Pulmonary thromboembolism (PTE) is a relatively common cardiovascular emergency and massive PTE has always been a major source of morbidity and mortality. The traditional window period for thrombolysis in patients presenting with acute PTE is two weeks. We present a series of three patients with sub-massive PTE, out of which two patients had acute and one patient subacute presentation. They had initially undergone catheter-based pulmonary embolectomy and intrapulmonary thrombolysis, but there was incomplete resolution of the thrombus in all three patients 48 hours after the procedures. Subsequently, they were treated with oral thrombolytic therapy (Lumbrokinase) for 12 weeks and all the patients had complete resolution of thrombus at three months follow-up and made a full recovery. To the best of our knowledge, the above-mentioned novel approach combined with adjunctive oral thrombolytic therapy is being reported for the first time.

**Case 1**
A 49-year-old Indonesian man, hypertensive and diabetic, presented with a three-week history of progressive dyspnea and chest pain, especially during breathing and one week history of hemoptysis prior to admission. On presentation, he was hemodynamically stable with oxygen saturation >95% on room air. The electrocardiogram (ECG) showed normal sinus rhythm. Laboratory analysis revealed a fibrin degradation test (D-Dimer) result of 4.08 μg/ml, Troponin I 0.19 ng/ml, and NT-ProBNP 2094 pg/ml. Computed tomography of pulmonary angiogram (CTPA) showed a large filling defect in the right pulmonary artery (PA) and a minimal filling defect in the left PA [Figure 1, pre-procedure, case 1]. The right ventricle (RV) was dilated. Catheter-based pulmonary thrombectomy was performed followed by intrapulmonary thrombolysis with Streptokinase for the next 10 hours. Repeat CTPA 48 hours post-procedure (pre-discharge) showed resolution of the thrombus in the left PA, but there was still a small thrombus in the right PA [Figure 1, pre-discharge, case 1]. The patient was discharged with dual antiplatelet and oral thrombolytic. Two capsules of Thromboles® (The Institute of Biophysics, Chinese Academy of Sciences, Beijing, China) each containing 250 mg of Lumbrokinase extract equivalent to 300,000 units of Lumbrokinase derived from an artificially cultured Lumbricus strain, were administered three times daily for 12 weeks. Follow-up CTPA at three months showed complete resolution of the thrombus in the right PA [Figure 1, follow up three months, case 1].

**Case 2**
A 37-year-old man, non-hypertensive and non-diabetic, presented with chest pain and dyspnea at rest for the previous one week prior to admission. He was hemodynamically stable. ECG showed sinus rhythm with T-wave inversion in V1-4. Laboratory results showed D-Dimer 5 μg/ml, Troponin I 0.35 ng/ml, and NT-ProBNP 5965 pg/ml. CTPA showed extensive thrombi in both left and right PAs [Figure 1, pre-procedure, case 2] and dilatation of the RV. Catheter-based pulmonary thrombectomy was performed, followed by intrapulmonary thrombolysis with Streptokinase for the next 10 hours. Repeat CTPA was performed 48 hours after the procedure (pre-discharge) and still showed thrombus in both PAs [Figure 1, pre-discharge, case 2]. He was discharged with dual anti-platelet
and oral thrombolytic (two capsules of Thromboles were administered three times daily for 12 weeks). Follow-up CTPA at three months showed complete resolution of thrombus in right PA [Figure 1, follow up three months, case 3 and Figure 2, case 3, follow up three months].

**Discussion**

Catheter-based interventions should be made an option in the presence of local expertise and availability of devices and facilities. Catheter-based management of PTE is important, and is usually combined with anticoagulant drugs. According to the 2014 ESC guideline for PE, patients without absolute contraindications to thrombolysis, catheter-directed thrombolysis or pharmacomechanical thrombolysis are preferred for these approaches.

All of our patients had undergone catheter-based thrombectomy with intrapulmonary artery thrombolysis. But this did not completely resolve all thrombi. Subsequently, they received Thromboles (Lumbrokinase) for 12 weeks on discharge and made a full recovery with complete resolution of thrombus in three months. Lumbrokinase is an State Food and Drug Administration (SFDA, China) approved pharmacotherapeutic. It is an oral potent fibrin-specific thrombolytic agent extracted from the earthworms. It is not only a plasminogen activator but also a fibrin-specific thrombolytic agent. Hence, it shows a double thrombolytic effect; it is specific in that it activates human tissue plasminogen activator (t-PA) and starts the normal cascade of our own system to dissolve the blood clots while it also has a great affinity for fibrin and specifically dissolves the clot.

Studies have shown that Lumbrokinase inhibits platelet activation and aggregation and blocks the intrinsic coagulation pathway. Unlike t-PA, Lumbrokinase exhibits thrombolytic activity only in the presence of fibrin. Therefore, Lumbrokinase has the advantage of not causing excessive bleeding. Lumbrokinase is safe, non-toxic, and has few side effects. It can be given orally, which is very convenient for patient use.

In China and other parts of the Far East, oral administration of earthworm powder has been used widely as a drug for the prevention and treatment of various diseases for several thousand years. Clinical studies indicate that orally administered Lumbrokinase is very effective in reducing coagulation of fibrin and blood platelets, and has no obvious side effects on nervous or respiratory system function, blood vessels, liver, or kidneys. Its use in thrombolytic therapy holds great promise for becoming an important therapeutic adjunct in the treatment of acute vascular occlusions, but such therapy has not reached the stage for general clinical use globally. Currently, there is no literature available evaluating the use of oral thrombolytics in massive PTE and its role and

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**Figure 1:** Pre procedure. Case 1: CTPA showing a large filling defect in the RPA (big arrow) and a minimal filling defect in the LPA (small arrow). Case 2: CTPA showing a large thrombus in the RPA (big arrow) and LPA (small arrow). Case 3: CTPA showing a large filling defect in the RPA (big arrow) and also large filling defect in the LPA (small arrow). Pre-discharge. Case 1: CTPA showing a filling defect only in the RPA (arrow). Case 2: CTPA showing a thrombus in the RPA (big arrow) and LPA (small arrow) although there was significant reduction of mean PA pressure. Case 3: CTPA showing no filling defect, neither in the RPA nor in LPA, but still seen in the right superior-anterior branch of RPA (see figure 2). CTPA denotes computed tomography of the pulmonary artery; RPA, right pulmonary artery and LPA, left pulmonary artery.
relationship with the clinical outcome. Our finding is based on only three patients, so our procedure and observations need further evaluation and verification in a greater number of patients with larger, multicenter, and randomized trials. This case report represents the first description of the use of oral Lumbrokinase in the treatment of PTE with mechanical thrombectomy with intrapulmonary arterial thrombolysis.

In conclusions, first, the use of an oral thrombolytic as an adjunctive maintenance therapy appears very promising and had a benefit in the treatment of this subset of PTE patients when catheter-based thrombectomy with intrapulmonary arterial thrombolysis was not enough to generate a full recovery with complete resolution of the thrombus. The safety profile of Lumbrokinase in patients with PTE has yet to be formally evaluated in large randomized trials. For complete resolution of thrombus we recommend post hospital discharge three months oral thrombolytic to continue even if RPA and LPA are free from thrombus at pre-discharge, because there are certain small branches which still can have some thrombus as seen in case 3 [Figure 2, case 3, pre-discharge].

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