

Thrombolytic-plus-Anticoagulant Therapy versus Anticoagulant-Alone Therapy in Submassive Pulmonary Thromboembolism (TVASPE Study): A Randomized Clinical Trial

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Abstract

Background: The use of thrombolytic agents in the treatment of hemodynamically stable patients with acute submassive pulmonary embolism (PTE) remains controversial. We, therefore, conducted this study to compare the effect of thrombolytic plus anticoagulation versus anticoagulation alone on early death and adverse outcome following submassive PTE.

Methods: We conducted a study of patients with acute pulmonary embolism and pulmonary hypertension or right ventricular dilatation/dysfunction but without arterial hypotension or shock. The patients were randomly assigned in a single-blind fashion to receive an anticoagulant [Enoxaparin (1 mg/kg twice a day)] plus a thrombolytic [Alteplase (100 mg) or Streptokinase (1500000 u/2 hours)] or an anticoagulant [Enoxaparin (1 mg/kg twice a day)] alone. The primary endpoint was in-hospital death or clinical deterioration requiring an escalation of treatment. The secondary endpoints of the study were major bleeding, pulmonary hypertension, right ventricular dilatation at the end of the first week, and exertional dyspnea at the end of the first month.

Results: Of 50 patients enrolled, 25 patients were randomly assigned to receive an anticoagulant plus a thrombolytic and the other 25 patients were given an anticoagulant alone. The incidence of the primary endpoints was significantly higher in the anticoagulant-alone group than in the thrombolytic-plus-anticoagulant group (p value = 0.022). At the time of discharge, pulmonary artery pressure was significantly higher in the anticoagulant-alone group than in the thrombolytic-plus-anticoagulant group (p value = 0.018); however, reduction in the right ventricular size or normalization of the right ventricle showed non-significant differences between the two groups. There was no significant difference regarding the New York Heart Association (NYHA) functional class between the two groups at the end of the first month (p value = 0.213). No fatal bleeding or cerebral bleeding occurred in the patients receiving an anticoagulant plus a thrombolytic.

Conclusion: When given in conjunction with anticoagulants, thrombolytics may improve the clinical course of stable patients who have acute submassive pulmonary embolism and prevent clinical deterioration.

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Introduction

Acute pulmonary embolism is a fatal event that occurs in 1 per 1000 patients and causes 50000 to 100000 deaths each year in the United States.¹⁻³

Pulmonary thromboembolism (PTE) is the obstruction of the pulmonary artery or one of its branches by a thrombus. The signs and symptoms vary from massive PTE, which can result in unstable hemodynamic status, to a small peripheral embolus, which can be asymptomatic and benign.⁴ The clinical outcomes of PTE vary greatly depending on the patient's characteristics and the type of PTE. The estimated 3-month mortality rate after diagnosis is 10% to 15%.^{1, 5} Nonetheless, 5% to 10% of patients with PTE have an unstable hemodynamic status and shock and, by comparison with patients without these characteristics, have a higher mortality rate of almost 60%.^{6, 7} Therefore, stratifying patients on the basis of their clinical signs and symptoms when PTE is suspected is of vital importance.

There is no clinical controversy as regards the treatment of patients with massive PTE and hemodynamic collapse. These patients warrant thrombolytic therapy unless contraindications preclude this management strategy. It is also clear that the PTE patients that present with a normal blood pressure and a normal right ventricular (RV) function tend to have excellent outcomes with anticoagulation therapy alone.^{8, 9} The debate centers on patients with submassive PTE who have RV dilatation and hypokinesia despite a normal blood pressure. The overall mortality and prognosis of patients with a normal systemic arterial pressure plus RV dilatation and dysfunction are grave compared with those of patients who have a normal systemic arterial pressure as well as a normal RV size and function.¹⁰ In patients with submassive PTE, degree of RV dilatation and dysfunction, severity of hypoxemia, and amount of clot burden in the pulmonary artery, although the prognosis is different, the clinical course may lead to either recovery or crisis. RV dilatation and hypokinesia will either resolve with supportive care or will evolve to hemodynamic collapse, requiring high-dose pressors, mechanical ventilation, or cardiopulmonary resuscitation and possibly death.

We designed a randomized clinical trial to compare the results of thrombolytic-plus-anticoagulant therapy and anticoagulant-alone therapy in patients with submassive PTE.

Methods

We performed a single-blind study in Loghman Hakim Hospital. The trial was initiated and followed by investigators and supported by Modarres Cardiovascular Research Center. The trial protocol was written by 3 of the academic investigators and reviewed, modified, and approved by the

research center. The data were gathered with the use of an electronic form, and the analyses were performed by an independent statistician.

Between April 2011 and November 2013, patients with submassive PTE whose diagnosis was confirmed by multi-slice computed tomography (CT) angiography were enrolled in our study sequentially. To be included in the trial, patients with PTE had to fulfill at least one of the following criteria, which were defined a priori: echocardiographically detected RV dysfunction or RV enlargement without left ventricular (LV) or mitral valve disease and echocardiographically detected pulmonary artery hypertension, defined as a tricuspid regurgitant jet velocity greater than 2.8 m per second.¹¹

Patients were excluded from the study if they had one or more of the following characteristics: age over 80 or under 18 years; hemodynamic instability, defined as persistent arterial hypotension (i.e. systolic pressure below 90 mmHg), with or without signs of cardiogenic shock; major surgery or biopsy within the preceding 7 days; major trauma within the preceding 10 days; stroke, transient ischemic attack, craniocerebral trauma, or neurologic surgery within the preceding 6 months; gastrointestinal bleeding within the preceding 3 months; uncontrolled hypertension; a known bleeding disorder; current therapy with an oral anticoagulant; current pregnancy or lactation; a life expectancy of less than 6 months because of underlying disease; or planned use of thrombolytic agents for extensive deep-vein thrombosis.

Written informed consent was obtained from all the patients. Assuming a power of 90% at an alpha level of 5% and on the basis of the data provided by Proudfoot et al.¹² with mortality up to 30% in Heparin-alone treatment compared with down to 0% in the thrombolytic-plus-Heparin group, we calculated that 25 patients would be required in each group. The eligible patients underwent randomization with the use of a computerized system, and randomization was performed in blocks to ensure the balanced distribution of the treatment groups.

Patients believed to have acute submassive PTE according to hemodynamic status and echocardiographic findings confirmed by pulmonary CT angiography (as previously defined) were enrolled in our study and randomly assigned to received Enoxaparin (1 mg/kg subcutaneous twice a day) as an anticoagulant versus Enoxaparin (1 mg/kg subcutaneous twice a day) plus Alteplase (100 mg/90 min) or Streptokinase (1500000 u/2 hours) as an anticoagulant plus a thrombolytic.

Overlapping oral anticoagulant therapy was started on day 3 after randomization, and the Warfarin dosage was adjusted to maintain an international normalized ratio of 2.5 to 3.5. The trial protocol permitted breaking of the randomization code if additional therapy had to be provided on an emergency basis to a patient whose condition was deteriorating.

The primary endpoint was in-hospital death or clinical deterioration necessitating an escalation of treatment.

Escalation of treatment was defined as the use of at least one of the following: infusion of a catecholamine because of persistent arterial hypotension or shock; secondary or “rescue” thrombolysis for one of the following indications: worsening clinical symptoms, particularly dyspnea, worsening respiratory failure due to pulmonary embolism, arterial hypotension or shock, and persistent or worsening pulmonary hypertension or RV dysfunction detected by echocardiography; endotracheal intubation; cardiopulmonary resuscitation; and emergency surgical embolectomy or thrombus fragmentation by catheter.

The secondary endpoints of the study were comprised of major bleeding or ischemic stroke during hospitalization, pulmonary hypertension, RV dilatation at the end of the first week, and exertional dyspnea at the end of the first month. Major bleeding was defined as fatal bleeding, hemorrhagic stroke, or a drop in the hemoglobin concentration by at least 4 g per deciliter, with or without the need for red-cell transfusion. Hemorrhagic or ischemic stroke was confirmed by CT or magnetic resonance imaging.

The patients were evaluated during and at the end of hospitalization. Transthoracic echocardiography parameters, consisting of the RV size and function and pulmonary artery pressure, were measured again at the end of the first week.

The data are presented as mean ± standard deviation. The

differences between the two groups in terms of the nominal variables were evaluated using the chi-squared and Fisher exact tests. The scale variables with normal distributions (based on the Kolmogorov-Smirnov test of normality and Q-Q plot) were compared between the two groups using the t-test. The non-normal scale variables and ordinal variables were compared using the Mann-Whitney test. In the last step, pulmonary artery pressure at discharge when considering the admission value of the participants was compared between the two groups using the analysis of covariance (ANCOVA). All the statistical analyses were performed using SPSS (version 21.0, IBM Co., Chicago IL). A p value < 0.05 was considered statistically significant.

Results

Totally, 125 consecutive patients were diagnosed with PTE in Lohman Hakim Hospital between April 2011 and November 2013. Among them, 59 (47%) had submassive PTE, but data registry was satisfied in only 50 patients. Fifty patients with submassive PTE and at least 1 month’s follow-up underwent randomization. Of these patients, 25 were assigned to the anticoagulant-plus-thrombolytic group and 25 to the anticoagulant-alone group. The two groups were well

Table 1. Characteristics of the two study groups*

	Total (n=50)	Thrombolytic plus anticoagulant group (n=25)	Anticoagulant alone group (n=25)	P value
Age (y)	55.7±12.4	54.8±14.1	56.6±10.5	0.612
Sex				0.999
M	20 (40.0)	10 (40.0)	10 (40.0)	
F	30 (60.0)	15 (60.0)	15 (60.0)	
PAP at admission (mmHg)	59.1±8.4	62.2±10.1	56.2±6.8	0.016
O ₂ Sat (%)	86.1±6.1	84.1±7.2	88.2±5.1	0.008

*Data are presented as mean±SD or n (%)

PAP, Pulmonary artery pressure; O₂ Sat, Oxygen saturation

Table 2. Treatment outcomes of the two study groups*

	Total (n=50)	Thrombolytic plus anticoagulant group (n=25)	Anticoagulant alone group (n=25)	P value
PAP (at the time of discharge) (mmHg)	33.0±9.2	31.5±9.1	34.5±9.2	0.018
NLRV				0.122
No	18/47 (38.3)	7/25 (28.0)	11/22 (50.0)	
Yes	29/47 (61.7)	18/25 (72.0)	11/22 (50.0)	
Success	44/50 (88.0)	25/25 (100)	19/25 (76.0)	0.022
NYHA FC				0.213
1	24/47 (51.1)	15/25 (60.0)	9/22 (40.9)	
2	16/47 (34.0)	7/25 (28.0)	9/22 (40.9)	
3	7/47 (14.9)	3/25 (12.0)	4/22 (18.2)	

*Data are presented as mean±SD or proportion(%)

PAP, Pulmonary artery pressure; NLRV, Normalized right ventricle; NYHA FC, New York Heart Association functional class



matched in terms of age and sex. Pulmonary artery pressure was elevated in both groups before treatment, but it was significantly higher in the thrombolytic-plus-anticoagulant group (62.2 ± 10.1 vs. 56.0 ± 6.8). O_2 saturation was significantly lower in the thrombolytic-plus-anticoagulant group (Table 1).

Table 2 demonstrates that the incidence of the primary endpoints was significantly higher in the anticoagulant-alone group than in the thrombolytic-plus-anticoagulant group (p value = 0.022). Death or escalation of treatment did not occur in the thrombolytic-plus-anticoagulant group, while it occurred in 6 of the 25 (24%) patients in the anticoagulant-alone group. Three (12%) patients in the anticoagulant-alone group died due to cardiac arrest secondary to PTE and 3 patients needed treatment escalation: one needed secondary thrombolysis because of arterial hypotension on the second day of admission; one needed endotracheal intubation owing to respiratory distress; and one was referred for surgical thrombectomy due to clinical deterioration on the third day.

Major bleeding did not occur in both groups. Hematuria occurred in one patient in the anticoagulant-alone group and in 2 patients in the thrombolytic-plus-anticoagulant group. The mean duration of hospital stay was 7.5 ± 1.5 days in both groups.

After treatment, pulmonary artery pressure was significantly higher in the anticoagulant-alone group than in the thrombolytic-plus-anticoagulant group (34.5 ± 9.2 vs. 31.5 ± 9.1) since pulmonary artery pressure was higher in the latter group before treatment.

No significant difference in the normalization of the RV was seen between the two groups.

At the end of the first month, the patients were evaluated for exertional dyspnea and their functional class was estimated according to the New York Heart Association (NYHA) classification, but there were no significant differences (Table 2).

Discussion

Previous studies have convincingly demonstrated the ability of thrombolytic agents to dissolve pulmonary emboli and to improve pulmonary perfusion and RV function.⁷⁻¹⁰

These medications are, therefore, recommended for the treatment of massive PTE. However, the efficacy of thrombolytic agents in the treatment of submassive PTE has remained unclear,¹² and identifying the patient population in which the benefits of thrombolysis may outweigh the associated risks of bleeding has been the subject of debate, mostly because of the lack of large-scale clinical trials.¹³ Our study was designed to address these issues directly. Our results indicate that thrombolytics, given with anticoagulants, improve the clinical course of hemodynamically stable patients who have acute submassive PTE and that they do so

with no risk of major hemorrhagic complications.

The clinical course and prognosis of patients with acute PTE vary widely, depending on their clinical and hemodynamic status at the time of diagnosis. In particular, RV dysfunction has been identified as a predictor of an adverse outcome.^{4, 5} Accordingly, in the current trial, we focused on patients presenting with evidence of pulmonary hypertension, RV dysfunction, or both of these conditions, which were prospectively defined according to strict echocardiographic and hemodynamic criteria.

In the current study, the patients in the two treatment groups were matched in terms of age and sex, but pretreatment pulmonary artery pressure was higher and O_2 saturation was lower in the thrombolytic-plus-anticoagulant group. Conversely, after treatment, pulmonary pressure was lower in this group. According to the results of the study, thrombolytic-plus-anticoagulation therapy decreased pulmonary artery pressure more than did anticoagulant-alone therapy (p value = 0.018).

By the end of the first week, 72% of the patients in the thrombolytic-plus-anticoagulation group had a normal RV compared to 50% in the anticoagulant-alone group, but the difference did not constitute statistical significance (p value = 0.100). In a study by Konstantinides et al.,¹⁴ (1998) who evaluated 40 consecutive patients with major PTE, at 12 hours systolic pulmonary artery pressure and RV size significantly decreased in the thrombolytic group; nonetheless, at the end of the first week, no difference was seen between the two groups regarding the overall change in the RV or LV dimensions or the final values of other echocardiographic parameters.

The in-hospital mortality rate was 6% in our study, and there was no significant difference between the two treatment groups. This finding chimes in with the result of the Analysis of the Management Strategies and Determinants of Outcome in Acute Major Pulmonary Embolism Registry,¹⁵ which reported a mortality rate of 8% among hemodynamically stable patients with RV dysfunction.

In our study, although there was no significant difference with respect to the in-hospital mortality between the two treatment groups, the incidence of primary endpoints, comprising in-hospital death and clinical deterioration requiring an escalation of treatment, was significantly higher in the anticoagulant-alone group than in the thrombolytic-plus-anticoagulant group (p value = 0.022). This result was concordant with that of the Konstantinides et al.¹⁶ study (2002), which compared Heparin plus Alteplase with Heparin alone in patients with submassive PTE and concluded that, when administered in conjunction with Heparin, Alteplase could improve the clinical course of stable patients with acute submassive PTE and could prevent clinical deterioration requiring treatment escalation during the hospital stay. Furthermore, event-free survival at 30 days was significantly better in the Alteplase group.

Thrombolysis may be associated with a significant increase in the risk of fatal or disabling hemorrhagic complications. However, the rates of bleeding in our patient population were very low, and no patient had intracranial or fatal hemorrhage after treatment with thrombolytics.

Our findings support the notion that thrombolytic therapy is a safe treatment modality for hemodynamically stable patients with acute submassive PTE, provided that it is not given to patients with contraindications to thrombolysis and provided that the patients' clinical condition and coagulation status are closely monitored.

We did not measure the markers of myocardial injury, which is one of the limitations of our study. Further studies on this group of PTE patients are required to shed more light on the subject.

Conclusion

When administered in conjunction with anticoagulants, thrombolytics may improve the clinical course of stable patients who have acute submassive PTE and prevent clinical deterioration, thereby obviating the need for treatment escalation during the hospital stay and reducing pulmonary hypertension effectively at the time of discharge. In light of the results of the present study, we believe that the indications for thrombolysis, which are currently limited to massive PTE, can be extended to include submassive PTE (manifested as RV pressure overload and dysfunction) in hemodynamically stable patients. Patients thus treated should be carefully monitored to ensure that they are at low risk of serious bleeding complications.

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