Pulmonary Embolism Successfully Treated with Tenecteplase: A Case Report

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Abstract:
Acute pulmonary embolism is a life threatening situation when presenting with hypotension is called high-risk (massive) pulmonary embolism (PE) which is associated with mortality, especially if there is hemodynamic instability, right ventricular dysfunction with thrombus. Thrombolytic therapy can be lifesaving and leads faster improvement in hemodynamics in patients with acute pulmonary embolism and cardiogenic shock which accelerates the resolution of thrombus, reduction of RV dilatation, mortality and recurrent PE. Only three fibrinolytic agents namely Recombinant tissue-type plasminogen activator (rtPA), Streptokinase and Urokinase have been approved in the treatment of PE. We report the case of a 64 years old Bangladeshi female with a history of immobilization due to unilateral cut injury of foot, who presented with shortness of breath and intermittent chest pain for a duration of 7 days during OPD visit. ECG showed sinus tachycardia (HR-120bpm, regular) and poor progression of R wave. Echocardiography revealed dilated RV,PA with RV dysfunction, presence of McConnell’s sign , RV apical & PA thrombus, flattened IVS, PHT, and minimal pericardial effusion, normal LV systolic function which was reported as suspected pulmonary embolism. Urgent hospitalization and CT pulmonary angiogram (CTPA) was done for confirmatory diagnosis which revealed large pulmonary thrombus in both right and left pulmonary artery. Thrombolysis with Tenecteplase (100ml) over 2 hours was started immediately along with intravenous normal saline and norepinephrine for hypotension, although, it was not recommended by the European Society of Cardiology (ESC) guideline, resulting a successful resolution of the PA thrombus and clinical improvement. She was discharged with oral anticoagulant Rivaroxaban.

Key Words: High-risk pulmonary embolism, Pulmonary artery thrombus, tenecteplase.

Introduction:
Acute pulmonary embolism (PE) is one of the most common, life-threatening cardiovascular events. In the past few years, the proportion of hospitalized PE patients has been gradually increasing. The most dreaded acute complication of PE is death & the estimated incidence of PE ranges from 39-115 per 100 000 population. Venous thromboembolism (VTE), clinically presenting as deep venous thrombosis or pulmonary embolism, is globally the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke. In 2019 guideline of the European Society of Cardiology (2019 ESC) presents risk stratification of patients with acute PE as high, intermediate and low risk. High- risk (Massive) pulmonary embolism (PE) is frequently complicated with hypotension and shock (hemodynamic compromise) leading to 90 days mortality rates of 58.3 % compared to 15.1% in intermediate-risk (sub-massive) PE. Up to 4% of patients who survive will develop chronic
thromboembolic pulmonary hypertension (CTEPH). Hemodynamic instability indicates a high risk of early (in-hospital, or 30 day) mortality and encompasses three forms of clinical presentation, cardiac arrest, obstructive shock and persistent hypotension. Conventional treatment of PE mainly refers to anticoagulation therapy including parenteral anticoagulation, such as low-molecular weight heparin (LMWH) or unfractionated heparin (UFH), and direct oral anticoagulation (DOACs). Those patients in particular benefit from more intensive therapy with thrombolytic agent in comparison to anticoagulant therapy alone, resulting in reduced mortality to less than 30% and improve right ventricular wall motion at 24h from baseline. Thrombolytic therapy leads to faster improvement in hemodynamics in patients with high-risk PE accompanied by a reduction in RV dilatation and RV dysfunction in echocardiography, a significant reduction in the combite outcome of mortality and recurrent PE, improving other parameters, such as pulmonary blood flow, lung perfusion. While its application in intermediate-risk PE was controversial. Streptokinase, urokinase and recombinant tissue-type plasminogen activator (rTPA, Alteplase) are thrombolytic agents approved for the treatment of PE, with Alteplase being explicitly identified as the agent indicated for acute massive PE. The international PEITHO (pulmonary embolism thrombolysis) trial found fibrinolytic therapy was associated with a 2.0% rate of hemorrhagic stroke and a 6.3% rate of major extra cranial hemorrhage for patients with intermediate-risk PE. Tenecteplase, a genetically modified variant of alteplase, can be administered as a bolus in an emergency and weight-based dosing may be preferable in elderly patients. It is less likely to cause allergic reaction compare to streptokinase, an antigenic thrombolytic agent.

This case report aims to demonstrate the importance of prompt imaging, early management and the efficacy of thrombolysis by TNK in complicated high risk (massive) PE. About 10% or more of cases of symptomatic PE are thought to be rapidly fatal and another 5% of patients are left with some residual symptoms and 2% developed thromboembolic pulmonary hypertension due to unresolved PE.

Case report:

A 64 years old hypertensive, diabetic Bangladeshi female visited as outdoor patient with complaints of progressive nature of shortness of breath associated with intermittent retrosternal chest pain for the duration of 7 days. One month prior to this event she reported that she had a cut injury on her left leg which was treated with suturing and was immobilized for a month. She was advised for echocardiography with relevant blood investigations. Her vital signs upon arrival to echo lab where a palpable SBP was 90 mmHg, HR of 120bpm, regular and Oxygen saturation of 90% at room air. ECG showed sinus tachycardia and poor progression of R wave (Figure-1). Emergency echocardiography was done, which showed dilated RV, PA with RV dysfunction, presence of McConnell’s sign (RV free wall hypokinetic with sparing apex) and RV apical and PA thrombus, flattened IVS, PHT, minimal pericardial effusion with normal LV function which was suspected pulmonary embolism (Figure-2). Urgent hospitalization and CTPA was done for confirmation of diagnosis and treatment.

On arrival to the CCU, patients was anxious, unable to speak a full sentence, cyanosed and needed 15 l of oxygen for maintaining oxygen saturation of 95%. Cardiac exam demonstrated tachycardia, raised JVP, fixed wide of the second heart sound, a right ventricular heave. Pulmonary findings consisted of bilateral crackles at the bases. RR-28 breaths /min. Her extremities were cool with non-recordable pulse and BP, healed wound in the left foot with no pain or swelling, rest of the general and systemic examination was unremarkable. Intravenous normal saline and Inotrope (noradrenalin) started to maintain BP and CTPA revealed multiple filling defects in both distal RPA/LPA, lobar and segmental branches predominantly lower vessels suggesting thrombus (Figure-3). Immediate thrombolysis was started with intravenous tenecteplase (100ml) over 2 hours as patient was elderly, hemodynamically unstable and needed urgent thrombolysis though it is not recommended in ESC guideline. The patient developed asystole 15 minutes after initiation of thrombolysis and reverted to sinus rhythm following 5 minutes of cardiopulmonary resuscitation (CPR). Tenecteplase was continued & 2 hours after thrombolysis there was subsequent clinical improvement with HR of 112bpm and BP found 100/60 mmHg with inotropic support, spo2 was 95% with high flow 02, RR was 32breath/min. Bed side echo revealed global hypokinesia with LVEF-45%, normal RV and resolution of PA thrombus 7 hours after thrombolysis. The next day the patient developed VT asystole and got DC shock with CPR multiple times, put on mechanical ventilator and reverted to sinus rhythm. D-dimer assay was positive, troponin I was raised, complete blood count (CBC) revealed neutrophilic leukocytosis the day after intubation. She also developed atrial fibrillation (Figure-4) with first ventricular rate and frequent non-sustained VT, got amiodaron during the course of her treatment. Gradually over day’s the patient’s condition was improved.
and inotropic support was decreased, Fio2 kept low. She was extubated on 6th day. Repeat CT pulmonary angiogram showed significant improvement of disease process compared with previous CTPA scan. Review echo revealed no thrombus or pulmonary hypertension, normal RV and normal LV function. Duplex USG of lower limb showed diffuse atherosclerotic changes in both lower limb arteries, mild flow reduction in right and left proximal ATA, PTA and severe flow reduction in left distal ATA and ADP. No venous thrombus or varicosity. Her treatment was followed by subcutaneous low molecular heparin (LMWH) for 5 days. Rivaroxaban given initially 15 mg twice daily for 21 days, then 20 mg once daily for 6 months. ECG during discharge showed sinus tachycardia, poor progression of R wave and SVE (Figure-5). She was asymptomatic at follow-up.
Fig.-3: CT pulmonary angiogram showing multiple filling defects in both distal Right & Left pulmonary artery, lobar and segmental branches suggesting thrombus.

Fig.-4: ECG after thrombolysis, showing Atrial fibrillation, HR 140 beats/min.

Fig.-5: ECG during discharge sinus tachycardia, poor progression of R wave and SVE.
Discussion:
This case of acute PE was presented with shock and followed by cardiopulmonary arrest is classified as high-risk pulmonary embolism as per European society of cardiology and massive PE according to American heart association (AHA). The ESC defines acute high-risk PE with persistent hypotension (systolic BP <90 mmHg, or systolic BP drop e’40 mmHg, lasting longer than 15 minutes and not caused by new onset arrhythmia, hypovolemia or sepsis or LV dysfunction).

Emergency multi-detector CTPA should be performed in hemodynamically unstable patients who are hypotensive or in shock because it allows adequate visualization of the pulmonary arteries down to the sub segmental level and it has 97% sensitivity for detecting emboli in the main pulmonary artery. If unavailable without delay, echocardiography should be performed to confirm the presence of right ventricular dysfunction.

Echocardiographic features of RV dysfunction such as RV dilatation (without hypertrophy), paradoxical septal systolic motion and pulmonary hypertension are independent predictive factors of adverse outcome in acute PE. It can also detect right heart & pulmonary artery thrombus which is a marker of worse prognosis with a prevalence of 4% to18% in the setting of an acute PE and those more hemodynamically compromised.

Elevated D-dimer which have a high negative predictive value, can be used for immediate risk stratification which increased in the short-term risk of death from PE. A normal D-dimer level renders acute PE or DVT unlikely. Elevation of cardiac troponin I or T indicated increased mortality and risk of complication.

Risk stratification of patients with acute PE is mandatory for determining the appropriate therapeutic management. Initial risk stratification is based on clinical symptoms and signs of hemodynamic instability, which indicate a high risk of early death. Remaining group of patients with PE without hemodynamic instability, further risk stratification requires to assess the prognostic criteria, namely clinical imaging and laboratory indicators of PE severity. This is related to the presence of RV dysfunction, presence of comorbidity and any other aggravating conditions that may adversely affect early prognosis. Of the clinical scores integrating PE severity and comorbidity, the pulmonary embolism severity index (PESI) score is the one most extensively validated to date, our patient had a pulmonary embolism severity index (PESI) score of 134, putting her in class-V with 30 day very high mortality risk of (10.0-24.5%) and warranting primary reperfusion. Pulmonary embolism severity index (PESI) scores used to estimate 30 day mortality and also be used as a tool to determine who can be safely managed as an outpatient and who should be considered for admission.

Thrombolytic treatment accelerates the dissolution of thrombus in acute PE and is potentially lifesaving. In critically ill patients where patient transport for CT is unsafe or unfeasible, thrombolysis should be considered in case of unequivocal signs of RV overload on bedside echocardiography has been associated with increased mortality in PE and multidetector CT should be performed later when the patient’s condition has been stabilized and the patients can be moved safely.

There are three thrombolytic regimens approved for the treatment of PE by the food and drug administration (FDA): streptokinase, urokinase and alteplase, with alteplase being explicitly identified as the agent indicated with a reduction in mortality among hemodynamically unstable patients with PE and This leads to a prompt reduction in pulmonary artery pressure and resistance, with a concomitant improvement of RV function and preventing of PE recurrence. A meta-analysis and systemic review done by Zhu Zhang et al. showed a total of six studies, with four randomized controlled trials (RCTs) and two cohort studies were included out of the 160 studies reviewed. For patients with high-risk PE, tenecteplase increased 30 day survival rate (16% vs. 6%, P=0.005) and did not increase the incidence of bleeding (6% vs. 5%; P=0.73). For patients with intermediate-risk PE, suggested that tenecteplase reduce RV insufficiency at 24 hour early in the onset and the incidence of hemodynamic failure without affecting mortality in a short /long term [<30 days RR=0.83, 95% CI(0.47,1.46); e’30 days RR=1.04, 95% CI (0.88, 1.22)]. However tenecteplase was associated with high bleeding risk [<30 days RR=1.79, 95% CI (1.61, 2.00);e’30 days RR=1.28, 95% CI (0.62, 2.64)]. Tenecteplase may represent a promising candidate for patients with high-risk PE. But tenecteplase is not recommended for patients with intermediate-risk PE because of high bleeding risk. LMWH tenecteplase at 3-month follow-up showed a better prognosis, quality of life, and functional capacity. In whom thrombolysis has failed or is absolutely contraindicated surgical embolectomy can be a lifesaving treatment option. Catheter based embolectomy is reserved for cases in which thrombolysis and surgical embolectomy is not possible.
As patients with acute pulmonary embolism are the risk for recurrent thromboembolism they should be given long term anticoagulation. The recommendation for PE secondary to a reversible risk factor is therapy with vit K antagonist for 3 months, titrated to a target INR of 2.0 to 3.0.\textsuperscript{2, 8} Novel oral anticoagulation (NOACs) i.e. Debigatran, rivaroxaban, apixaban are as effective and safe as warfarin for the treatment of venous thromboembolism.\textsuperscript{2, 8, 13} The Anti-Clot Treatment Scale (ACTS): rivaroxaban treatment was reported to result in improved treatment satisfaction compared with enoxaparin/VKA, particularly by reducing the patient-reported anticoagulation burden.\textsuperscript{20}

Follow-up of patients is important due to implications of long term anticoagulation and the probability of chronic thromboembolic pulmonary hypertension after or acute PE, the incidence of which up to 3.8% two years after the acute events.\textsuperscript{4}

**Conclusion:**

Acute high-risk pulmonary embolism can present with hemodynamic instability and RV dysfunction in predisposed patients. Pulmonary artery thrombus, although common, therefore, prompt diagnosis by confirmation with appropriate imaging techniques and rapid decision to thrombolysis such cases can be life-saving. Tenecteplase may represent a promising candidate for patients with high-risk PE. More large scale studies focused on tenecteplase are needed for PE patients.

**Conflict of interest:** None

**References:**


