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Safety and Effectiveness of Lower Alteplase Dose Driven by Impending Clinical Deterioration Factors in very Elderly Submassive Pulmonary Embolism Patients. Case Series

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Abstract

Although thrombolysis improves the outcome and mortality in submassive (SM) and massive PE, its role is controversial because of the high rate of intracranial hemorrhage. In addition, safety and efficacy are unclear since randomized controlled studies have excluded very elderly patients because of frailty, multiple comorbidities, and a higher risk of bleeding. Therefore, the best thrombolytic regimen is unknown. Furthermore, it is unclear whether the decision-making for thrombolysis is performed according to the guidelines or based on clinical risk factors associated with poor outcomes. We report three very elderly SMPE associated with several impending clinical deterioration factors (ICDF) (in-transit thrombus, saddle thrombus, etc.). Therefore, we decided on 25 mg alteplase in one- or two-hour continuous infusion based on ICDF rather than clinical instability and systolic hypotension. In addition, we initiate DOACs around 48 hours after stopping unfractionated heparin (UFH). As a result, all patients improve right ventricular performance without bleeding complications. Our results suggest that the lower alteplase dose in one- or two-hour continuous infusion, followed by weight-adjusted UFH, was effective and safe, involving a complicated scenario as an in-transit thrombus. Also, DOACs standard doses driven by the patient´s characteristics were unrelated to bleeding complications avoiding recurrence in very elderly SMPE.

Keywords: Alteplase; Massive Pulmonary Embolism; Pulmonary Embolism; Submassive Pulmonary Embolism; Thrombolysis

Introduction

Pulmonary embolism (PE) is the third leading cause of mortality after ST-elevation myocardial infarction and stroke [1,2]. Also, PE remains a significant cause of death in special groups, including pregnant women [2], cancer, traumatic injuries, and very elderly patients [1–3]. Although thrombolysis improves outcomes and mortality in submassive (SM) [4,5] and massive PE [6], respectively, its role is controversial because of the high intracranial hemorrhage rate, especially in >60 years [5]. Furthermore, although 100 mg of alteplase in a two-hour infusion improves mortality compared to heparin alone, minor bleeding complications in octogenarians have increased [7]. Additionally, second and third-generation thrombolytic efficacy and safety are unclear since randomized controlled studies have excluded >75 years

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[5] because of frailty, multiple comorbidities, and higher bleeding complication risks. Therefore, we are unaware of the best thrombolytic regimen for this population [8]. On the other hand, it is unclear whether advanced treatment decisions are made according to the guidelines [8] or depend on the clinician's perception of clinical severity indicators associated with poor outcomes in SMPE patients [1]. In a post-hoc analysis of the PEITHO trial [9], the authors state the need to recognize more appropriate candidates for thrombolysis through clinical indicators of severity (systolic blood pressure <110 mmHg, respiratory rate >20 breaths/minute, or chronic heart failure) [9]. Recent exploratory analysis suggests thrombolysis decision-making is based on impending clinical deterioration factors other than systolic blood pressure <90 mmHg in very elderly SMPE patients [1]. Both observations indicate the necessity of identifying a subgroup with a higher risk profile that could benefit from advanced treatment in SMPE patients. Therefore, we report that 25 mg alteplase in a one- or two-hour continuous infusion was safe and effective in three very elderly SMPE patients. Additionally, we decided on advanced treatment based on impending clinical deterioration factors (1) rather than clinical instability and systolic hypotension [8].

Case 1

ER Clinical Presentation

A 79-year-old woman with a history of right knee arthroplasty, frailty, and GI bleeding six months early. She started with syncope and dyspnea three days earlier. Table 1 shows pre-thrombolysis vital signs. Physical examination showed venous distention, a loud second heart sound, tenderness, warmth edema, and erythema in the left leg. Chest X-ray was not diagnostic. Table 1 shows pre-thrombolysis, ECG, laboratory, and biomarker findings. Table 1 also displays bedside transthoracic echocardiography (TTE) (Video 1) (Figure 1A), computed tomography pulmonary angiography (CTPA) (Figure 1B), and lower limbs ultrasound findings. We confirmed an SMPE and started enoxaparin at 1mg/kg twice daily. On the second day, the dyspnea and D-dimer and cardiac biomarkers improved significantly (Table 2). However, forty-eight hours later, we observed progressive biomarkers increase (Table 2) and new T wave inversion in V1-V3 on ECG despite clinical stability. Therefore, we decided on a treatment escalation using the lower alteplase dose (Table 1) based on three impending clinical deterioration factors [1] increasing biomarkers measurement (Table 2), remaining right ventricular dysfunction (TAPSE 11 mm), and ECG new dynamic ST changes, suggesting enoxaparin therapeutic failure and the possibility of impending clinical instability. We also considered severe pulmonary hypertension and chronic renal disease for clinical decision-making. Additionally, age-associated frailty was determinant

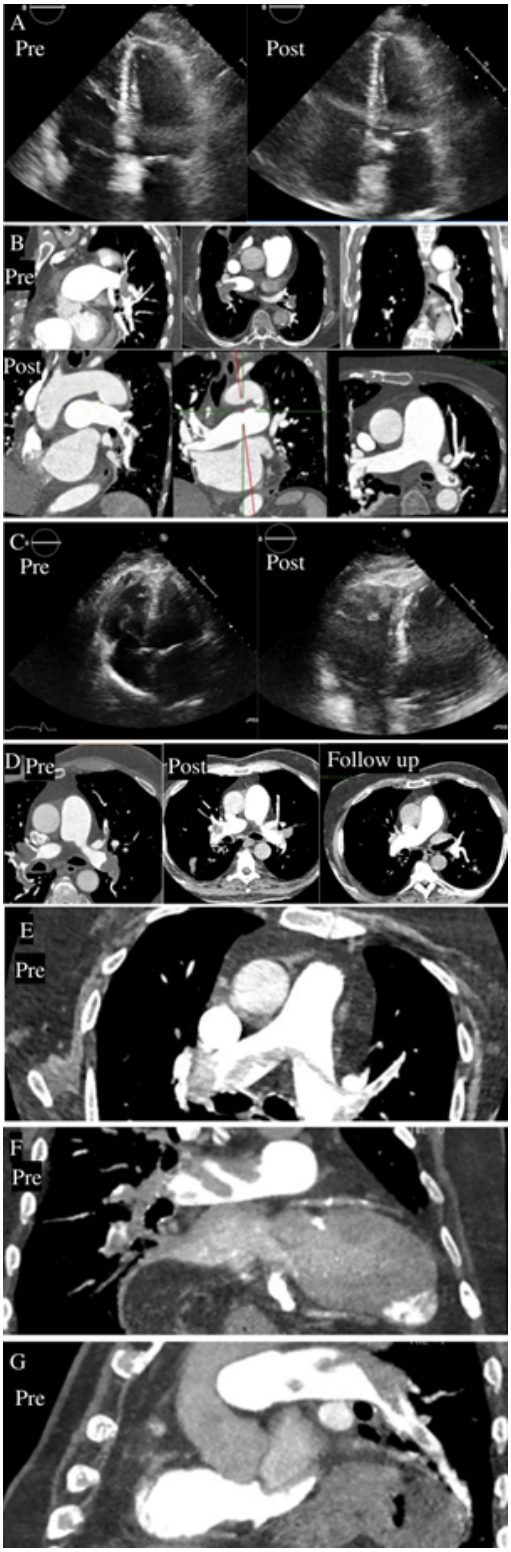

Figure 1: Pre and post-thrombolysis image studies. A) Case 1 pre and post-thrombolysis echo. B) Case 1 pre and post-thrombolysis CTPA. C) Case 2 pre and post-thrombolysis echo. D) Case 2 pre, and post-thrombolysis and follow-up CTPA. E) Case 3 pre and post-thrombolysis CTPA.

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for using a lower alteplase regimen and weight-adjusted unfractionated heparin (UFH) as an adjunctive treatment [4] without major or minor bleeding complications (Table 1). Table 1 shows post-thrombolysis TTE, CTPA (Figures 1A and 1B), and ultrasound findings. We also identified biomarkers that improved after thrombolysis and during the follow-up (Tables 1 and 2). She was discharged seven days after with apixaban 5 mg BID. During the six-month follow-up, she was asymptomatic and without recurrences. She had macroscopic hematuria with apixaban temporary discontinuation in a two years-follow-up. Currently, she is in functional class I on apixaban 2.5 mg BID for extension treatment.

Case 2

Community Hospital Clinical Presentation

An 81-year-old male patient presents shortness of breath, eight weeks of edema in the lower extremities, and one week of worsening dyspnea. His medical history includes hypertension, diabetes, ischemic heart disease, and coronary bypass (sixteen years ago). He had clinical stability (130/80 mmHg) and oxygen desaturation (88%). ECG had the right bundle branch block, right ventricular pressure overload, and ST dynamic changes. The patient was diagnosed with non-ST elevation myocardial infarction and received UFH and dual antiplatelet therapy.

Table 1: Pre and post-thrombolysis vital signs, ECG, laboratories, risk stratification and biomarker findings.

	Before alteplase	After alteplase	Before alteplase	After alteplase	Before alteplase	After alteplase
Variable	Case 1	Case 1	Case 2	Case 2	Case 3	Case 3
Systolic BP (mmHg)	136	125	140	161	122	140
Heart rate (bpm)	72	68	84	82	116	66
Respiratory Rate (rpm)	22	18	24	22	26	16
O2 Saturation (%)	89	98	97	96	86	100
sPESI	1	-	1	-	1	-
ECG	Non-specific findings	T wave inversion V1-V4	RBBB, RV overload, and ST dynamic changes	No RBBB	S1Q3T3, ST dynamic changes, negative T waves	Improved dynamic ST changes, atrial fibrillation
TTE	PSAP 76 mmHg, TAPSE 11 mm, RV/LV >2:1, and McConnell sign	PSAP 59 mmHg, improved RV systolic function, TAPSE 18 mm	Systolic septal flattening, McConnell's sign, in-transit thrombus type A	No in-transit thrombus, RV performance improvement	Severe RVD, McConnell sign, PASP 46 mmHg, TAPSE of 14.7 mm.	-
CTPA	Main pulmonary arteries thrombi	Substantial thrombus burden reduction	Main pulmonary arteries thrombi	Significant thrombus burden decrease	Saddle thrombus	-
LLUS	DVT left femoral and popliteal veins	Decrease in thrombi burden	DVT right tibioperoneal vein		DVT right popliteal vein and right posterior tibial vein.	-
Hemoglobin (gr/dL)	14.5	-	17	-	17.5	-
Leucocytes (cells/mm²)	15,400	-	9,400	-	13,670	-
Platelets (cells/mm²)	263,000	-	256,000	-	235,000	-
Creatinine (mg/dL)	2.8	-	1.2	-	0.8	-
eGFR (mL/min)	40	-	91	-	119	-
D-dimer ng/mL	8,149	6,700	7,000	-	6, 452	14,191
BNP pg/dL	2,349.50	640	648.7	423	226.4	167.9
hscTnI ng/L	178	19.1	304	315.5	125.1	81.2
Alteplase	25 mg in 2 hours	-	25 mg in 1 hour	-	25 mg in 1 hour	-
Adjunctive treatment	* UFH 24 hours		* UFH 24 hours		* UFH 24 hours	
Anticoagulation	Apixaban 5 mg BID		Rivaroxaban 15 mg BID		Apixaban 5 mg BID	

RBBB: Right Bundle Branch Block; TTE: Transthoracic Echocardiogram; CTPA: Computed Tomography Pulmonary Angiography; LLUS: Lower Limbs Ultrasound; sGFR: Glomerular Filtration Rate; BNP: B-Type Natriuretic Peptide; hs-cTnI: High-Sensitive Cardiac Troponin I; * Weight-Adjusted Unfractionated Heparin: a constant infusion (12 U/Kg per hour, maximum 1,000 U/h) adjusted to maintain an activated partial thromboplastin time of 50–70 s for 24–48 h.

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Table 2: Biomarker outcome in very elderly pulmonary embolism patients.

Variable	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Case 1												
DD ng/mL	8,149	7,022	3,453	3,596	-	11,200	19,600	6,700	6,900	2,495	2,139	2,932
BNP pg/dL	2,349	1,767	1,741	500	-	1,030	1,016	640	721	529	399	150
hscTnI ng/L	178.7	127.2	80.4	10.5	-	24.4	26.1	19.1	16.9	12.2	13.3	10.4
Case 2												
DD ng/mL	7,000	-	3,773	-	829	-	-	-	-	-	-	-
BNP pg/dL	648.7	423	125	-	88.9	-	-	-	-	-	-	-
hscTnI ng/	304	315.5	140.1	-	43.6	-	-	-	-	-	-	-
Case 3												
DD ng/mL	6, 452	14,191	8,636	-	-	-	-	-	-	-	-	-
BNP pg/dL	226.4	167.9	61.3	-	-	-	-	-	-	-	-	-
hscTnI ng/L	125.1	125.1	24.4	-	-	-	-	-	-	-	-	-

DD: D- Dimer; BNP: B-Type Natriuretic Peptide; hscTnI: High Sensitivity Cardiac Troponin I

ER Clinical Presentation

The patient was transferred to our hospital. Physical examination revealed obesity and warm extremities. Hoffman's sign was negative. Pre-thrombolysis vital signs are shown in Table 1. The chest X-ray revealed a bilateral Westermark sign, lung infarction, and right diaphragm elevation. Table 1 shows pre-thrombolysis ECG, laboratory, and biomarker findings. Table 1 also displays bedside TTE (Video 2) (Figure 1C), computed tomography pulmonary angiography (CTPA) (Figure 1D), and lower limbs ultrasound findings. After a fast-track meeting with the PREVENTION team [10], we decided lower the alteplase dose (Table 1) based on seven impending clinical deterioration factors [1]: right bundle branch block, ST dynamic changes, higher BNP and hs-cTnI measurements, right ventricular hypokinesia, a significant thrombus burden, and an in-transit thrombus type A. Additionally, age was determinant for using a lower alteplase regimen and weight-adjusted unfractionated heparin (UFH) as an adjunctive treatment [4] without major or minor bleeding complications (Table 1). Table 1 shows post-thrombolysis TTE (Video 2) (Figure 1C), CTPA (Figure 1D), and ultrasound findings. Table 2 shows biomarkers findings. After 24 hours on UFH, we started rivaroxaban with biomarkers improvement (Table 1) (Table 2). At discharge, the patient was asymptomatic with rivaroxaban 20 mg OD. CTPA showed no thrombus in the pulmonary arteries (Figure 1D) in a one-month follow-visit. The patient is alive, without recurrence, in a 19-month follow-up.

Case 3

ER Clinical Presentation

An 83-year-old male arrives with sudden dyspnea and O_2 saturation of 86%. He has a past medical history of hypertension, hypothyroidism, ectopic atrial beats, and deep venous thrombosis. Table 1 shows pre and post-thrombolysis vital signs. The physical exam showed a loud second heart sound and bilateral edema. The chest X-ray had a bilateral Westermark sign. Table 1 shows pre and post-thrombolysis baseline ECG, laboratory, and biomarker findings. Table 1 also displays bedside TTE, CTPA (Figure 1E, 1F, 1G), and lower limbs ultrasound findings. Based on clinical presentation and results, we confirmed an SMPE. After a fast-track meeting with the PREVENTION team [10], we decided on advanced treatment based on four impending clinical deterioration factors [1]: hypoxemia <90%, saddle thrombus, right ventricular hypokinesis, and TAPSE of 14.7 mm. Therefore, we started lower the alteplase dose and UFH (Table 1). After thrombolysis, we observed clinical, ECG (Table 1) and biomarkers improvement (Table 2). The patient was discharged on the fifth-day post-thrombolysis without major or minor bleeding complications. Currently, the patient is alive, receiving apixaban without recurrence or bleeding complications in a 3-month follow-up.

We performed a systematic review from 1990 to December 2021, including SM and massive PE patients treated with a systemic lower alteplase dose (<50 mg) through PubMed, ScienceDirect, and Wiley. We used the following terms: ("pulmonary embolism/drug therapy" [MESH]) and "thrombolytic therapy" [MESH]) and (low dose)) or (quarter dose)) or (safe dose) and (1990:2021[pdat])) not (catheter directed)) not (children)) and (alteplase [MESH terms])) not (stroke)) not (catheter)) not (myocardial infarction)) not (pleural infection)) not (hemodialysis)) not (prosthetic valve thrombosis)) not (endovascular)) not (tenecteplase). We identified thirteen papers, including 61 massive and 87 SMPE patients (Table 2) (references in supplementary material).

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Table 3: Systematic review shows demographic characteristics, thrombolysis regimen, indication, success, bleeding complications, and mortality.

Author	No pts	Age	Gender	Dose mg	Time of infusion	Findings	Thrombolysis Indication	Reperfusion	MB	mB	Anticoagulation	Mortality
Massive												
Biteker, M, et al. (2009) [S1]	1	85	Female	20*	1.5 hours	In-transit thrombus	Guidelines MPE thrombolysis recommendation	Yes	NR	NR	UFH, subsequently warfarin	No
Biteker, M, et al. (2010) [S2]	1	21	Female	25	3 hours	In-transit thrombus	Guidelines MPE thrombolysis recommendation	Yes	No	No	UFH, subsequently warfarin	No
Yildiz, M, et al. (2013) [S3]	1	95	Female	25	6 hours	In-transit thrombus	Guidelines MPE thrombolysis recommendation	Yes	NR	NR	UFH, subsequently warfarin	No
Sen, F, et al. (2014) [S4]	1	66	Female	25	6 hours	Bilateral pulmonary arterial embolism	Guidelines MPE thrombolysis recommendation	Yes	No	No	NR	NR
Aykan, A, et al. (2014) [S5]	1	37	Female	25 mg	6 hours	Thrombus in iliac veins extending to right atrium and embolism in lobar pulmonary arteries	NR, possibly guidelines MPE thrombolysis recommendation	Yes	NR	NR	UFH, subsequently warfarin	NR
Shen, L, et al. (2016) [S6]	1	73	Male	25•	Bolus followed by 1.5 hours	Left pulmonary artery embolism	Guidelines MPE thrombolysis recommendation	Yes	Yes	NR	LMWH, subsequently dabigatran	No
Aykan, A, et al. (2016) [S7]	52	72.8	NR	25 mg	6 hours	NR	NR, possibly guidelines MPE thrombolysis recommendation	Yes	NR	NR	NR	1 in hospital 3 outpatient
Zencirkiran, H, et al. (2018) [S8]	1	49	Male	50§	6 hours followed by 3 hours	Bilateral pulmonary arterial thrombosis	Guidelines MPE thrombolysis recommendation	Yes	NR	NR	UFH, subsequently warfarin	No
Kalkan, ME, et al. (2020) [S9]	2	44	1 Female 1 Male	25 mg	6 hours	RV dilatation, paradoxical septal movement, PASP >35 mmHg	Guidelines MPE thrombolysis recommendation	Yes	No	NR	UFH, subsequently warfarin	No
Submassive												
Lozier, JN, et al. (2018) [S10]	5	61.8	4 Female 1 Male	12¶	6 hours	3 patients with left/ right pulmonary arterial thrombus 2 patients with mismatched perfusion defect on V/Q scan	Empiric treatment	Yes	NR	NR	3 patients UFH, subsequently enoxaparin 1 patient UFH, subsequently apixaban 1 patient argatroban, subsequently warfarin	No
Zhang, LY, et al. (2018) [S11]	33	60.5	15 Female 18 Male	30	2 hours	Thrombus in at least 1 main or proximal pulmonary artery of the lower lobe	Compare the safety and efficacy between thrombolysis and standard anticoagulation	Yes	No	8	UFH, subsequently enoxaparin and lastly warfarin	No

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Sharifi, M, et al. (2019) [13]	42	NR	NR	25 mg•	Bolus followed by 2 hours	NR	NR	Yes	No	NR	UFH, subsequently direct oral anticoagulant	No
Kalkan, ME, et al. (2020) [S9]	3	60.3	1 Female 2 Male	25 mg	6 hours	RV dilatation, paradoxical septal movement, PASP > 35 mmHg	NR (Evaluated safety of thrombolysis)	Yes	No	NR	UFH, subsequently warfarin	No
Guru, PK, et al. (2022) [26]	4	69.2	3 Female 1 Male	25 mg⧫	24 hours	Bilateral thrombus in the main, lobar, segmental or subsegmental pulmonary artery, saddle thrombus and RV dilation	Clinical deterioration (persistence of symptoms, shock index, respiratory distress), PESI, cloth burden, impending RV failure and associated bleeding risk	Yes	No	No	3 UFH before thrombolysis, subsequently OAC 1 LMWH within 12 hours of thrombolysis, subsequently OAC	No

Pat: Patients; MB: Major Bleeding; mB: Minor Bleeding; MPE: Massive Pulmonary Embolism; UHF: Unfractionated Heparin; OAC: Oral Anticoagulation; *Two doses. § Firstdose of 25 mg with hemodynamic improvement, a second dose of 25 mg with complete resolution.

¶ 6 mg dose per day for two days. •First dose of 10 mg, second dose of 15 mg. ⧫Continuous 1mg/h for 24 hours. ⍰Author postulated that a safer dose could be used. NR: Not reported. PASP: Pulmonary artery systolic pressure.

Discussion

Our cases had three relevant findings. First, alteplase 25 mg in short-term continuous infusion and adjunctive treatment weight-adjusted UFH [4] was effective and safe in very elderly SMPE patients, including an in-transit thrombus. Second, our results extended the safety and effectiveness of direct-acting oral anticoagulants (DOAC), improving quality of life and simplifying PE treatment after thrombolysis [11–13]. Finally, early recognition of clinical severity indicators to identify those that could potentially benefit from thrombolysis use through control trials in SMPE is mandatory [1,9,14,15]. There is a worldwide trend in reducing thrombolysis regimens in younger [16] and very elderly ST-elevation myocardial infarction [17], left atrial thrombus [18], obstructive mechanical valve thrombosis [19], and PE with [20] or without COVID-19 [21–24]. However, reduced-dose regimens evidence is insufficient to support their efficacy and safety in PE [15]. The rationality for reducing the alteplase dose to 50 mg [21] is based on the lungs receiving a total cardiac output and convergence point for the whole molecules improving efficacy. Furthermore, after the first passage, repetitious recycling of those molecules occurs by continuously re-entering the lungs, causing "multiple hits" [11]. Therefore, the effectiveness and safety of a "safe dose" is supported by 304 SM and massive PE patients [11,12,21]. However, these studies did not include very elderly patients, so their effectiveness and safety are unknown in this population. Furthermore, the optimal thrombolysis regimen remains uncertain since randomized clinical trials excluded this population [5]. For our patients, the decision-making of the antithrombotic approach was challenging because they are at high risk of thromboembolic and bleeding complications because of age-related changes [25]. Because of this, we have decided to use the lower alteplase dose (25 mg) in a one- or two-hour infusion for those with higher thrombus burden and in-transit thrombus instead of a prolonged lower-dose infusion (Tables 1 and 3). As a result, our patients' in-hospital outcome was free of major, clinically relevant, minor bleeding complications and recurrence. The systematic review identified the safety and effectiveness of prolonged lower-dose (<25 mg) alteplase infusion in recent surgery, pregnancy, cancer, in-transit thrombus, and very elderly SMPE and massive patients (Table 3). Our results also reproduce the effectiveness and safety of the "safer" thrombolysis dose (10 mg alteplase bolus in one minute, followed by 15 mg in 2 hours), UFH 10 units /Kg/ hour for 24 hours, followed by DOAC maintenance dose, 15 minutes after heparin discontinuation [13]. This regimen reduces PSAP, improves right ventricular performance, eliminates ICU stay, and promotes early discharge in 42 SMPE patients [13]. Unfortunately, the results lack the patient's age and thrombolysis decision-making and have not been published extensively. Nevertheless, the rationality for reducing the alteplase dose to 25 mg is similar to 50 mg reduction [21]. Independent of the infusion time, the "safe," [21] "safer," (13), ultra-low- [26], and lower alteplase doses in short- or long-term infusion seem to improve the outcome with no increase in significant bleeding complications (Table 1). After the "safe" dose [21], DOAC were safe and effective, modifying the quality of life associated with parenteral anticoagulation and reducing in-hospital stays and costs for patients sixty-seven years of age or younger [11,12]. We reproduced the safety and effectiveness of DOAC when initiated 24 hours after discontinuing UFH [11,12]. We also decided to avoid the loading dose to reduce bleeding risk. Additionally, we are selecting apixaban or rivaroxaban

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depending on the patient´s characteristics (frailty, bleeding risk, and renal function). Finally, PEITHO-3 will allow any class of DOAC after 48 hours of low-molecular-weight heparin or UHF adjunctive treatment. The results will provide current and robust evidence for the safety and effectiveness of DOAC following a lower alteplase dose [15]. Currently, despite guideline recommendations [8], clinical decision-making for thrombolysis use does not seem to depend on systolic hypotension [1,4,9,11–13,21,26,27], including eighty-seven SMPE patients identified in our systematic review (Table 3). Therefore, proper recognition through clinical severity indicators is mandatory [1,9,14]. In our cases, the number of impending clinical deterioration factors [1] historically related to poor outcomes and pulmonary thrombus burden drove the clinical decision-making for one- or two-hour continuous infusion. PEITHO-3 [15] is a randomized, placebo-controlled, double-blind, multicenter, and multinational trial with long-term follow-up to compare the efficacy and safety of a reduced-dose alteplase regimen with standard heparin anticoagulation. The study will enroll 659 SMPE patients and fulfill at least one clinical criterion of severity: systolic blood pressure <110mm Hg, respiratory rate >20 breaths/min, or history of heart failure [9,15]. The primary efficacy outcome is the composite of all-cause death, hemodynamics, or recurrence within 30 days of randomization. Key secondary outcomes to be included are fatal or GUSTO severe or life-threatening bleeding, net clinical benefit (primary efficacy outcome plus severe or life-threatening bleeding), and all-cause death within 30 days [15]. If the hypothesis of PEITHO-3 is confirmed, international clinical practice guidelines [8] will most likely revisit their recommendations by including reperfusion and reduced-dose systemic thrombolysis as first-line treatments in a new phenotype of SMPE [15]. Conversely, if the hypothesis is rejected, catheter-directed thrombolysis may become the only option for improving the prognosis of SMPE patients [14,15].

Limitations

We acknowledge that the data in this case series is insufficient to establish the safety and effectiveness of one- or two-hour continuous infusion followed by DOAC in elderly SMPE patients. We cannot identify definitive clinical criteria to recognize “more appropriate” candidates for thrombolysis among submassive PE patients [9]. Nevertheless, our findings are another piece of evidence that supports a worldwide trend, the requirement for clinical severity indicators at presentation [1,4,9,11–13,21,26,27] rather than hemodynamic monitoring and systolic hypotension [8] to start advanced treatment in well-selected SMPE patients [15]. Additionally, our results could help to generate hypotheses that should validate in randomized controlled trials to come [9,15].

Conclusion

Our results suggest that the lower alteplase dose in one- or two-hour continuous infusion, followed by weight-adjusted UFH, was effective and safe, involving a complicated scenario as an in-transit thrombus. Also, after stopping UHF, standard doses of DOAC driven by the patient´s characteristics were unrelated to bleeding complications avoiding recurrence in very elderly SMPE patients.

Authors Contributions

Juan Quintanilla; Was the physician in charge of patient care, creating the alteplase dose, and then reading, reviewing, and approving the manuscript. Maria Fernanda Reyes-Chavez; Project coordination, data extraction from the articles for the systematic review, creation of tables, images, and videos, writing, and case revision. Then read, reviewed, and approved the manuscript. Carlos Jerjes-Sanchez; Coordination and conduction of the project with the cardiology residents and students. Supervised the tables, images, and videos. Revise cases and write the manuscript. Melissa Galindo-Garza; Coordination and planification of the project with the cardiology residents. She performed journal article searching and data extraction for the systematic review, created table No.2, and revised the cases. Then, read, reviewed, and approved the manuscript. Aldo F Ponce-Barahona; Contributed to searching journal articles for the systematic review, creating tables, revising the cases, write the first case. Read, reviewed, and approved the manuscript. Vanessa Alegria-Saldivar; Contributed to the data extraction from the articles for the systematic review, creating tables and images, and writing and revising the cases. Read, reviewed, and approved the manuscript. Arturo Adrian Martínez Ibarra; Searching for journal articles and data extraction for the systematic review, creating table No.2, revising the cases, and making the final manuscript. Read, reviewed, and approved the manuscript. Armando Osorio-Salazar; Contributed to creating tables, writing, and revising the cases and manuscript. Read, reviewed, and approved the manuscript. José Alfredo Salinas-Casanova- Contributed to the data extraction from the articles for the systematic review, creation of table, revision of the cases, and final manuscript. Read, reviewed, and approved the manuscript. Ricardo J. Estrada-Mendizabal; Contributed to table creation, writing, and revising the cases and manuscript. Read, reviewed, and approved the manuscript. Renata Quevedo-Salazar; Contributed to table creation, writing, and revision of the cases. Read, reviewed, and approved the manuscript. Sofía Guardado Vázquez; Contributed tables creation, writing, and revision of the cases. Read, reviewed, and approved the manuscript. Paola Gutierrez-Gallegos; Contributed to table creation, writing, and revising the cases and manuscript.

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Read, reviewed, and approved the manuscript. Victor E. Lozano-Corres; Contributed table creation and writing of the cases. Read, reviewed, and approved the manuscript.

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Supplementary Material

References Table 3

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