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Catheter-directed aspiration thrombectomy and low-dose thrombolysis for patients with acute unstable pulmonary embolism: Prospective outcomes from a PE registry

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ABSTRACT

Objectives: To evaluate the efficacy and safety of aspiration thrombectomy in combination with low-dose catheter-directed thrombolysis for acute unstable pulmonary embolism (**PE**).

Background: Acute unstable (**PE**) is a life-threatening condition requiring treatment escalation, but many patients cannot receive full-dose systemic thrombolysis due to contraindications.

Methods: Eligible patients had a PE with sustained hypotension. We used a 115-cm, 8-F continuous aspiration mechanical thrombectomy catheter to perform mechanical thrombectomy, followed by catheter-directed thrombolysis with low-dose urokinase. The primary efficacy outcome was the change in the pulmonary artery pressure after aspiration thrombectomy and catheter-directed thrombolysis. Secondary efficacy outcomes were stabilization of hemodynamics post-procedure and survival to hospital discharge. The primary safety outcome was major procedure-related complications and major bleeding events.

Results: We included 54 patients with acute unstable PE. After thrombectomy, mean systolic pulmonary artery pressure decreased from 60.2 mm Hg to 55.2 mm Hg ($P < 0.01$), and to 40.5 mm Hg after catheter thrombolysis ($P < 0.0001$). The in-hospital PE-related death occurred in six patients (11%; 95% confidence interval [**CI**], 4.2–23%) at a mean follow-up of 1.1 days, and hemodynamics stabilized in the remaining 48 patients. Minor complications after thrombectomy included arrhythmias (4 of 48 patients, 8.3%; 95% CI, 2.3–20%), and minor bleeding episodes (3 of 48 patients; 6.2%; 95% CI, 1.3–17%). Major complication occurred in one patient (2.1%; 95% CI, 0.1–11%) who developed hemorrhagic transformation of paradoxical embolic stroke following catheter-directed thrombolysis.

Conclusions: Aspiration thrombectomy followed by catheter-directed thrombolysis was overall effective and safe in treating patients with acute unstable PE.

1. Introduction

Pulmonary embolism (**PE**) remains a worldwide major health issue [1]. Previous observational data have shown that short-term mortality in patients with acute PE has decreased over time [2]. The emergence of pulmonary embolism response teams have facilitated evaluation and delivery of advanced therapies for severe PE [3], such as systemic or catheter-based thrombolytic therapy (with or without ultrasound assistance) [4–8], catheter thrombectomy [9], and inferior vena cava filters in certain subgroups [10].

Concern over the risk of intracranial hemorrhage, which approaches 3% to 5% outside of clinical trials [11,12], has dampened clinician enthusiasm for full-dose systemic thrombolysis in patients with severe PE and has sparked development of alternative advanced therapies with lower bleeding risk. In patients with unstable PE, aspiration thrombectomy may allow rapid restoration of blood flow through obstructed pulmonary arteries thereby alleviating right ventricular (**RV**) dysfunction, while avoiding bleeding complications. However,

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there are few prospective studies that have assessed the efficacy and safety of aspiration thrombectomy for unstable PE treatment. We therefore aimed at assessing the feasibility of the aspiration mechanical thrombectomy treatment in patients presenting with unstable PE. To this end, we analyzed data gathered in a prospective registry of consecutive patients with symptomatic, objectively confirmed, severe PE.

2. Methods

In a prospective registry, we enrolled consecutive patients presenting with acute unstable PE who received catheter-directed aspiration thrombectomy. All patients provided written or oral informed consent for participation in the registry in accordance with local ethics committee requirements and approved by the regional and institutional review board (PI18/105). For the preparation of this manuscript, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (**STROBE**) statement guidelines for observational cohort studies [13].

2.1. Patients, setting, and eligibility criteria

For this study, we screened patients who presented to the Emergency Department of Hospital Lozano Blesa, Zaragoza, Spain, with symptoms of acute PE (<14 days) from January 1, 2016, through March 31, 2018.

We included patients who had acute unstable proximal PE (filling defect in at least 1 main or lobar pulmonary artery) confirmed by objective testing, age 18 years or older, and PE symptom duration <14 days. For the diagnosis of acute PE, an intraluminal filling defect was identified on contrast-enhanced helical chest multidetector computed tomography (**MDCT**) PE-protocol [14]. Patients were excluded if they were aged <18 years, had contraindications to therapeutic anticoagulation (active bleeding or recent major bleeding, known bleeding diathesis or coagulation disorder, platelet count <100,000/mm^3, recent major surgery or trauma, or invasive procedures within the previous 10 days), pregnancy, renal insufficiency (creatinine clearance <30 mL/min), inability to complete MDCT testing (e.g., allergy to intravenous contrast agents, unavailability of MDCT, patient too ill), or had tumor thrombus in the pulmonary arteries.

2.2. Definition of unstable PE

We defined unstable PE as the presence of sustained hypotension (i.e., systolic blood pressure <90 mm Hg for ≥15 min requiring administration of vasopressors) not caused by new-onset arrhythmia, hypovolaemia, or sepsis [15].

2.3. Procedures

Before the procedure, we inserted an inferior vena cava (**IVC**) filter (Gunther-Tulip Cook-medical, Limerick, Ireland) in every patient. We then inserted a 10F short sheath introducer (Cook Medical, 13 cm, Limerick, Ireland) via the right jugular approach, and then inserted an 8F angled pigtail diagnostic catheter (Cordis, 115 cm, Miami Lakes, Florida) to catheterize the main pulmonary arteries. Angiography was performed by injecting 20 mL of contrast media (Ioversol 320 mg/mL, Mallinckrodt Medical Imaging, Dublin, Ireland) at 10 mL/s. Patients received 100,000–250,000 IU of urokinase (UCB Pharma S.A., Anderlecht, Belgium) by bolus injection in the pulmonary arteries. We then performed continuous aspiration mechanical thrombectomy with the Indigo CAT8 (XTORQ, 115 cm, Penumbra, Alameda, California) connected to a suction pump (Pump MAX™ & MAX Canister, Penumbra, Alameda, California), which exerted negative pressure (20–40 cm H_20) to attempt clot aspiration. An associated wire separator (SEP, Penumbra, Alameda, California) was used to unclog the catheter during aspiration. We measured and recorded the pulmonary artery pressure (**PAP**) before, during and after aspiration thrombectomy through the aspiration catheter connected to a pressure transducer. Criteria for termination of the aspiration procedure were when interventional radiologists agreed that the thrombus had been significantly reduced (reduction about 50–70%) and/or the PAP had decreased at least 10 mm Hg. Following mechanical clot debulking, low-dose hourly urokinase infusion was administered if deemed necessary for a period of 12–24 h.

Anticoagulation was initiated with unfractionated heparin (**UFH**) of 80 units per kilogram body weight with a target activated partial thromboplastin time of 60 to 80 s, followed by an infusion of 18 IU/kg per hour [16]. For patients who had already received low-molecular-weight heparin, the initiation of intravenous UFH was delayed 12 h. During the procedure, UFH was continued at intermediate intensity with a goal activated partial thromboplastin time (**aPTT**) of 40–60 s. After the procedure, full therapeutic anticoagulation with UFH or low-molecular-weight heparin was reinitiated [17].

2.4. Study outcomes

The primary efficacy outcomes were the changes in PAP after aspiration thrombectomy and after catheter-directed thrombolysis. Secondary efficacy outcomes were stabilization of hemodynamics, and survival to hospital discharge. Stabilization of hemodynamics was defined as resolution of hemodynamic instability with no need for pressor support.

Safety outcomes were major and minor procedure-related complications, and major and minor bleeding events within 72 h post-procedure. Major bleeding episodes were defined as those that required a transfusion of at least 2 units of blood, were retroperitoneal, spinal or intracranial, or were fatal [18].

2.5. Statistical analysis

We used chi-square or Fisher's exact tests to compare categorical data between groups. We used the Shapiro-Wilk test to assess continuous data for a normal distribution. We used two-tailed unpaired *t*-tests to compare parametric continuous data between two unpaired groups, and we used the Mann-Whitney *U* test for non-parametric data comparisons.

We conducted statistical analyses using STATA version 13.1 (STATA Corp, College Station, Texas). All hypothesis tests were two-sided, with a significance level of 0.05.

3. Results

3.1. Baseline demographics and clinical characteristics

The eligible study cohort included 54 patients (23 men and 31 women) with acute unstable PE. PE was initially diagnosed by spiral computed tomographic (**CT**) scan in 54 patients (100%). The mean age was 60 ± 17 years (age range, 24 to 85 years) and 85% of patients presented to the hospital within 6 days of symptoms. Common risk factors for PE included immobility within 30 days of PE diagnosis (78%), cancer (15%), obesity (13%), and surgery (11%) (Table 1). The mean PESI score was 143 ± 30 points. Forty-eight patients (89%) had severe sustained tachycardia and 91% had severe hypoxemia. Mean saturation was 84 ± 5%. Mean serum creatinine was 0.8 mg/dl and mean serum hemoglobin was 12.8 mg/dL.

The initial transthoracic echocardiographic examination revealed the presence of RV dysfunction in 87% of patients. The mean systolic PAP was 60.2 ± 8.2 mm Hg, and the mean tricuspid annular plane

Table 1
Baseline characteristics and treatment information for patients with unstable acute symptomatic pulmonary embolism.

	All patients N = 54
Clinical characteristics,	
Age, years (mean ± SD)	59.7 ± 16.8
Age > 65 years	23 (43%)
Male sex	23 (43%)
Risk factors for VTE,	
Obesity	7 (13%)
History of VTE	1 (0.2%)
Cancer[a]	8 (15%)
Recent surgery[b]	6 (11%)
Immobilization[c]	42 (78%)
Comorbid diseases,	
Recent major bleeding[b]	2 (3.7%)
Chronic obstructive pulmonary disease (COPD)	4 (7.4%)
Congestive heart failure	3 (5.6%)
Concomitant DVT	34 (63%)
Clinical symptoms and signs at presentation	
Syncope	7 (13%)
Chest pain	17 (31%)
Dyspnea	31 (57%)
Heart rate ≥ 110/min	48 (89%)
Arterial oxyhemoglobin saturation < 90%	49 (91%)
RV dysfunction	42 (78%)
NT-proBNP, pg/mL (mean ± SD)	2093.2 ± 2861.6
hsTnT, ng/L (mean ± SD)	501.0 ± 448.0
Laboratory findings	
Hemoglobin, g/dL (mean ± SD)	12.8 ± 2.3
Creatinine, mg/dL (mean ± SD)	0.8 ± 0.3

Abbreviations: SD, standard deviation; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; RV, right ventricle, NT-proBNP, N-terminal pro-brain natriuretic peptide; hsTnT, high-sensitivity troponin T.
[a] Active or under treatment in the last year.
[b] In the previous month.
[c] Immobilized patients are defined in this analysis as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the month prior to PE diagnosis.

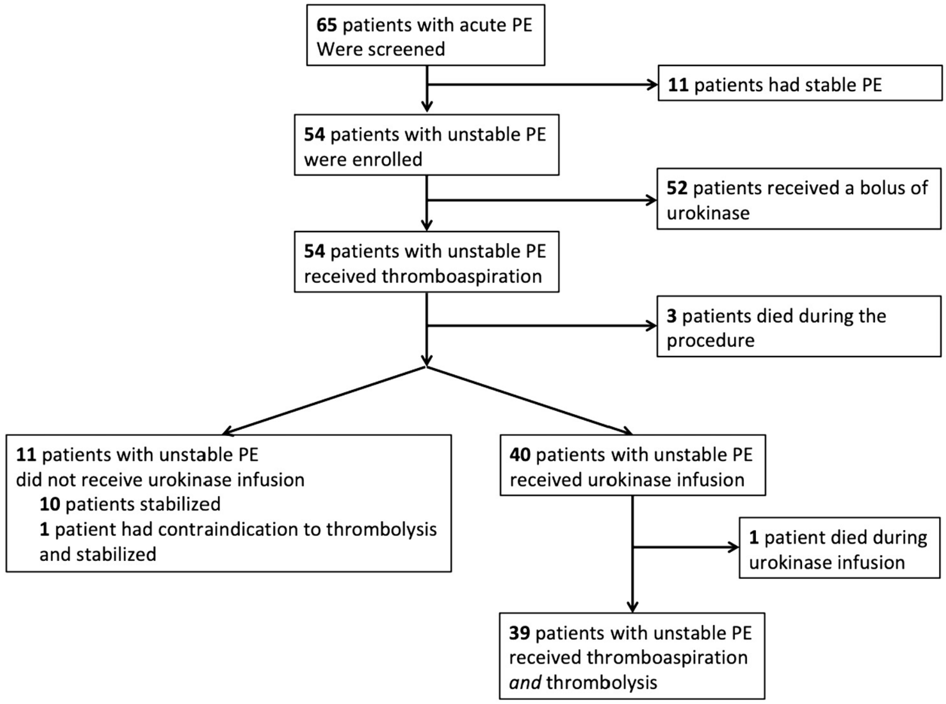

Fig. 1. Flow of patients through each stage of the study. PE, pulmonary embolism.

systolic excursion (**TAPSE**) was 15.5 ± 3.0 mm. The mean RV/left ventricle (**LV**) diameter ratio on chest computed tomography (**CT**) was 2.1 ± 0.4.

3.2. Procedural characteristics

Catheter-directed therapy was first-line therapy beyond anticoagulation in 100% (54 of 54) (Fig. 1). The mean duration (i.e., fluoroscopy time) of the procedure was 17 min (range, 14–75 min). A bolus injection of urokinase was administered to 52 (96%) patients via catheter and continuous aspiration thrombectomy was initiated. Following mechanical clot debulking, clinical stabilization was achieved in 11 (20%) patients, and low-dose hourly urokinase infusion was administered to the remaining 40 (74%) survivors (Fig. 1). The average thrombolytic dose infused through catheter was 994,629.6 ± 608,594.0 IU of urokinase. None of the patients required extracorporeal membrane oxygenation (**ECMO**) support before or during the procedure.

3.3. Efficacy outcomes

Overall, 14% (7 of 51; 95% confidence interval [**CI**], 5.7–26%) of patients showed a reduction in systolic pulmonary artery pressure of at least 10 mm Hg after aspiration thrombectomy, and 84% (42 of 50; 95% confidence interval [**CI**], 71–93%) after local thrombolysis. Thirty-nine of 50 (78%; 95% CI, 64–88%) patients showed improvement in RV dysfunction after thrombectomy and catheter thrombolysis (Table 2). After aspiration thrombectomy, mean pulmonary artery systolic pressure decreased from 60.2 mm Hg to 55.2 mm Hg ($P < 0.01$), and then to 40.5 mm Hg after catheter thrombolysis ($P < 0.0001$) (Fig. 2). The mean RV/LV diameter ratio improved from 2.1 ± 0.4 to 0.8 ± 0.1 after thrombectomy and catheter thrombolysis ($P < 0.0001$). The mean pO_2/FiO_2 improved from 160 ± 55 to 316 ± 89 after thrombectomy and catheter thrombolysis ($P < 0.0001$). The in-hospital PE-related death occurred in six patients (11%; 95% confidence interval [**CI**], 4.2–23%) (3 patients during thromboaspiration, 1 patient during urokinase infusion, and 2 patients following treatment) at a mean follow-up of 1.1 days. In the remaining 48 patients, hemodynamic stability was achieved.

At 30-day follow-up, systolic pulmonary artery pressure further improved to 29.2 ± 5.7 mm Hg, and only 4 patients (4 of 48 patients; 8.3%; 95% CI, 2.3–20%) showed residual RV dysfunction.

3.4. Safety outcomes

There were no major bleeding complications. Minor complications after thrombectomy included arrhythmias (4 of 48 patients, 8.3%; 95% CI, 2.3–20%), and minor (mild according to the Global Use of Strategies to Open Occluded Arteries [**GUSTO**] criteria [19]) bleeding episodes (3 of 48 patients; 6.2%; 95% CI, 1.3–17%) as follows: 2 access site hematomas and 1 gross hematuria. All these bleeding episodes were self-limited and required no blood transfusions. There was one major procedural complication: one patient (2.1%; 95% CI, 0.1–11%) experienced a

Table 2
Preintervention and postintervention data for patients with unstable acute symptomatic pulmonary embolism.

	Before procedures (N = 54)	After thrombectomy (N = 51)	After thrombolysis (N = 50)	Day 30 (N = 48)
mPAP, mm Hg (mean ± SD)	60.2 ± 8.2	55.2 ± 9.3	40.5 ± 11.7	29.2 ± 5.7
Reduction of at least 10 mm Hg in sPAP, n (%)	0 (0%)	7 (8.4%)	42 (84%)	48 (100%)
TAPSE, mm (mean ± SD)	15.5 ± 3.0	–	17.4 ± 2.5	23.0 ± 2.1
RV dysfunction, n (%)	47 (87%)	40 (78%)	11 (22%)	4 (8.3%)
Stabilization of hemodynamics, n (%)	0 (0%)	11 (20%)	50 (100%)	48 (100%)
RV/LV (mean ± SD)	2.1 ± 0.4	–	–	0.8 ± 0.1

Abbreviations: mPAP, mean pulmonary artery pressure; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; LV, left ventricle.

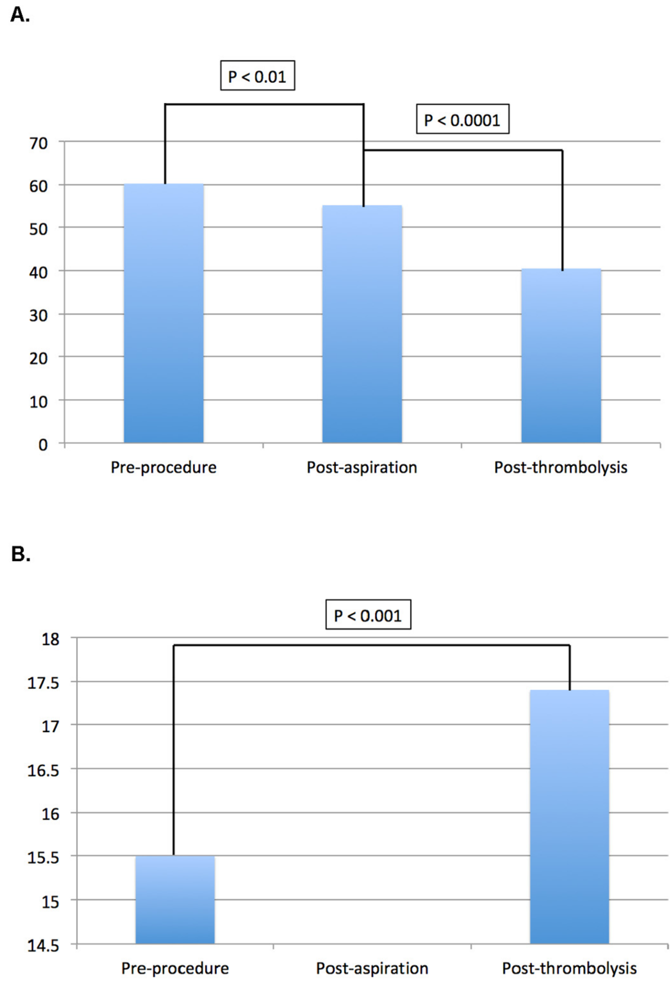

Fig. 2. Efficacy outcomes for patients with unstable acute symptomatic pulmonary embolism. Panel A. Change in invasively measured mean systolic pulmonary artery pressure (mm Hg) before and after intervention. Panel B. Change in TAPSE (mm) before and after intervention.

hemorrhagic transformation of paradoxical embolic stroke after administration of catheter-directed low-dose thrombolysis.

There were no further complications within the first 30 days of anticoagulant therapy.

4. Discussion

In patients with acute unstable PE, treatment escalation is required to prevent death. Current guidelines state that catheter-directed therapy may be warranted in patients with contraindications to full-dose thrombolysis, in patients who have failed systemic thrombolytic therapy, and in patients in whom there is no time to deliver full-dose systemic thrombolysis [9,15]. In addition, a prior meta-analysis also showed that catheter-directed therapy may be used as first-line therapy for patients with massive PE [20], but prospective data on use of catheter-directed therapy for unstable PE are sparse in the literature. In our prospective study, percutaneous catheter-directed thromboaspiration in combination with low-dose catheter-directed thrombolysis significantly reduced pulmonary hypertension and improved RV function leading to high rate of survival in a cohort of patients with life-threatening unstable PE. Furthermore, our rates of survival (87%) and major bleeding (2.1%) compared favorably with those outcomes reported after systemic thrombolysis in the Registro Informatizado de la Enfermedad TromboEmbólica (**RIETE**) Registry [21].

The high risk of death in patients with acute PE associated with hypotension/shock requires emergent aggressive treatment (e.g., thrombolysis, thrombectomy) according to American College of Chest Physicians (**ACCP**) and American Heart Association (**AHA**) guidelines [22,23]; however, many patients are not candidates for systemic thrombolysis due to bleeding risks. In the large RIETE registry from 325 hospitals in 24 countries, only one fifth of hemodynamically unstable patients received advanced therapies [21] beyond anticoagulation. This underscores the need for further research and education on the use of advanced thrombolytic therapies including catheter-based treatment in this population.

Our study expands on the prior experience of percutaneous aspiration thrombectomy in patients with unstable PE and demonstrates the potential benefits of this technique when used in combination with low-dose catheter-directed thrombolysis. After the procedure, echocardiography parameters of right ventricular function (RV dysfunction, RV diameter, and TAPSE) improved significantly, indicating a decrease in right ventricle overload. Interestingly, we found additional improvement in all assessed hemodynamic parameters after low-dose catheter-based thrombolytic therapy, and there was only one episode of major bleeding in a patient with prior embolic stroke. We believe this case emphasizes an important contraindication to the use of any thrombolytic drug even at low dose.

There are limitations to the current study. The major limitation of our study was the lack of a comparator group. Because we did not include a comparator group, we cannot comment on the efficacy or safety of aspiration thrombectomy compared with other reperfusion procedures (i.e., full-dose systemic fibrinolysis, half-dose systemic fibrinolysis, or catheter thrombolysis). However, it should be acknowledged that conducting a randomized trial on patients with life-threatening massive PE might not be feasible especially with regards to a comparison to systemic thrombolysis since many patients have contraindications to this treatment. The potential for selection bias could have skewed the study sample, and it could have biased the results in favor of a greater treatment efficacy and safety by excluding sicker patients; however, all patients met the definition for acute unstable PE. The relatively small sample size of the cohort lowered the statistical power of the study. Finally, there was limited follow-up on long-term clinical outcomes after treatment.

In conclusion, aspiration thrombectomy in combination with low-dose catheter-directed thrombolysis is effective and safe as a first-line treatment option for patients with acute unstable PE. Further prospective trials in larger cohorts may help validate these results and also potentially identify other groups of PE patients (e.g. intermediate-high risk PE) that may also benefit from this catheter-based protocol.

Author contributions

Study concept and design: De Gregorio, Guirola, Jimenez

Acquisition of data; analysis and interpretation of data; statistical analysis: De Gregorio, Guirola, Kuo, Serrano, Urbano, Figueredo, Sierre, Quezada, Barbero, Jimenez

Critical revision of the manuscript for important intellectual content: De Gregorio, Guirola, Kuo, Serrano, Urbano, Figueredo, Sierre, Quezada, Barbero, Jimenez

Study supervision: De Gregorio, Jimenez

The corresponding author, David Jiménez, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest statement

None reported.

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