Acoustic Pulse Thrombolysis for Treatment of Submassive Pulmonary Embolism

Noah J. Jones, MD
Mount Carmel Health System, Columbus, Ohio

Abstract: Pulmonary embolism (PE) is a major cause of mortality in the United States. Submassive (intermediate-risk) PE represents a treatment challenge. Systemic thrombolysis reduces mortality but increases the risk for major bleeding. Acoustic pulse thrombolysis (APT) is an endovascular-based catheter therapy FDA-approved to treat pulmonary embolus. Several recent studies suggest that APT effectively improves RV/LV ratio in submassive PE with minimal bleeding risk.

Key words: pulmonary embolism, acoustic pulse thrombolysis, OPTALYSE PE

Pulmonary embolism (PE) is a major cause of mortality in the United States, with 100,000 to 180,000 deaths attributed to PE annually, according to the US Surgeon General.1 Most patients (70%) who present with acute PE are deemed low risk because they have normal blood pressure and right ventricular (RV) function, and they typically only require anticoagulation. A small portion of patients (5%) present with massive PE, characterized by sustained hypotension, cardiogenic shock, syncope, respiratory failure, or cardiac arrest. Systemic thrombolysis reduces mortality in massive PE; nonetheless, more than half of cases are fatal.2

Between these two extremes are the roughly 25% of patients with PE who are normotensive but have evidence (either from echocardiography, computed tomography, or elevated cardiac biomarkers) of RV dysfunction. The latter group are categorized as having submassive (or intermediate-risk) PE, which is associated with poor outcomes and increased mortality. Data from the International Cooperative Pulmonary Embolism Registry (ICOPER) indicate a 90-day mortality rate of 15.1% in submassive PE.3

Patients in this latter category present a treatment challenge. Systemic thrombolysis reduces mortality in submassive PE patients by half yet is associated with a nearly three-fold increased risk of major bleeding, including intracranial hemorrhage (ICH), according to one meta-analysis.4 Moreover, there are a number of absolute contraindications to systemic thrombolysis, such as active bleeding, prior intracranial hemorrhage, or recent brain or spinal surgery. Additionally, there are many relative contraindications to systemic thrombolysis, suggesting that the therapy is only acceptable if the benefits clearly outweigh the risks of bleeding. Some of these contraindications include female gender, advanced age (75 years or older), any recent surgery, diastolic blood pressure greater than 100 mm Hg, diabetic retinopathy, and many others.5

Thus, new treatment options for submassive PE that confer lower bleeding risk are under investigation, including endovascular-based catheter therapies. The results of several earlier studies found that one endovascular modality recently approved by the US Food and Drug Administration—acoustic pulse thrombolysis (APT) with the EKOS device (BTG)—effectively reduced clot burden and improved RV/LV ratio and other features of submassive PE while using a fraction of the tissue plasminogen activator (tPA) required in systemic thrombolysis.6,7 Now, the recent multi-center OPTimum Duration and Dose of r-tPA with the Acoustic Pulse ThromboLYSis ProcEdure for Intermediate-Risk (Submassive) Pulmonary Embolism (OPTALYSE PE) found that very low doses of tPA, administered for shorter durations, effectively and rapidly resolved the RV dysfunction associated with submassive PEs with very low bleeding rates—and these results were supported by a full year of follow-up data.8,9 The results of OPTALYSE PE suggest that clinicians now have greater flexibility in selection of therapy, which enhances patient safety, and this could lead some institutions to change protocols for the treatment of submassive PE.

CASE DESCRIPTION

A 42-year-old woman with no history of vascular disease who had recently undergone knee surgery arrived at our hospital with symptoms of PE, including shortness of breath and tachycardia. Clinically, the patient’s vital signs were stable. She only required 2 liters of oxygen per minute. However, computed tomography revealed significant central clot burden. Her right ventricular to left ventricular (RV/LV) diameter ratio was 1.78 mm and her troponin was elevated at 1.5 ng/mL. The patient’s presentation was consistent with submassive PE and significant RV dysfunction and ischemia.

Given this patient’s age and history of recent surgery, we determined that she was a candidate for APT instead of systemic thrombolysis. Prior to OPTALYSE PE, our standard approach for treating this type of patient with submassive PE was to administer 1 mg of tPA bilaterally per hour for 12 hours, for a total of 24 mg with APT therapy. This regimen was demonstrated to be safe and...
Case Report

Effective in the SEATTLE II Trial, so we were comfortable adopting it as our institutional protocol for treatment of submassive PE. However, OPTALYSE PE, which included 17 medical centers, found that APT with EKOS therapy using doses as low as 8 mg of tPA over 2 hours (for bilateral PE) reduced right heart strain from PE (measured as RV/LV ratio) as effectively as the higher dose and longer duration of therapy used in SEATTLE II.

As a result of this patient’s increased bleeding risk, we elected to treat her with bilateral APT therapy with administration of 1 mg of tPA per hour through each catheter for 4 hours, for a total of 8 mg. Her symptoms resolved, she had no bleeding complications, and she was released the next day on oral anticoagulation.

Discussion

Using low-power ultrasound administered by catheter, APT is hypothesized to mechanically disturb the fibrin fibers of a thrombus and thereby promote greater penetration of tPA. Previously, the Ultrasound Accelerated Thrombolytic Pulmonary Embolism (ULTIMA) trial found that APT was superior to anticoagulation with heparin alone for the reversal of RV dilatation at 24 hours, with no increase in bleeding complications. In the single-arm SEATTLE II trial, ultrasound-facilitated, catheter-directed therapy with 24 mg of tPA decreased RV dilation, reduced pulmonary hypertension, and decreased thrombus burden. Major bleeding occurred in 10% of patients. No patients experienced intracranial hemorrhage (ICH).

The OPTALYSE PE trial builds on these studies, indicating that APT offers similar therapeutic benefits in submassive PE at significantly lower doses of tPA, which resulted in very low bleeding risks. The trial randomized 101 patients (mean age, 57.5; BMI, 35.9; 48%, female; Caucasian, 59%) with submassive PE to one of 4 cohorts:

- Cohort 1 received 2-hour duration of treatment with 2 mg/hr mg tPA per catheter bilaterally (for a total of 8 mg tPA).
- Cohort 2 received 4-hour duration of treatment with 1 mg/hr of tPA per catheter bilaterally (for a total of 8 mg tPA).
- Cohort 3 received 6-hour duration of treatment with 1 mg/hr of tPA per catheter bilaterally (for a total of 12 mg tPA).
- Cohort 4 received 6-hour duration of treatment with 2 mg/hr of tPA per catheter bilaterally (for a total of 24 mg of tPA).

Improvement in RV/LV ratio was statistically significant and similar across the 4 cohorts (ranging from 23% to 26%). Three out of 101 patients experienced major bleeding, for a rate of 3%. There were no major bleeding events in cohorts 1 and 3; there was 1 in cohort 2 and 2 in cohort 4 (including one ICH). We now have follow-up data from OPTALYSE PE indicating that patients in all 4 cohorts continued to improve over time. At 1 year, mean RV/LV ratio had fallen from >1.0 at baseline to the 0.7 range. Quality of life measures (including the Pulmonary Embolism Quality of Life Questionnaire and PROMIS-PF6) recorded valuable improvements in symptoms and ability to perform daily activities. All-cause mortality and recurrent PE were also very low (2%) as compared to other studies that exist in which anticoagulation was the treatment method.

In addition to enhancing patient safety, the lower, briefer dosing regimens demonstrated to be effective in OPTALYSE PE may have institutional benefits. For example, our ability to treat submassive PE with lower tPA doses and shorter duration has resulted in less time in the ICU for our patients. When we based our protocol for treating submassive PE on SEATTLE II, we would typically bring a patient into the catheterization lab at 7:30 am and put in the EKOS devices, which is a relatively quick procedure. The patient would then be brought to the intensive care unit (ICU) to receive the 12-hour infusion. That means the infusion would be complete at about 8:00 pm, which is after hours. As a result, the patient would remain in the ICU overnight, with the devices in place until they could be removed the next morning.

Today, typical infusions at our hospitals using the OPTALYSE PE protocol last 4 to 6 hours. That means we can often evaluate a patient and decide whether he or she can be transferred from the ICU to a regular hospital bed before the end of the day. For the clinician, that means more efficient patient management. The shorter duration of therapy using the OPTALYSE PE protocol allows us to free up beds in the ICU sooner, making them available for other patients. Prior to the completion of OPTALYSE PE, the submassive PE patients we treated with EKOS therapy remained in the ICU for 2 to 3 days, on average. Now, when we start EKOS therapy in the morning and use the OPTALYSE PE protocol, we routinely transfer patients out of the ICU on the same day as the procedure. This has the potential to produce a positive financial impact for the hospital.

We have treated more than 400 patients with APT at our institution since 2012. Despite the lower thrombolytic dose and shorter duration of infusion times, we still discuss the risks of minor and major bleeding with our patients at length, as well as other risks associated with the APT EKOS procedure.

Submassive PE represents a significant clinical challenge, particularly with regard to identifying the best treatment options for patients at increased risk for bleeding from fibrinolysis and who are at increased risk of clinical deterioration from ongoing RV dysfunction and ischemia. The availability of APT with the EKOS device provides one more tool for managing submassive PE, and the results of OPTALYSE PE give us greater flexibility to offer lower thrombolytic dose and shorter infusion times for our patients.

Disclosure: The author has completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The author reports that he is a paid speaker/consultant for BTG/EKOS.

Manuscript submitted November 30, 2017; accepted February 7, 2018.

Address for correspondence: Noah Jones, MD, Mount Carmel Health System, Columbus, Ohio. Email: njones@mchs.com

References


3. Goldhaber SZ, Buring JE, Lipnick RJ, Hennekens CH. Pooled...


