Original Article

Use of reteplase for thrombolysis in patients with massive pulmonary embolism diagnosed by bedside transthoracic echocardiography: A retrospective study of safety and efficacy

Bhupendra Verma[1], Avinash K. Singh[2]

[1]Department of Cardiology, Ujala Hospital, Kashipur, Uttarakhand, [2]Department of Cardiology, Khushlok Hospital, Bareilly, Uttar Pradesh, India

Abstract

Background: Pulmonary embolism (PE) is a lethal clinical condition requiring immediate systemic thrombolysis to decrease mortality. Reteplase has been extensively used in acute myocardial infarction but studies in massive PE are rare. We have presented here efficacy and safety of reteplase in patients with high risk PE diagnosed on basis of bedside transthoracic echocardiography. **Methods:** This was retrospective study including 20 patients of massive PE undergoing thrombolysis with reteplase. Bedside TTE was used to evaluate presence of RV dysfunction and thrombi in these patients with hemodynamic compromise. Safety and efficacy outcomes were analysed till three months of follow up. **Results:** 12 patients (60%) included in the study were males and mean age was 41 ± 19 years. The dyspnoea, chest pain and haemoptysis improved in all patients after thrombolysis. At discharge, RV dilatation normalised, systolic pulmonary artery pressure decreased, systolic blood pressure significantly increased and hypoxemia had completely corrected. Two patients had minor self-limiting bleeding episodes in form of mild haematuria and oral bleeding. During the follow up period of 3 months all patients were clinically stable and there were no bleeding episodes or death. Moreover, there was no recurrence of PE and/or DVT. **Conclusion:** Reteplase is highly efficacious in massive pulmonary embolism and results in rapid clinical improvement. Moreover, it can be safely used without increased risk of significant bleeding or mortality. Although limited by retrospective nature, reteplase appears to be an attractive option for massive PE but large prospective studies are further required.

Keywords: Anticoagulation, dabigatran, fibrinolytic therapy, low molecular weight heparin, thrombolytic therapy

Introduction

Acute pulmonary embolism (PE) is the most serious presentation of venous thromboembolism (VTE), which is the third leading cause of cardiovascular deaths after myocardial infarction and stroke.[1,2] Prevalence is increasing with ageing population since the risk of PE doubles with each decade after 40 years of age.[2] PE is clinically suspected usually on the basis of dyspnoea, cough, chest pain, hemoptysis, and/or poor oxygen saturation. The clinical classification of acute PE is based on the estimated risk of early mortality. The severity of PE is stratified into massive (high risk), submassive (moderate risk), and nonmassive or low-risk.[2,3] Massive PE represents right ventricular dysfunction leading to hemodynamic compromise being suspected or confirmed in the presence of shock or persistent arterial hypotension. This clinical stratification has important implications both for the diagnostic and therapeutic strategies. The International Cooperative Pulmonary Embolism Registry (ICOPER) demonstrated 90-day mortality rates of 58.3% in patients with massive PE versus 15.1% in submassive PE.[4]

Address for correspondence: Dr. Bhupendra Verma, Ujala Hospital, Kashipur - 244 713, US Nagar, Uttarakhand, India.
E-mail: bhupendra.269@gmail.com

Received: 30-06-2019 **Revised:** 22-08-2019 **Accepted:** 05-09-2019

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_512_19

How to cite this article: Verma B, Singh AK. Use of reteplase for thrombolysis in patients with massive pulmonary embolism diagnosed by bedside transthoracic echocardiography: A retrospective study of safety and efficacy. J Family Med Prim Care 2019;8:3155-9.

In patients with massive PE, systemic thrombolytic therapy is associated with lower all-cause mortality, decreases the risk of chronic thromboembolic pulmonary hypertension (CTEPH), and improves quality of life.[2,3,5-7] Therefore, persistent hypotension or shock (i.e. a systolic blood pressure <90 mmHg or a decrease in the systolic blood pressure by ≥40 mmHg from baseline) in the setting of acute PE is an emergency and requires immediate systemic thrombolysis.[8,9] Endovascular treatment strategies are recommended only in the event of treatment failure in this subset of patients.[7,10] The early and rapid resolution of pulmonary obstruction compared to anticoagulation alone leads to prompt reduction of pulmonary artery pressure and improvement of RV function. More than 90% patients benefit from thrombolysis when treatment is initiated within 48 h of symptom onset.[11]

Streptokinase, urokinase, and recombinant tissue plasminogen activator (rtPA) have been approved for thrombolysis in acute PE.[2,9] Newer thrombolytic drugs (reteplase and tenecteplase) are being increasingly used nowadays owing to putative advantages, such as ease of delivery (bolus dosing) and better fibrin specificity. Reteplase has an added advantage of weight independent (fixed) dosing. Moreover, reteplase has been shown to have similar results in terms of hemodynamic parameters when compared against rtPA (alteplase) in acute PE.[12] However, none of these agents are approved for use in PE due to lack of studies. Despite increasing off-label use of reteplase for massive PE, the available literature is limited to few case reports and small case series. Although the effectiveness of reteplase in acute myocardial infarction is known, few case reports and case studies have reported its utility in acute massive and submassive PTE.[12-16] Moreover, there is no data on use of reteplase in massive PE from Indian subcontinent.

In suspected massive acute PE, computed tomographic pulmonary angiography (CTPA) is recommended for diagnostic purposes.[2] However, use of CTPA is limited by availability, especially in resource poor third world countries. Suspected massive PE is a life-threatening situation and requires immediate diagnosis and treatment. The most useful test in this situation is bedside transthoracic echocardiography (TTE), which can show evidence of RV dysfunction and exclude other causes like acute valvular dysfunction, tamponade, acute coronary syndrome (ACS), and aortic dissection. Moreover, in a hemodynamically compromised patient with suspected PE, unequivocal signs of RV pressure overload and dysfunction justify emergency reperfusion treatment for PE if immediate CT angiography is not feasible (Class IC).[2,5,6]

In this study, we have reported 20 cases of massive acute PE, which were diagnosed on the basis of bedside TTE due to unavailability on-site CTPA. All these cases underwent systemic thrombolysis using reteplase. To our knowledge, this the largest study regarding use of reteplase in PE. Moreover, this is the first study of use of reteplase for thrombolysis in massive PE from Indian subcontinent.

Materials and Methods

Study population

The present study is a retrospective observational study carried out at a tertiary care hospital from December 2016 to March 2019. All patients admitted with acute massive PE and thrombolysed with reteplase were included in the study. Bedside TTE was used in all such suspected cases and systemic thrombolysis was done on the evidence of RV dysfunction in setting of hemodynamic compromise.[2] CTPA for confirmation after thrombolysis could be done only in 3 patients. Hospital records of all patients were reviewed for demographic data, predisposing factors, clinical presentation, diagnostic studies, hemodynamic status, and outcomes.

Study protocol

Bedside TTE was done by Esaote Mylab 50 Xvision with a 5-MHz transducer. In addition, in all patient's ECG, chest X-ray, ABG, hematological profile, serum troponin I levels, D-dimer, and hypercoagulability profile were done. Systemic thrombolysis was done by reteplase 10 units IV bolus over 2 min repeated after 30 min. Low-molecular-weight heparin (LMWH) was used for anticoagulation, which has greater effectiveness and safety and lower mortality compared to unfractionated heparin.[17] The ACCP recommends the use of direct-acting anticoagulants over warfarin for VTE treatment in patients without cancer.[18] Dabigatran was started next day of thrombolysis at a dose of 150 mg orally twice daily with concomitant parenteral anticoagulation for 5 to 10 days. Among newer novel OACs, only dabigatran has a commercially available reversal agent, idarucizumab, a monoclonal antibody that binds dabigatran in the serum.[19,20] Hospital discharge was done when the patient had clinically improved and was hemodynamically stable. The oral anticoagulation was continued and patients were followed up for at least 3 months.[18,21]

Definitions

Patients with PE were classified as high risk (massive) if there was evidence of hemodynamic compromise (defined as systolic blood pressure <90 mmHg or a decrease in the systolic blood pressure by ≥40 mmHg from baseline).[2] D-dimer testing was done using enzyme linked fluorescent assay and any value greater than 500 ng/ml was considered positive. Troponin I was done using electrochemiluminescence method and a value greater than 0.03 was considered abnormal. Echocardiographic criteria of RV dysfunction include RV dilation and/or an increased end-diastolic RV–LV diameter ratio (>0.9), hypokinesia of the free RV wall, increased velocity of the tricuspid regurgitation jet; or combinations of these.[2] Pulmonary hypertension was defined as pulmonary artery systolic pressures >40 mmHg.

Statistical analysis

The data were analyzed using GraphPad Prism 7, version 7.04 (GraphPad Software, Inc.). Baseline and follow-up information were summarized with descriptive statistics. Continuous variables were presented as means and SDs and categorical variables

Table 1: Baseline patient characteristics (*n*=20)

Age (years), mean±SD	41±19
Male sex	12 (60)
Elevated troponin I	15 (75)
Elevated D-dimer	19 (95)
Clinical presentation	
Dyspnoea	20 (100)
Cough	14 (70)
Chest pain	12 (60)
Hemoptysis	6 (30)
Presyncope/syncope	7 (35)
Signs of DVT	6 (30)
Poor oxygen saturation	18 (90)
Tachycardia	20 (100)
Tachypnoea	19 (95)
Raised JVP	11 (55)
Risk factors	
Previous PE/DVT	3 (15)
Surgery/Immobilisation	5 (25)
Cancer	1 (5)
Smoking	9 (45)
Diabetes mellitus	6 (30)
Hypertension	7 (35)
OCP/HRT	3 (15)
Hypercoagulable state	4 (20)
No obvious risk factors	5 (25)

Values shown represent numbers (percentages), except where otherwise noted. SD=standard deviation, JVP=jugular venous pressure, PE=pulmonary embolism, DVT=deep vein thrombosis, OCP=oral contraceptive pills, HRT=hormone replacement therapy

were expressed as frequencies and percentages. The *P* value for comparing two independent continuous variables was from unpaired student's *t*-test and for comparing two proportions was from the Chi-square test or Fisher exact test. All tests were two-sided, and statistical significance was at $P < 0.05$.

Results

Patient characteristics

Baseline patient characteristics are presented in Table 1. Out of 20 patients included in the study, 12 (60%) were males and mean age was 41 ± 19 years. The most frequent presenting symptom was dyspnoea seen in all patients followed by cough in 14 (70%), chest pain in 12 (60%), presyncope/syncope in 7 (35%), and hemoptysis in 6 patients (30%). The most common clinical sign was tachycardia (100%) followed by tachypnoea in 95% and poor oxygen saturation in 90% patients. Six patients (30%) had signs of DVT, and 11 patients (55%) had raised jugular venous pressure suggesting right heart failure. Overall, one or more risk factors of PE could be identified in 15 patients (75%) and in rest 5 patients (25%) no obvious cause was found. The risk factors seen were smoking (45%), hypertension (35%), diabetes mellitus (30%), prior surgery/immobilization (25%), hypercoagulable state (20%) and OCP/HRT use in 3 patients (15%). Elevated serum troponin I levels were seen in 15 patients (75%) and D-dimer was elevated in 19 patients (95%).

Table 2: ECG findings (*n*=20)

Sinus tachycardia	20 (100)
New-onset atrial arrhythmias	5 (35)
New RBBB (complete or incomplete)	13 (65)
Right axis deviation	7 (35)
QR pattern in V1	6 (30)
P pulmonale	5 (25)
S1Q3T3	12 (60)
T wave inversion in V1 through V4	14 (70)
T inversion in inferior and right precordial leads	7 (35)
ST segment changes	9 (45)
Clockwise rotation	2 (10)
Normal ECG excluding tachycardia	3 (15)

Values shown represent numbers (percentages), except where otherwise noted. ECG=electrocardiography, RBBB=right bundle-branch

ECG findings

Sinus tachycardia in ECG was seen in all patients. After excluding tachycardia, ECG appeared to be essentially normal in 3 patients (15%). The most frequent ECG abnormalities were T inversion in V1-V4 in 14 patients (70%), followed by new complete/incomplete RBBB in 65%, S1Q3T3 in 60%, and ST-T changes in 45% patients. Other findings were atrial arrhythmias (35%), right axis deviation (35%), QR pattern in V1 (30%), P-pulmonale (25%), and clockwise rotation 10% patients. ECG findings are depicted in Table 2.

Echocardiography findings

The most frequent echocardiography finding was RV dilatation (suggestive of RV dysfunction) seen in 18 patients (90%). Other common findings were McConnell's sign (65%), pulmonary hypertension (60%), paradoxical septal motion (65%), septal flattening (60%), and loss of respirophasic IVC collapse (60%). Less common features were tricuspid annulus plane systolic excursion (TAPSE) <17 mm in 40% patients, pulmonary ejection acceleration time <80 ms in 25% patients, and 60/60 sign in 20% patients. Pulmonary artery thrombi were seen in 3 patients (15%). Echocardiography findings are depicted in Table 3.

Outcome of therapy: Efficacy

The efficacy outcomes of reteplase therapy are shown in Table 4. The dyspnoea, chest pain, and hemoptysis improved in all patients after thrombolysis. At discharge, the RV dilatation normalized in all patients and systolic pulmonary artery pressure decreased from 56 ± 16 to 28 ± 12 mm of Hg ($P < 0.01$) and 63.9 ± 21.6 mmHg to 34.4 ± 19.8 mmHg ($P = 0.02$). The heart rate and respiration rate also decreased significantly till discharge. Moreover, the systolic blood pressure significantly increased from 79 ± 10 to 111 ± 18 mm of Hg. Hypoxemia rapidly improved with a significant increase in PaO_2 (62 ± 17 to 82 ± 11 mm of Hg) and SaO_2 (83 ± 13% to 97 ± 2%). RBBB completely improved in all patients after reteplase therapy. However, the resolution of PE on CTPA was documented in only 3 patients.

Table 3: Echocardiography findings (*n*=20)

RV dilatation (RV diameter/LV diameter >0.9)	18 (90)
RV free wall hypokinesis with apical sparing (McConnell's sign)	13 (65)
60/60 sign#	4 (20)
Pulmonary ejection acceleration time <80 msec	5 (25)
Paradoxical leftward septal motion	13 (65)
Interventricular septal flattening	12 (60)
Presence of PH*	12 (60)
Loss of respirophasic IVC collapse	12 (60)
Tricuspid annulus plane systolic excursion (TAPSE) <17 mm	8 (40)
Right heart thrombi	0 (0)
Pulmonary artery thrombi	3 (15)

Values shown represent numbers (percentages), except where otherwise noted. RV=right ventricle, LV=left ventricle, TR=tricuspid regurgitation, PH=pulmonary hypertension, IVC=inferior vena cava. # RV acceleration time of <or=60 ms in presence of tricuspid regurgitation pressure gradient <or=60 mm Hg. *Defined as pulmonary artery systolic pressure >40 mm of Hg

Table 4: Outcome of thrombolysis with reteplase in massive acute PE (*n*=20)

	At presentation	At discharge	*P*
Dyspnoea	20 (100)	0	<0.01
Chest pain	6 (30)	0	<0.01
Hemoptysis	12 (60)	0	<0.01
Heart rate (min)*	125±21	79±11	<0.01
Respiration rate (min)*	26±5	19±6	<0.01
PaO_2 (mm of Hg) *	62±17	82±11	<0.01
SaO_2 (%) *	83±13	97±2	<0.01
RV dilatation	14 (70)	0	<0.01
Systolic PAP (mm of Hg) *	56±16	28±12	<0.01
SBP (mm of Hg) *	79±10	111±18	<0.01
Patients with RBBB	13 (65)	0	<0.01

Values shown represent numbers (percentages), except where otherwise noted. * Mean±SD. PE=pulmonary embolism, RV=right ventricle, PAP=pulmonary artery pressure, SBP=systolic blood pressure, RBBB=right bundle branch block

Outcome of therapy: Safety

There were no major bleeding events defined as bleeding requiring hospitalization, blood transfusion, intracranial hemorrhage, or fatal bleeding during the study period. Two patients had minor bleeding episodes in form of mild hematuria and oral bleeding. No other clinically relevant events were observed during thrombolytic treatment. During the follow-up period of 3 months, all patients were clinically stable and there were no bleeding episodes or death. Moreover, there was no recurrent PE or deep-vein thrombosis (DVT) during the 3 months follow-up.

Discussion

Massive PE presenting with hemodynamic compromise is an emergency, leading to up to 60% mortality within 3 months.[4] The early and rapid resolution of pulmonary obstruction by systemic thrombolysis had been shown to decrease mortality and improve quality of life.[2,3] Accordingly, the current guidelines recommended the use of thrombolytics in high-risk patients with massive PE.[2,3,7] Reteplase is being increasingly used for thrombolysis in varied indications owing to lower bleeding, higher efficacy, greater fibrin specificity, bolus dosing, and weight independent dosing. However, its use in massive PE is limited to case reports. In this study, we have reported largest case series of use of reteplase for systemic thrombolysis in massive PE.

We have reported 20 cases of massive PE treated successfully with reteplase. All patients improved clinically along with improvement in hemodynamic and echocardiographic parameters. Liu and Wang reported that reteplase significantly relieved symptoms and hemodynamic state in a case series of 18 patients.[15] Similarly clinical improvement with reteplase had been reported in few recent studies.[13,16] Furthermore, all these studies including ours have shown rapid and significant improvement in hemodynamic and echocardiographic parameters.[13,15,16]

Moreover, reteplase had excellent safety profile with no major bleeding. During 3-month follow-up, all patients were clinically stable, there were no bleeding episodes, recurrent PE or DVT. Only two patients in our study had minor self-limited bleeding in the form of mild hematuria and oral bleeding. Reteplase has been shown to have similar safety and efficacy to alteplase in massive PE.[12] Similarly, bleeding complication of reteplase has been very infrequent in other case series.[13,15,16] No mortality was seen in our study during hospitalization and up to 3 months of follow-up. Similarly, in a case series of 10 patients of PE with intermediate risk there was no mortality.[13] However, in another case series of 18 patients with massive PE, there was 27.5% mortality. But in their study, clinical improvement was seen in only 66% patients and additionally one patient died due to cerebral hemorrhage.

Implications for primary care/healthcare professionals

From this retrospective study and earlier case reports, there is clear suggestion that reteplase is highly effective in massive PE with excellent safety profile. All patients in this study improved clinically with no mortality and major bleeding. This study adds to evidence base of current increasing off-label use of reteplase for thrombolysis. Reteplase appears to be suitable treatment alternative to first generation thrombolytics in massive PE. This view is further supported by the clear advantage of reteplase in other clinical settings like acute myocardial infarction. There is clear need for future research in the form of large prospective and randomized studies.

Study limitations

The major strengths of this study include the largest number of patients studied in context to reteplase till date and relatively longer duration of follow-up. This series adds to the current evidence supporting use of reteplase for thrombolysis in massive PE. However, there are significant limitation too. First, this was a retrospective study from a single center. Second, sensitivity and specificity of echocardiography for the diagnosis are limited compared with CTPA. Third, the sample size of patients with massive in this study is small. Finally, the findings of this study are subject to confounding and bias that are inherent to the observational studies.

Conclusion

Massive PE is a life-threatening condition requiring immediate systemic thrombolysis. In the present study, we have shown that reteplase is highly efficacious in this context and results in rapid clinical improvement. Moreover, it can be safely used without increased risk of significant bleeding or mortality. Although limited by retrospective nature, reteplase appears to be an attractive option for massive PE but large prospective studies are further required.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Wilbur J, Shian B. Deep venous thrombosis and pulmonary embolism: Current therapy. Am Fam Physician 2017;95:295-302.
2. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, *et al.* ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35:3033-69, 69a-69k.
3. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, *et al.* Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. Circulation 2011;123:1788-30.
4. Aggarwal V, Nicolais CD, Lee A, Riyaz Bashir R. (Oct 24, 2017). Acute Management of Pulmonary Embolism. Available from: https://www.acc.org/latest-in-cardiology/articles/2017/10/23/12/12/acute-management-of-pulmonary-embolism.
5. Roy PM, Colombet I, Durieux P, Chatellier G, Sors H, Meyer G. Systematic review and meta-analysis of strategies for the diagnosis of suspected pulmonary embolism. BMJ 2005;331:259.
6. Kucher N, Luder CM, Dörnhöfer T, Windecker S, Meier B, Hess OM. Novel management strategy for patients with suspected pulmonary embolism. Eur Heart J 2003;24:366-76.
7. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, *et al.* Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141 (2 Suppl):e419S-94S.
8. Tapson VF, Weinberg AS. Thrombolytic (fibrinolytic) therapy in acute pulmonary embolism and lower extremity deep vein thrombosis (Internet). 2019 [cited 2019 Jun 30]. Available from: https://www.uptodate.com/contents/ thrombolytic-fibrinolytic-therapy-in-acute-pulmonary-embolism-and-lower-extremity-deep-vein-thrombosis.
9. Hao Q, Dong BR, Yue J, Wu T, Liu GJ. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev 2018, Issue 12. Art. No.: CD004437. doi: 10.1002/14651858.CD004437.pub5.
10. Vedantham S, Piazza G, Sista AK, Goldenberg NA. Guidance for the use of thrombolytic therapy for the treatment of venous thromboembolism. J Thromb Thrombolysis 2016;41:68-80.
11. Meneveau N, Se×ronde MF, Blonde MC, Legalery P, Didier-Petit K, Briand F, *et al.* Management of unsuccessful thrombolysis in acute massive pulmonary embolism. Chest 2006;129:1043-50.
12. Tebbe U, Graf A, Kamke W, Zahn R, Forycki F, Kratzsch G, *et al.* Hemodynamic effects of double bolus reteplase versus alteplase infusion in massive pulmonary embolism. Am Heart J 1999;138:39-44.
13. Zhao HG, Wang SX, Lu ZN, Yan XX, Lyu ZC, Peng FH, *et al.* Clinical efficacy and safety of thrombolytic treatment with reteplase in patients with intermediate-risk acute pulmonary embolism. Zhonghua Xin Xue Guan Bing Za Zhi 2017;45:314-7.
14. Theron C, Laidlow DC. Life threatening massive pulmonary embolism treated with reteplase: A case report. Crit Care Resusc 2000;2:278-81.
15. Liu Z, Wang J. The use of reteplase in patients with pulmonary embolism reteplase after haemodynamic changes. Heart 2012;98(Suppl 2):E281-2.
16. Ghobadi H, Amirajam Z, Habibzadeh A. Successful treatment of massive pulmonary thromboembolism with reteplase: Case series. Tanaffos 2018;17:53-6.
17. Erkens PM, Prins MH. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev 2010:CD001100.
18. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, *et al.* Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315-52.
19. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, *et al.* Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511-20.
20. Verma B, Singh A, Kumar M. Use of dabigatran for treatment of left ventricular thrombus: A tertiary care center experience. J Family Med Prim Care 2019;8:2656-60.
21. Kearon C, Akl EA. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. Blood 2014;123:1794-801.