Design and rationale of a randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism

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ABSTRACT

Background: Catheter-directed interventions for the treatment of patients with submassive pulmonary embolism (sPE) have shown promise in rapidly improving right-sided heart strain and preventing decompensation to massive pulmonary embolism. Among various catheter interventions, ultrasound-assisted thrombolysis (USAT) has attracted interest as potentially having more efficient lytic effect that could achieve thrombolysis faster and with a reduced lytic dose. However, based on clinical evidence, it is unclear whether USAT is superior to standard catheter-directed thrombolysis (SCDT). We herein describe the study design of the Standard vs UltrasouNd-assiSted CathEter Thrombolysis for Submassive Pulmonary Embolism (SUNSET sPE) trial, an ongoing randomized clinical trial designed to address this question.

Methods: Adults with sPE presenting or referred to our institution are considered for enrollment in the trial. At the discretion of the treatment team, all patients undergo a catheter-directed intervention plus concomitant therapeutic anticoagulation. Participants are randomized 1:1 to a USAT catheter or an SCDT catheter. Study assessors are blinded to treatment group. The primary outcome is clearance of pulmonary thrombus burden, assessed by postprocedure computed tomography angiography. Secondary outcomes include resolution of right ventricular strain by echocardiography; improvement in pulmonary artery pressures; and 3- and 12-month improvement in echocardiographic, functional capacity, and quality of life measures. The study is powered to detect a 50% improvement in pulmonary artery thrombus clearance. Our enrollment target is 40 patients per treatment arm.

Conclusions: SUNSET sPE is an ongoing randomized, head-to-head, single-blinded clinical trial with the goal of assessing whether USAT results in superior thrombus clearance compared with SCDT in patients with sPE. We expect the results of our study to inform future guidelines on choice of thrombolysis modality in this population of challenging patients. (J Vasc Surg: Venous and Lym Dis 2018;6:126-32.)

Acute pulmonary embolism (PE) carries a high morbidity and is the third leading cause of cardiovascular mortality in the Western world. It accounts for 5% to 10% of in-hospital deaths, which for the United States translates to 200,000 deaths per year.[1] Recent registries and cohort studies suggest that approximately 10% of all patients with acute PE die during the first 1 to 3 months after diagnosis.[1-5] Studies that have observed survivors for >3 months have reported an incidence of chronic thromboembolic pulmonary hypertension (CTEPH) up to 5% as a result of residual thrombi causing increased pulmonary vascular resistance. CTEPH is an incapacitating long-term complication with a significant impact on the patient's quality of life and prognosis.[6-10]

Once PE is diagnosed, risk stratification is necessary to define appropriate management. It is typically stratified into three risk categories: high risk or massive, intermediate risk or submassive, and low risk. The distinction between these three groups is primarily based on hemodynamics and the presence of right-sided heart strain, which reflects the acute increase in pulmonary vascular resistance. Massive PE is characterized by circulatory shock and hypotension. Submassive PE (sPE) is characterized by clinical, radiographic, or biochemical evidence of right-sided heart strain in the absence of hypotension. Patients without any evidence of right-sided heart strain are classified as having low-risk PE.[3]

TREATMENT OF PE

The goals of treatment in patients with acute PE include prevention of decompensation to hemodynamic instability (if stable) and short- and long-term mortality[9,11,12] as well as potential prevention of CTEPH.[13-15]

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These outcomes have been linked to successful clearance of arterial thrombus burden.[3,9,11,12,14,15] Initial systemic anticoagulation (AC) is the standard of care and is used in nearly all patients. In patients with a low-risk PE, AC alone is sufficient to enable endogenous reduction of thrombus. However, in patients with evidence of right-sided heart strain or hemodynamic changes, treatment may be escalated with thrombolysis targeting faster thrombus reduction.

The introduction of catheter-directed therapies has provided an alternative to the use of systemic thrombolysis, which is effective in clearing thrombus but is plagued with high bleeding rates.[11,12] Proponents of catheter-directed therapies for PE suggest that they may provide therapeutic benefits similar to systemic thrombolysis but with lower doses of thrombolytic agent, thus potentially reducing the rate of bleeding events. The American Heart Association and European Society of Cardiology have both acknowledged catheter-directed therapies as a viable alternative to systemic thrombolysis, particularly in patients at high risk for a bleeding complication.[3,5] Standard catheter-directed thrombolysis (SCDT) requires placement of a multi-side hole infusion catheter within the pulmonary artery (PA) thrombus under angiographic guidance. Thrombolytic agents are slowly infused through the catheter, which is left in place for the duration of the treatment. Ultrasound-assisted thrombolysis (USAT) is a modification of this therapy using a proprietary system of local high-frequency, low-power ultrasound waves to dissociate the fibrin matrix of the thrombus, allowing deeper penetration of lytic medication.

Several observational noncontrolled series have demonstrated the efficacy of catheter-directed therapies in improving clinical and hemodynamic parameters and reducing clot burden in patients with sPE.[16-22] The Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial was the first randomized controlled trial comparing USAT plus AC with AC alone in the treatment of sPE in 59 patients.[23] The investigators found that the right ventricular to left ventricular (RV/LV) diameter ratio, the most commonly used echocardiographic measure of right-sided heart strain, was significantly reduced at 24 hours in the USAT group but not in the control group, although this difference was not evident at 90 days. In both study groups, there were no major bleeding events, and minor bleeding complications were rare. A Prospective, Single-arm, Multicenter Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (SEATTLE II) trial evaluated the effectiveness of USAT in patients with sPE, and it also showed an improvement in RV/LV ratio at 48 hours.[24] In our outcomes evaluation of the National Inpatient Sample, catheter-directed interventions for PE were associated with similar rates of in-hospital mortality but a significant reduction in the rate of hemorrhagic stroke compared with systemic thrombolysis.[25]

USAT VS SCDT

In vitro studies have demonstrated the improved penetration of thrombolytic agents with USAT.[26,27] The purported clinical benefit of this technology is that similar thrombus clearance may be achieved using lower doses of lytic agents or shorter duration of therapy. This, in turn, would be expected to decrease the rate of bleeding complications.

However, USAT compared with SCDT is costly and requires special equipment, adding some complexity. Little is known about whether USAT is superior to SCDT in the treatment of sPE in the clinical setting. Both the ULTIMA and SEATTLE II trials along with multiple other series used USAT only and did not enable any assessment of the contribution of ultrasound to clinical outcomes. Although favorable compared with systemic thrombolysis, these studies were associated with an estimated 3.5% major bleeding rate.[23,24,28,29] One series of 33 patients is the largest study to show equal thrombus clearance with reduced thrombolytic infusion time and treatment-related complications with USAT compared with SCDT.[28] A large prospective multicenter registry, on the other hand, noted no difference in outcomes by modality used.[21] Our retrospective analysis of 102 patients showed similar rates of survival, hemodynamic stabilization, and echocardiographic parameters between the two treatments.[22] A recent systematic review and meta-analysis of available data concluded that current evidence did not support the superiority of USAT over SCDT.[29]

To date, there are no randomized controlled trials comparing USAT with SCDT in patients with sPE. However, the BERN Ultrasound-enhanced Thrombolysis for Ilio-Femoral Deep Vein Thrombosis versUs Standard Catheter Directed thromboLysis (BERNUTIFUL) trial did compare USAT with SCDT in the treatment of 48 patients with acute iliofemoral deep venous thrombosis. The investigators found no difference in thrombus load reduction, venous patency, or symptoms of post-thrombotic syndrome to support an incremental benefit of USAT over SCDT.[16] Whether similar results would be found for sPE remains unknown. In an era of increasing focus on quality and cost-consciousness, the use of USAT over SCDT should be justified by prospectively demonstrated improvements in efficacy and safety. The Standard vs Ultrasound-assisted Catheter Thrombolysis for Submassive Pulmonary Embolism (SUNSET sPE) trial is an ongoing randomized, head-to-head, single-blinded clinical trial designed to address these objectives.

STUDY OBJECTIVES

Our primary objective is to determine whether USAT is associated with superior thrombus load reduction compared with SCDT in patients presenting with sPE. Our secondary objectives are to determine the change in RV function within 48 hours, in-hospital clinical