Standard vs Ultrasound-assisted Catheter Thrombolysis for Submassive Pulmonary Embolism

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SUMMARY

Background: Acute pulmonary embolism (PE) accounts for 5-10% of in-hospital deaths. Systemic anticoagulation (AC) is the standard of care and thrombolysis is recommended for those at a higher mortality risk. Catheter-directed therapies mainly standard catheter thrombolysis (CDT) and ultrasound-accelerated thrombolysis (USAT) have been introduced as new more effective and safer treatment modalities. USAT is a modification of standard catheter lysis utilizing a system of local ultrasound to dissociate the fibrin matrix of the thrombus, allowing deeper penetration of lytics. However, there is limited comparative effectiveness data against standard multi-sidehole catheter infusion. More rapid clearance of pulmonary thrombus by USAT compared to standard CDT may prove to be clinically and cost effective. Alternatively, if thrombus clearance is similar, the cost of USAT may exceed the cost of CDT (equipment and disposables), without offering any potential advantage.

Hypothesis: Ultrasound Accelerated Thrombolysis is superior to Standard Catheter Thrombolysis for patients with submassive PE

Objectives/Aims: 1. Determine differences in the percentage of thrombus load reduction (CTA Obstruction Index) from baseline to the termination of lysis; 2. Determine differences in cardiopulmonary and clinical outcomes; **3.** Determine differences in the impact of catheter directed intervention on functional capacity (NYHA score and 6-min walk test) and health-related quality of life outcomes (SF36, PE QOL, and San Diego Shortness of Breath questionnaires at 3 and 12 months; 4. Detail the cost differences in hospital resource utilization (i.e., procedure costs, adverse event costs, and hospital stay) and discharge costs (nursing care, subsequent outpatient care) to inform a Markov state-transition cost-effectiveness model.

Design: Randomized controlled trial.

Statistical Power: The study is powered on the primary endpoint. 40 patients will be needed at each group for a power of 0.80.

RESEARCH PLAN

a. SPECIFIC AIMS

Hypothesis: Ultrasound Accelerated Thrombolysis is superior to Standard Catheter Thrombolysis for patients with submassive PE

Aim 1: Determine differences in the percentage of thrombus load reduction from baseline to the termination of lysis between the two techniques

Aim 2: Determine differences in cardiopulmonary (echocardiographic, hemodynamic and respiratory parameters) and clinical outcomes (decompensation, mortality, complications, ICU stay) between the two techniques

Aim 3: Determine differences in the impact of catheter directed interventions on functional capacity and health-related quality of life outcomes at 3 and 12 months

Aim 4: Perform a cost effectiveness analysis to compare quality adjust life years and costs of the two techniques.

b. BACKGROUND AND SIGNIFICANCE

Acute pulmonary embolism (PE) carries a high morbidity and is the third-leading cause of cardiovascular mortality in the western world. It accounts for 5-10% of in-hospital deaths that 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) 1-5% within 2-3 years after PE.[6-10] It is an incapacitating long-term complication of thromboembolic disease with a negative impact on the patient's quality of life and prognosis.

The management acute PE is mainly guided by the acuity and severity of clinical presentation. Initial systemic anticoagulation (AC) is the standard of care and treatment is escalated based on the clinical presentation and patient characteristics that may stratify them at a higher mortality risk. The goals of therapy are to primarily prevent mortality, and secondarily potentially prevent late onset chronic thromboembolic pulmonary hypertension (CTEPH) and improve quality of life.[2, 3, 5, 11-14]

Massive PE is defined as PE associated with sustained hemodynamic instability, whereas submassive PE (sPE) is defined as PE without hemodynamic instability but with abnormal right ventricular (RV) function and/or evidence of myocardial necrosis.[3] It is notable that there is ongoing interest to accurately risk stratify sPE to identify the patients who are at increased risk of decompensating and/or dying. Clinical scores, imaging tests and biomarkers are under investigation, yet an ideal prognostic tool is still pending. A novel cardiac biomarker, heart-type fatty acid-binding protein (h-FABP), is emerging as a significant predictor of mortality in patients with submassive PE.[15, 16]

Systemic intravenous thrombolysis is universally recommended by all guideline bodies for massive pulmonary embolism, but remains controversial for submassive PE.[3-5, 17] In the most recent metaanalysis, the subgroup analysis of 8 submassive PE trials (1993-2014, n=1775)

showed that thrombolytic therapy was associated with a mortality reduction (1.39% vs 2.92%) but with an increase in major bleeding (7.74% vs 2.25%).[11] These results were mainly driven by the largest randomized trial (PEITHO, 1006 patients) which compared a single, weight-adapted i.v. bolus of tenecteplase with standard anticoagulation.[18]

The recent development of catheter-directed therapies such as catheter-directed thrombolysis (CDT), ultrasound-accelerated thrombolysis (USAT), and pharmacomechanical or aspiration thrombectomy has introduced more tools for the treatment of acute PE.[2] Proponents of these techniques suggest that they may provide a similar therapeutic benefit as systemic thrombolysis, while decreasing the dose of thrombolytic required and potentially decreasing the risk of adverse bleeding events.[19-24] Both the American Heart Association and more recently European Society of Cardiology have acknowledged CDT as a viable treatment alternative for high risk acute sPE (echocardiographic RV dysfunction and elevated cardiac biomarkers), if appropriate expertise is available and particularly when the bleeding risk is high.[3, 5]

Catheter-directed thrombolysis requires placement of a multi-sidehole infusion catheter within the pulmonary arterial thrombus burden under angiographic guidance. Thrombolytic medications are slowly infused through the catheter, which is left in place for the duration of the treatment. USAT is a modification of this therapy utilizing a proprietary system of local high frequency, low-power ultrasound to dissociate the fibrin matrix of the thrombus, allowing deeper penetration of lytic medication.

Several observational non-controlled series have demonstrated the efficacy of catheter-directed techniques in improving clinical and hemodynamic parameters and reducing clot burden while demonstrating a favorable safety profile.[2, 19, 23, 25-28] The ULTIMA trial was the first randomized controlled trial to include CDIs for sPE comparing standardized fixed-dose of USAT (10mg rtPA per lung over 15 hours) and AC to AC alone.[21] In the USAT group, but not in the heparin group, the mean RV/LV ratio was significantly reduced at 24 hours, but became comparable between the two groups at 90 days. The RV systolic function was significantly improved in the USAT group vs. the heparin group at both 24 hours and 90 days. In both study groups minor bleeding complications were rare and there were no major bleeding complications. The SEATTLE II trial, a single-arm study evaluating the effectiveness of USAT, showed also an RV/LV ratio improvement at 48 hours.[29]

Limited data exists for comparing different catheter-directed therapies for acute PE. The majority of recent series for catheter-directed interventions utilize USAT exclusively; however there is limited comparative effectiveness data comparing this modality to standard multi-sidehole catheter infusion.[15, 16, 19, 30] Preliminary, non-controlled data are conflicting. One series by Lin and colleagues of 33 high-risk PE patients suggested benefit for USAT for angiographic clearance of thrombus burden with more bleeding events in the CDT group.[31] Kuo and colleagues noted no difference in outcomes and treatment specifics between USAT and CDT in the recently published early results of a multicenter prospective registry.[28] Our retrospective analysis of 63 patients suggests that there may be no difference between the two treatment modalities, demonstrating similar rates of outcomes such as survival, hemodynamic stabilization, and echocardiographic parameters in both groups with similar procedure length and lytic dose in the time-adjusted cohorts.[32] Selection bias cannot be underestimated in all these studies.

The expected benefit of USAT has been dependent on the device's ability to increase penetration of lytic into thrombus using high frequency, low power ultrasound, due to its reversible effects on fibrin dissociation.[19, 21] This benefit has been shown to result in faster thrombus clearance in selected vascular beds in some studies, such as the recently published DUET study comparing USAT and CDT in arterial occlusions.[33] Evidence from the venous circulation, coming

from the recent BERNUTIFUL trial demonstrated no difference in time to thrombus clearance in lower extremity deep venous thrombosis.[34]

c. INNOVATION

There are no randomized controlled studies that have compared the outcomes of catheter directed thrombolysis with and without ultrasound acceleration. More rapid clearance of pulmonary thrombus by USAT compared to standard CDT may prove to be clinically and cost effective (e.g. via reduced length of ICU and hospital stay). Alternatively, if thrombus clearance is similar, the cost of USAT may exceed the cost of CDT (proprietary equipment and disposables), without offering any potential advantage.

Preliminary, non-controlled data are conflicting. One series by Lin and colleagues of 33 high-risk PE patients suggested benefit for USAT for angiographic clearance of thrombus burden with more bleeding events in the CDT group.[31] Kuo and colleagues noted no difference in outcomes and treatment specifics between USAT and CDT in the recently published early results of a multicenter prospective registry.[28] Our retrospective analysis of 63 patients suggests that there may be no difference between the two treatment modalities, demonstrating similar rates of outcomes such as survival, hemodynamic stabilization, and echocardiographic parameters in both groups with similar procedure length and lytic dose in the time-adjusted cohorts.[32] Selection bias cannot be underestimated in all these studies.

A controlled randomized study will better determine if ultrasound acceleration adds any benefits in the outcomes and costs of catheter directed thrombolysis for patients with acute submassive PE.

d. APPROACH

The study will be designed as a randomized controlled trial comparing standard catheter directed thrombolysis to ultrasound accelerated thrombolysis for the treatment of acute submassive PE.

The study will include patients eligible for catheter directed thrombolysis per the study protocol for submassive PE (CT or echocardiographic RV strain (defined as RV/LV ratio >1) without persisting hypotension <90mmHg or drop of systolic blood pressure by at least 40mm Hg for at least 15 minutes with signs of end-organ hypoperfusion (cold extremities or low urinary output <30 mL/h or mental confusion) and without the need of catecholamine support or cardiopulmonary resuscitation).

The treatment with CDT or USAT are standard of care for submassive PE. All the procedures, tests and follow up visits are according to current standard of care.

Exclusion criteria: age <18; pregnancy; index PE symptom duration >14 days; high bleeding risk (any prior intracranial hemorrhage, known structural intracranial cerebrovascular disease or neoplasm, ischemic stroke within 3 months, suspected aortic dissection, active bleeding or bleeding diathesis, recent spinal or cranial/brain surgery, recent closed-head or facial trauma with bony fracture or brain injury); participation in any other investigational drug or device study; life expectancy <90 days; and inability to comply with study assessments.

At baseline all patients need to have

1. Chest CT angiogram with contrast diagnostic of PE
2. Baseline transthoracic echocardiogram
3. Baseline cardiac biomarkers
    a. Cardiac troponin (cTn)
    b. Brain Natriuretic Peptide (BNP) and/or N-terminal pro-BNP (NT-proBNP)

All patients will be treated initially with unfractionated heparin by using a standardized dosing protocol. Immediately after consent, vital signs will be recorded, a pulse oximetry reading will be obtained with the patient breathing room air for 2 min.

All eligible patients will undergo catheter-directed thrombolysis randomized to either a standard commercially available multi-sidehole catheter or a USAT catheter.

Technical considerations (access, intraoperative tPA bolus, tPA dripping dose etc) will be left to the discretion and preference of the operator. Invasive pressure tracings will be obtained from the drug delivery catheters when positioned in the pulmonary arteries (main, right or left). The maximum tPA dosing should not exceed 24mg.

Termination of lysis will be left to the discretion of the operator. As a general recommendation lysis should be terminated once clinical (e.g. O2 requirements), hemodynamic (e.g. pulse rate or blood pressure) and/or echocardiographic parameters (e.g. RV dilatation) improve or if a complication occurs. Lysis catheters and sheaths can be removed at the bedside. Before removal, invasive pressure tracings will be recorded from the drug delivery catheter.

A transthoracic echocardiogram should be obtained just before or within 24 hours after the termination of lysis.

Within 48h after the termination of lysis patients will get a chest CTA examination.

Patients will be followed up at 3 months and 12 months.

Primary Endpoint: PE thrombus load reduction (CT obstruction index) from baseline to the termination of lysis.

The pre and post lysis CTA will be compared by 2 blinded independent radiologists. For determining the CT obstruction index, the arterial tree of each lung will be considered to have 10 segmental arteries (three to the upper lobes, two to both the middle lobe and the lingula, and five to the lower lobes). The vascular obstruction scores will be determined as previously described by Qanadli et al. and Mastora et al.[35,36]

Secondary Endpoints:

1. Clinical outcomes comparison
    a. In hospital and 90-day mortality
    b. Decompensation to massive PE (hypotension <90mmHg and use of catecholamines)
    c. Major and minor bleeding. Major bleeding is defined as overt bleeding associated with a fall in the hemoglobin level of at least 2.0 g/dL or with transfusion of ≥2 U of red blood cells or involvement of a critical site (intracranial, intraspi-nal, intraocular, retroperitoneal, intra-articular or pericardial, or intra-muscular with compartment

syndrome). Clinically overt bleeding not fulfilling the criteria of major bleeding is classified as a minor bleeding complication.

d. Recurrent venous thromboembolism (VTE) during 90-day follow-up. There will be no routine surveillance for asymptomatic recurrent VTE. Recurrent VTE will be diagnosed if suspected symptoms or signs of deep vein thrombosis or acute PE are objectively confirmed by an imaging test (new filling defect by pulmonary angiography or contrast-enhanced chest CT, new high-probability perfusion defect revealed by lung scan, or positive compression ultrasound study for deep vein thrombosis).
e. Major adverse events up to 90 days after randomization.
f. Clinical success: PE related decompensation prevention without a 90-day major adverse event or death.
g. ICU length of stay

2. Echocardiographic parameters comparison
    a. RV/LV, TAPSE (Tricuspid annular plane systolic excursion) and RVSP (Right Ventricular Systolic Pressure) improvement from baseline to the termination of lysis
    b. RV/LV, TAPSE and RVSP at 90 days
    c. RV/LV, TAPSE and RVSP at 12 months

    The echocardiograms will be interpreted by 2 blinded independent cardiologists.

3. Functional status and quality of life
    At the 3 and 12-month follow-up visit, patients will complete a written survey to assess the NYHA score and answer other questions about functional status. Patients will then perform a 6-minute walk test according to published guidelines.[37,38]Transthoracic echocardiography will be also performed as described earlier.

    Quality of life will be assessed at 3 and 12 months using SF36, PE QOL, and San Diego Shortness of Breath questionnaires.

4. Cost effectiveness analysis
    A Markov state-transition, cost effectiveness model will be created to simulate patient oriented outcomes assuming a societal perspective with a 12-month time horizon. All point estimates for model parameters will be determined from the prospectively collected data, as described above. Quality adjusted life years will be determined for each therapy based on survival, freedom from major adverse events, discharge status, functional status, and quality of life measures. Costs will be calculated for each therapy based on in-hospital resource utilization (i.e., length of stay in the ICU, operating room and procedure costs, and associated adverse event costs) and out-of-hospital costs (outpatient nursing care, loss of work, outpatient testing and follow-up).

Schedule of Events

	Baseline	Screening	Randomization US assisted or standard catheter thrombolysis	Lysis Procedure	Prior to Lysis Termination or within 24h post lysis	Within 48hrs post lysis	3month f-up +/-14 days	12month f-up +/- 30 days
Informed Consent		X						
Chest CTA	X					X		
Transthoracic Echocardiogram	X				X		X	X
Cardiac troponin (cTn)	X							
Brain Natriuretic Peptide (BNP)	X							
N-terminal pro-BNP(NT-proBNP)	X							
IV Unfractionated Heparin		X						
Vital Signs		X						
2min Pulse Ox		X						
Ultrasound Catheter Placement			X	X				
Standard Catheter placement			X	X				
Invasive Pressure Tracings from drug delivery catheter				X(a)	X(b)			
Functional Status NYHA							X	X
Quality of Life Questionnaires							X	X
Six Minute Walk Test							X	X

(a) Before lytics administered

(b) After lytics administered

Statistical Analysis:

The study is powered on the primary endpoint that is thrombus load reduction (obstruction index). We propose to compare standard CDT and USAT at post-treatment with analysis of covariance, controlling for differences remaining after randomization. Population parameters for the obstruction score have not been published, so we consulted several relevant studies reporting on thrombus reduction scores in order to predict sample size.[19,31,34,39] We assumed that CDT with ultrasound enhancement (USAT group) should be ≥50% more effective than without ultrasound enhancement (control group) and calculated an expected relative mean thrombus reduction of 43% in the CDT control group.[40.41] We estimated a sample size of 40 per group to detect the differences with a power of 0.80.

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