124	Bilateral	1.1	50	+	−	−
6	68	Female	Dyspnea, palpitation	−	4	108	Bilateral	1.2	50	+	−	−
7	75	Male	Dyspnea, palpitation	+	4	125	Bilateral	1.0	50	+	+(Epistaxis)	−
8	65	Female	Dyspnea, palpitation	−	3	105	Bilateral	1.4	50	+	−	−
9	49	Male	Dyspnea, palpitation	+	3	99	Bilateral	1.0	50	+	−	−
10	59	Male	Syncope, dyspnea	+	4	109	Saddle	1.0	50	+	−	−
11	68	Male	Dyspnea, palpitation	−	4	118	Bilateral	1.2	50	+	−	−
12	71	Female	Dyspnea, palpitation	+	4	121	Bilateral	1.0	50	+	−	−
13	95	Female	Dyspnea, tachypnea	−	4	125	MPA	1.2	25	+	−	−
14	90	Male	Dyspnea, palpitation	−	4	109	Bilateral	1.1	50	+	−	−
15	85	Female	Dyspnea, tachypnea	−	4	118	MPA	1.2	50	+	−	−
16	76	Male	Dyspnea, chest pain	−	4	121	Bilateral	1.2	50	+	+(Haemoptysis)	−

DVT, deep vein thrombosis; LV, left ventricle; MPA, main pulmonary artery; PESI, pulmonary embolism severity index; PTE, pulmonary thromboembolism; RV, right ventricle; t-PA, tissue type plasminogen activator; TT, thrombolytic therapy.

infusion of t-PA regimen in patients with intermediate-high risk pulmonary embolism. This thrombolytic therapy regimen has been associated with significant reduction in the SPAP at early and mid-term follow-up and considered successful in all patients with acceptable minor complication rates and without any major complication or 60-day mortality. The results have demonstrated that thrombolytic therapy with low dose, slow infusion of t-PA regimen may be safe and effective in the management of these patients. These findings are consistent with previously published data [6,10,13].

Potential hemodynamic and clinical benefits of thrombolytic therapy in the management of massive pulmonary embolism patients and some submassive patients have been previously established [4,10–14,31–34]. Thrombolytic therapy is a 'double-edged sword'; its clinical efficacy has been provided in the seemingly integral 'cost' of bleeding complications specific to the induction of a systemic lytic condition [4,5]. However, t-PA is used as an acceptable therapeutic agent in patients with pulmonary embolism that causes hemodynamic deterioration [4], even if there is a risk of major bleeding (including intracranial) due to its nature. On the other hand, accelerated systemic thrombolytic therapy (100 mg t-PA in 2 h) in intermediate-high risk pulmonary embolism 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 [13,14]. Major cardiovascular guidelines regarding pulmonary embolism have considered full-dose systemic thrombolysis as Class 3 indication for submassive pulmonary embolism [4,5]. Various alternative strategies have been designed to reduce bleeding complications without loss of efficacy [10–19]. Previously, Kucher *et al.* [17] have randomized 61 submassive pulmonary embolism patients to catheter-directed thrombolysis or heparin therapy and did not report any mortality or major bleeding. On the contrary, this promising result was not validated in the subsequent larger prospective nonrandomized SEATTLE 2 trial enrolling 150 massive and submassive pulmonary embolism patients, which showed clinical benefit without intracranial bleeding, but was still associated with an 11.4% GUSTO moderate bleeding rate, 20% of which were related to access site complications [18]. Noninvasive 'low-dose' systemic thrombolytic therapy (50 mg t-PA) has been advocated, based on the hypothesis that all venous return and right heart output washes the pulmonary circulation, with lower dosage and avoidance of 'invasive' vascular access can maintain increased thrombolytic efficacy with less bleeding. This approach has previously been reported with a limited number of data which dramatically eliminated major bleeding complications while achieving excellent clinical results [10,13,34]. Current literature included multiple case reports regarding the use of low-dose t-PA for the treatment of pulmonary embolism. The doses and administration times are inconsistent, and many of these case reports use low-dose t-PA in patients with massive pulmonary embolism when full-dose t-PA was contraindicated or relatively contraindicated [35,36]. Previously, Sharifi *et al.* [10] reported that low-dose thrombolytic therapy (a 10-mg bolus by an intravenous push within 1 min 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 pulmonary embolism. Based on these promising results, we have adopted this low-dose systemic thrombolytic therapy with a 6-h infusion strategy as an option for 'escalation of care' in pulmonary embolism cases who had intermediate-high risk. The current study demonstrated that this regimen was associated with an overall excellent clinical outcome, in contrast to these prior reports which eliminated bleeding complications. Contrary to a previous report [13], the incidence of the total bleeding ($n = 2$, epistaxis and hemoptysis) in our study was 12.5% with

this thrombolytic therapy regimen. However, comparison of both studies revealed no significant difference between HAS-BLED scores. To best of our knowledge, this is the first study reporting the use of low dose, slow infusion of t-PA for the treatment of intermediate-high risk pulmonary embolism.

There are some remarkable points about pulmonary circulation. Unlike other organs that take part of the CO, the lungs take the integrity of the CO (in the absence of a shunt). From the existing guidelines, the 'standard practice' uses the same or similar t-PA dose for pulmonary embolism that is used for thrombolysis in the systemic arterial circulation [4,5]. For instance, in acute MI, 100 mg of t-PA is given within 1.5 h for a thrombus in the coronary circulation, which receives only 5% of the CO [37]. Similarly, 0.9 mg/kg of t-PA is used in acute ischemic stroke in which the cerebral circulation receives 15% of the CO [38]. These doses have the potency to withstand 'route attrition': t-PA is given into the venous circulation, it traverses the lung capillaries, enters the arterial circulation, reaches a steady-state, and is still capable of dissolving arterial clots. However, the crucial point, is whether it is necessary to use the same dose designed for thrombolysis in the systemic circulation for the lungs or not? Furthermore, another essential point is that it does not matter from which venous access site the t-PA is given as all t-PA molecules converge in the lungs. The corollary of this perspective might be applied to catheter-directed thrombolysis except for isolated segmental or subsegmental pulmonary embolism. In contrast to almost every other vascular bed with thrombosis, which would benefit from catheter-directed thrombolysis, in the lungs it would probably not be necessary if the pulmonary embolism is massive and diffuse because the lungs are the center of convergence of all venous flow, and, ultimately, all administered molecules of t-PA would reach the pulmonary circulation. We do not dispute the established efficacy of catheter-directed thrombolysis in the treatment of pulmonary embolism [17–19] but only suggest that a similar result might be obtained by thrombolytic therapy through the peripheral venous circulation using similar low doses.

Limitations of the study

It is important to emphasize limitations pertinent to the methods of this study. First of all, the current study included patients assigned to receive low dose, slow infusion of thrombolytic therapy regimen based on management adjudicated by different clinical multidisciplinary teams, with individual decisions. Second, this was a retrospective study and included a small patient population. Third, it should be emphasized that the decision of treatment strategy is clinical team's decisions regarding the method of thrombolytic therapy are profoundly influenced by bleeding risk. In general, patients at greater bleeding risk were typically referred for anticoagulation, whereas those at lower risk or those deemed to be sicker requiring more expedited care due to pronounced tachycardia and RV dysfunction were preferentially considered for low dose, slow infusion of thrombolytic therapy regimen. Finally, the very low average HAS-BLED score in the present case series reflects this clinically logical preferential bias; yet despite their low risk, this systemic thrombolytic therapy strategy was still associated with minor bleeding complications.

Conclusion

Prolonged thrombolytic therapy regimen with low dose, slow infusion of t-PA was found to be associated with a lower risk of major bleeding in patients with acute intermediate-high risk pulmonary embolism. These findings show that extending the duration of administration of thrombolytic therapy may increase safety without comprimising effectiveness. However, larger series of randomized controlled trials are needed to consider this regimen as an acceptable treatment modality.

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Conflicts of interest

All of the authors have no conflicts of interest.

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