



Original Article

Thrombolysis with reteplase in acute pulmonary embolism

K.R. Nishanth^{a, *}, Ravi S. Math^a, Mythri Shankar^b, K.S. Ravindranath^a, C.N. Manjunath^a^a Sri Jayadeva Institute of Cardiovascular Sciences & Research, Bengaluru, India^b Institute of Nephro Urology, Bengaluru, India

ARTICLE INFO

Article history:

Received 10 February 2019

Accepted 1 September 2019

Available online 20 September 2019

Keywords:

Acute pulmonary embolism

Reteplase

Thrombolysis

ABSTRACT

Objective: Reteplase (recombinant plasminogen activator) is a mutant of alteplase. It has a longer half-life than its parent molecule and has shown better vessel patency rates in acute myocardial infarction. In this study, we analyzed the efficacy and safety of reteplase in acute pulmonary embolism (PE).

Methods: This observational study included patients with high- and intermediate-risk acute PE, presenting within 14 days of symptom onset. The patients were treated with reteplase, which was given in two bolus doses of 10 U each, 30 min apart, along with intravenous heparin. Patients with hemodynamic compromise (high-risk or massive PE) and normotensive patients with evidence of right ventricular (RV) dysfunction (intermediate-risk or submassive PE) on echocardiography or computed tomography were included in the study. The efficacy outcomes assessed were in-hospital death and improvement of RV function by echocardiography. The safety outcomes were major bleeding, minor bleeding, and ischemic or hemorrhagic stroke during hospitalization.

Results: Of the 40 patients included, 25% were classified as high risk with hemodynamic compromise and 75% were classified as intermediate risk. RV dysfunction was present in all the patients (100%). Concomitant lower extremity deep vein thrombosis was present in 55% of the patients. The mortality rate was 5%. There was significant improvement in RV function and reduction in pulmonary artery systolic pressure and tricuspid regurgitation severity. There was no major bleeding event or stroke, and 7.5% patients had minor extracranial bleeding.

Conclusions: Double-bolus reteplase given with heparin is effective in the treatment of high- and intermediate-risk PE, with minimal risk of bleeding.

© 2019 Cardiological Society of India. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Thrombolytic therapy is an established treatment modality in acute high-risk (or massive) pulmonary embolism (PE) with hemodynamic instability.¹ It effectively resolves thromboembolic obstruction and promptly reduces pulmonary artery pressure and

resistance with an increase in cardiac output. It has also shown to be superior compared with anticoagulation in intermediate-risk (or submassive) PE.^{2–6} Thrombolytic agents that have been shown to be of proven efficacy include streptokinase, urokinase, alteplase, and tenecteplase.^{1,7–10}

Reteplase is a third-generation fibrin-specific recombinant tissue plasminogen activator that lacks the finger, epidermal growth factor, and kringle 1 domains.¹¹ The slower clearance resulting from these changes in the molecular structure allows reteplase to be given as a nonweight-adjusted bolus.¹² In patients with acute myocardial infarction (MI), reteplase achieved more rapid and more complete thrombolysis of the infarct-related artery than alteplase, with no difference in bleeding rates.^{13–15}

Although the efficacy of reteplase in acute MI is known, only few case reports and case series have reported its utility in high- and intermediate-risk PE.^{16,17} In this study, we examine the efficacy and safety of reteplase in acute PE.

Abbreviations: aPTT, Activated partial tissue thromboplastin time; CT, Computed tomography; DVT, Deep vein thrombosis; ESC, European Society of Cardiology; INR, International normalized ratio; ISTH, International Society on Thrombosis and Hemostasis; MI, Myocardial infarction; STEMI, ST elevation myocardial infarction; PASP, Pulmonary artery systolic pressure; PE, Pulmonary embolism; RV, Right ventricle; SD, Standard deviation; TAPSE, Tricuspid annular plane systolic excursion; TTE, Transthoracic echocardiography; TR, Tricuspid regurgitation.

* Corresponding author. Sri Jayadeva Institute of Cardiovascular Sciences & Research, Bannerghatta Road, Bengaluru, 560102, India.

E-mail address: kr.nishanth@gmail.com (K.R. Nishanth).

<https://doi.org/10.1016/j.ihj.2019.09.011>

0019-4832/© 2019 Cardiological Society of India. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

2. Methods

2.1. Study design and patients

This was a prospective observational study conducted at a tertiary cardiac care center in India between January 2017 and March 2018.

Patients were included in the study if they met the following criteria: an age of 18 years or older, objectively confirmed acute PE with a symptom duration of 14 days or less, and right ventricular (RV) dysfunction confirmed by two-dimensional transthoracic echocardiography (TTE) or computed tomography (CT) of the chest. The diagnosis of PE was confirmed by CT of the chest.

Patients were excluded from the study if they had one or more of the following characteristics: prior intracranial hemorrhage, known cerebrovascular lesion, intracranial neoplasm, ischemic stroke within 3 months, active bleeding (except menses), known bleeding disorder, major surgery or major trauma within the preceding 3 weeks, gastrointestinal bleeding within the preceding 1 month, uncontrolled hypertension, current therapy with an oral anticoagulant, current pregnancy, or lactation.

Written informed consent was obtained from all patients before thrombolysis.

The choice of the thrombolytic agent was at the discretion of the treating physicians. The study protocol was approved by the local ethics committee.

2.2. Drug regimen

Patients diagnosed to have acute PE received an intravenous bolus of 5000 U of unfractionated heparin and two bolus doses of 10 U of reteplase given 30 min apart. Intravenous heparin infusion or subcutaneous enoxaparin was started 6 h after administration of the second bolus dose of reteplase. The heparin infusion rate was 1000 U per hour, and the rate was subsequently adjusted to maintain the activated partial thromboplastin time (aPTT) at 2.0 to 2.5 times the upper limit of normal. aPTT measurements were taken at 6-hour intervals. Enoxaparin was administered subcutaneously at a dose of 1 mg/kg twice daily. Overlapping oral anticoagulant therapy with warfarin was initiated on day 2 after thrombolysis, and the dosage was adjusted to maintain an international normalized ratio of 2.0–3.0.

2.3. Outcome assessment

After thrombolysis, the patients were evaluated upto the end of hospital stay and earlier if any clinical deterioration occurred. TTE was performed to assess RV function and pulmonary artery systolic pressure (PASP) 12–24 h after administration of reteplase and before discharge and earlier in case if any clinical deterioration. Efficacy of thrombolysis was assessed in terms of in-hospital death and persistent RV dysfunction with elevated PASP at discharge. The tricuspid annular plane systolic excursion (TAPSE) value of <17 mm measured by M-mode was considered RV systolic dysfunction.¹⁸ PASP estimated by the tricuspid regurgitation (TR) jet of >40 mm Hg was considered elevated.

Bleeding complications were classified as intracranial and extracranial. Extracranial bleeding was classified as major as per the criteria of International Society on Thrombosis and Hemostasis (ISTH)¹⁹ if it resulted in hemodynamic compromise, required transfusion or symptomatic bleeding in the critical area. The remainder of the bleeding was classified as minor.

2.4. Statistical analysis

Descriptive and inferential statistical analyses have been used in this study. The results of continuous measurements are presented as mean \pm standard deviation (minimum–maximum), and the results of categorical measurements are presented as number (%). Significance was assessed at a level of 5%. The Student *t*-test (two-tailed, independent) was used to find the significance of improvement in study parameters before and after thrombolysis. The chi-square/Fisher Exact test was used to find the significance of study parameters on the categorical scale between the different groups. The Fisher Exact test was used when cell samples were very small. A *p* value of <0.05 was considered significant. Data were analyzed using statistical software SPSS 18.0 and R environment version 3.2.2.

3. Results

3.1. Patient data

A total of 40 patients received reteplase for acute PE during the study period. The baseline characteristics of the patients are summarized in Table 1. The mean age of the patients was 39.3 \pm 12.6 years; the oldest patient was 71 years. Dyspnea was the most common symptom at presentation present in 95% patients. The time interval between symptom onset and thrombolysis (window period) was fewer than 3 days in 42.5%, 3–10 days in 37.5%, and more than 10 days in 20% of the patients. Concomitant lower extremity deep vein thrombosis confirmed by venous Doppler was seen in 55% patients. There was an identifiable provocation factor in

Table 1
Baseline characteristics of the study patients.

Characteristics	
Sex, no. (%)	
Male	29 (72.5)
Female	11 (27.5)
Mean age, yrs	39.3 \pm 12.6
Symptoms, no. (%)	
Dyspnea	38 (95)
Syncope	5 (12.5)
Fatigue	3 (7.5)
Chest pain	6 (15)
Window period, no. (%)	
< 3 days	17 (42.5)
3–10 days	15 (37.5)
>10 days	8 (20.0)
Blood pressure, no. (%)	
< 90 mm Hg	10 (25)
>90 mm Hg	30 (75)
Lower extremity DVT, no. (%)	22 (55)
RV systolic dysfunction, no. (%)	40 (100)
Mean PASP, mm Hg	64.5 \pm 12.9
Severity of tricuspid regurgitation, no. (%)	
Mild	11 (27.5)
Moderate	25 (62.5)
Severe	4 (10)
Risk stratification, ^a no. (%)	
High	10 (25)
Intermediate	30 (75)
PESI score, mean \pm SD	
High-risk patient group	132.2 \pm 22.5
Intermediate-risk patient group	81.4 \pm 24.5

DVT: deep vein thrombosis; PASP: pulmonary artery systolic pressure; RV: right ventricular; PESI: Pulmonary Embolism Severity Index; SD: standard deviation; ESC: European Society of Cardiology.

^a ESC definition of clinical risk.²⁰

only 17.5% of the patients (postpartum: 7.5%, recent surgery/immobilization: 10%). Detailed hypercoagulable workup could not be performed in the remainder of the patients owing to financial constraints. Twenty-five percent of the patients were classified as high risk and the remaining 75% were classified as intermediate risk based on the European Society of Cardiology definition for the level of clinical risk.²⁰ All the patients included in the study had RV systolic dysfunction before thrombolysis. The mean PASP estimated from the TR jet velocity by TTE was 64.5 ± 12.9 mm Hg. TR was severe in 10% patients, moderate in 62.5%, and mild in 27.5%. After thrombolysis, enoxaparin was administered to 55% of the patients, and the remaining received unfractionated heparin, followed by overlapping oral anticoagulant therapy.

3.2. Efficacy outcomes

The efficacy outcomes are summarized in Tables 2 and 3. The mortality rate in the study was 5% ($n = 2$). Both patients had hemodynamic compromise at presentation and died within 12 h owing to cardiogenic shock. There was no mortality in the intermediate-risk patients. RV systolic function assessed by TTE normalized in 80% patients ($p < 0.001$). The TAPSE improved from a baseline mean of 12.3 ± 1.6 mm to 20.3 ± 2.8 mm. The mean PASP reduced from a baseline of 64.5 ± 12.9 mm Hg to 37.1 ± 15 ($p < 0.001$). TR severity improved by at least one grade in 90% patients ($p < 0.001$). Of the 6 patients with persistent RV dysfunction with high PASP, 1 patient underwent emergency surgical pulmonary embolectomy in view of persistent hypotension and 2 (5%) patients received repeat thrombolysis with streptokinase 48 h after the reteplase dose. RV dysfunction persisted after repeat thrombolysis in both patients, and they were advised surgical embolectomy on follow-up.

3.3. Safety outcomes

None of the patients had intracranial bleeding or stroke. No major bleeding (as per ISTH criteria) was seen. Minor extracranial

Table 2
Efficacy and safety outcomes.

Outcomes	No. (%)
Death from any cause	2 (5)
Normalization of RV function	32 (80)
Improvement of TR severity	36 (90)
Repeat thrombolysis	2 (5)
Surgical embolectomy	1 (2.5)
Bleeding	
Intracranial	0 (0)
Major extracranial	0 (0)
Minor extracranial	3 (7.5)

RV: right ventricular; TR: tricuspid regurgitation.

Table 3
RV function, PASP, and TR: before and after fibrinolysis.

Parameter assessed	Before fibrinolysis	After fibrinolysis	<i>p</i> value
RV dysfunction, no (%)	40 (100)	8 (20)	<0.001 ^a
PASP mean, mm Hg	64.5 ± 12.9	37.1 ± 15	<0.001 ^b
Tricuspid regurgitation, no (%)			
Mild	11 (27.5)	34 (85)	<0.001 ^a
Moderate	25 (62.5)	4 (10)	
Severe	4 (10)	2 (5)	

RV: right ventricular; PASP: pulmonary artery systolic pressure; TR: tricuspid regurgitation.

^a Paired proportion test.

^b Student *t*-test.

bleeding occurred in 3 (7.5%) patients. The safety outcomes are summarized in Table 2.

4. Discussion

PE remains a common disease with a case fatality rate in the acute phase ranging from 7% to 11% despite thrombolytic therapy.^{21–23} Thrombolysis rapidly dissolves and reduces thrombus burden, thereby improving hemodynamics, gas exchange, and overall survival. Various thrombolytic agents have been tried including streptokinase, urokinase, alteplase, and tenecteplase. The first three need to be given as an infusion, whereas only tenecteplase can be given as a weight-adjusted bolus. Reteplase also has the advantage of bolus administration and does not need weight adjustment, thereby further simplifying its usage. Unlike tenecteplase, reteplase has been shown to have greater infarct-related patency in patients with acute MI than alteplase, although this did not transform into a mortality benefit.²⁴ With the availability of generic reteplase in India, its usage for ST elevation myocardial infarction has increased. We sought to evaluate the role of reteplase in intermediate-high risk PE. Before our study, one small randomized trial and few case studies have evaluated the efficacy of reteplase for PE.

In a randomized trial of 36 patients (23, reteplase and 13, alteplase), Tebbe et al¹⁷ demonstrated that reteplase led to greater and more rapid improvement in total pulmonary resistance, mean pulmonary artery pressure, and the cardiac index compared with alteplase. However, there was no difference at 24 h between the two groups. A thrombolytic therapy that leads to a more rapid reduction in pulmonary resistance could lead to faster hemodynamic improvement and potentially greater mortality reduction. The present study also noted a significant improvement in RV function, TR severity, and reduction of PASP. The RV systolic function normalized in 80% of cases. There was no significant difference between the high-risk and intermediate-risk patients in terms of improvement of aforementioned parameters. However, a higher mortality was observed in patients with high-risk PE, persistent RV dysfunction, and high PASP owing to hemodynamic instability, which lead to rapid clinical deterioration.

The mortality rate in the study was 5%, which included both high-risk and intermediate-risk PE. No patients with intermediate-risk PE in our study died. A review of randomized trials with other thrombolytic agents showed a mortality of 9.4% for high-risk PE⁹ and 2.2% for intermediate-risk PE.⁶ A recent case series by Ghobadi et al²⁵ reported successful thrombolysis of massive (high-risk) PE with the use of reteplase in 5 patients, with no mortality. A meta-analysis of intermediate-risk PE reported a clinical deterioration rate of 4.1% in patients receiving thrombolytic agents and 14.1% in the anticoagulant group.⁶ In our study, 7.5% of the patients had clinical deterioration, needing escalation of therapy in the form of repeat thrombolysis and surgical embolectomy.

Thrombolytic treatment is known to carry a risk of major bleeding, including intracranial hemorrhage. The reported incidence of major bleeding with thrombolytic therapy in PE ranges from 8.1% to 9.9%.^{1,6} In the present study, there was no major bleeding event, and minor bleeding occurred in 7.5% patients, which included bleeding gums, hemoptysis, and worsening of menstrual bleed. In the study by Tebbe et al,¹⁷ there was no stroke or intracranial bleeding reported with the use of reteplase. The low bleeding risk in our study may be due to the relatively low mean age of the patient population compared with other studies. The bleeding risk with the use of reteplase is not significantly different from other fibrin-specific agents.^{1,6,13} In the GUSTO III trial with the use of reteplase for acute MI, the rate of serious life-threatening bleeding was 0.95% and moderate bleeding was 6.9%.¹³

Our study has a number of limitations, the most important being the absence of a comparator arm. Although, this was a prospective study, patients receiving reteplase constituted only a minority of patients who were chosen for thrombolytic therapy. For economic reasons, the default thrombolytic agent in our institute is streptokinase. The decision to administer reteplase was at the discretion of the treating physician, which could bias the study results. It is possible that patients who received reteplase may have been chosen on the basis of a higher perceived risk. The third limitation is the relatively fewer number of patients. Yet the present study represents the largest experience until date with the use of reteplase in the treatment of PE.

5. Conclusion

In conclusion, our study indicates that reteplase given with heparin is effective in the treatment of intermediate- and high-risk PE with only a minor bleeding risk. The ease of nonweight-based bolus administration and the lower cost compared with other fibrin-specific agents makes it a good therapeutic option for thrombolysis in acute PE.

Conflicts of interest

All authors have none to declare.

Funding

None.

References

- Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J*. 2015;36:605–614.
- Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370:1402–1411.
- Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med*. 2002;347:1143–1150.
- Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the “MOPETT” trial). *Am J Cardiol*. 2013;111:273–277.
- Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost*. 2014;12:459–468.
- Xu Q, Huang K, Zhai Z, et al. Initial thrombolysis treatment compared with anticoagulation for acute intermediate-risk pulmonary embolism: a meta-analysis. *J Thorac Dis*. 2015;7:810–821.
- Thabut G, Thabut D, Myers RP, et al. Thrombolytic therapy of pulmonary embolism: a meta-analysis. *J Am Coll Cardiol*. 2002;40:1660–1667.
- Dong BR, Hao Q, Yue J, et al. Thrombolytic therapy for pulmonary embolism. *Cochrane Database Syst Rev*. 2009 Jul 8;(3). CD004437.
- Wan S, Quinlan DJ, Agnelli G, et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation*. 2004;110:744–749.
- Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *J Am Med Assoc*. 2014;311:2414–2421.
- Martin U, Bader R, Böhm E, et al. BM 06.022: a novel recombinant plasminogen activator. *Cardiovasc Drug Rev*. 1993;11:299–311.
- Simpson D, Siddiqui MA, Scott LJ, et al. Reteplase: a review of its use in the management of thrombotic occlusive disorders. *Am J Cardiovasc Drugs*. 2006;6(4):265–285.
- Global use of strategies to open occluded coronary arteries (GUSTO III) investigators. A comparison of reteplase with alteplase for acute myocardial infarction. Global use of strategies to open occluded coronary arteries (GUSTO III) investigators. *N Engl J Med*. 1997 Oct 16;337:1118–1123.
- Smalling RW, Bode C, Kalbfleisch J, et al. More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. *Circulation*. 1995;91:2725–2732.
- Bode C, Smalling RW, Berg G, et al. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. *Circulation*. 1996;94:891–898.
- Theron C, Laidlow DC. Life threatening massive pulmonary embolism treated with reteplase: a case report. *Crit Care Resusc*. 2000;2(4):278–281.
- Tebbe U, Graf A, Kamke W, et al. Hemodynamic effects of double bolus reteplase versus alteplase infusion in massive pulmonary embolism. *Am Heart J*. 1999;138:39–44.
- Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr*. 2015;1:1–39.
- Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694.
- Konstantinides SV, Torbicki A, Agnelli G. ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35(43):3033–3073.
- Laporte S, Mismetti P, Decousus H, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. *Circulation*. 2008;117:1711–1716.
- Aujesky D, Hughes R, Jimenez D. Short-term prognosis of pulmonary embolism. *J Thromb Haemost*. 2009;7(Suppl. 1):318–321.
- Stein PD, Kayali F, Olson RE. Estimated case fatality rate of pulmonary embolism, 1979 to 1998. *Am J Cardiol*. 2004;93:1197–1199.
- Cannon CP, Gibson CM, McCabe CH, et al. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators. *Circulation*. 1998;98(25):2805–2814. December 22–29.
- Ghobadi H, Amirajam Z, Habibzadeh A. Successful treatment of massive pulmonary thromboembolism with reteplase: case series. *Tanaffos*. 2018;17(1):53–56.