Local Thrombolysis in High-Risk Pulmonary Embolism—13 Years Single-Center Experience

Liviu Macovei, MD, PhD[1,2], Razvan Mihai Presura, MD[1],
Robert Magopet, MD[1] ⓘ, Cristina Prisecariu, MD, PhD[1,2] ⓘ,
Carmen Macovei, MD[3], Gabriela Omete, MD[1],
Igor Nedelciuc, MD, PhD[1], and Mircea Balasanian, MD, PhD[1,2]

Abstract

To evaluate the prognosis after local thrombolysis compared to systemic thrombolysis in high-risk pulmonary embolism. Observational study during 13 years which included 37 patients with high-risk pulmonary embolism treated with local thrombolysis and 36 patients with systemic thrombolysis (streptokinase, 250 000 UI/30 minutes followed by 100 000 UI/h). Cardiogenic shock has totally remitted in the group with local thrombolysis ($P = .002$). The decrease in pressure gradient between right ventricle and right atrium was comparable in both groups in the acute period (the results being influenced by the higher in-hospital mortality after systemic thrombolysis), but significantly better in the next 24 months follow-up after in situ thrombolysis. Major and minor bleeding did not have significant differences. In hospital, mortality was significantly lower in the group with local thrombolysis ($P = .003$), but for the next 24 months follow-up, the survival was comparable in both groups. Local thrombolysis, during the hospitalization, was associated with lower mortality rate comparing with systemic thrombolysis. In the next 24 months follow-up, the evolution of residual pulmonary hypertension was significantly better after in situ thrombolysis.

Keywords

Introduction

Pulmonary embolism (PE) is a significant cause of morbidity and mortality that occurs in 60 to 112 per 100 000 people/year with a fatality rate in the acute phase of 7% to 11%.[1-3] In the United States, up to 600 000 cases of PE are diagnosed annually and 150 000 die every year.[4,5] In high-risk PE (previously defined as massive PE), the 30-day mortality rate is considered to be as high as 60%.[4] In Europe, PE is estimated to be associated with more than 300 000 deaths per year.[6] Costs related to the management of acute PE are substantial. In the United States, total venous thromboembolism costs ranged from US$13.5 to US$69.3 billion.[7,8] A recent analysis in Germany calculated the cost for the first year of PE treatment for 1 patient at over 20 000 Euros.[6,9]

The effect of systemic thrombolysis on recurrent PE and mortality is controversial.[10-15] An alternative to systemic thrombolysis is represented by local thrombolysis, though there is a continuous controversy regarding the superior benefits with lower risk of bleeding.[10,16] A randomized trial of 34 patients with large (massive) PE showed similar safety. Meanwhile, in a more recent prospective registry of 101 high-risk PE patients treated with catheter-based therapy (mostly local fibrinolysis), there was a significant decrease in pulmonary artery (PA) pressure, without major complications.[12,17,18]

The aim of our study was to assess the efficiency and safety of local thrombolysis with streptokinase (SK) as compared to systemic thrombolysis, on short and long term. In this study, we compared 2 groups of patients with high-risk PE: systemic versus intrapulmonary administration of SK.

[1] "Prof. Dr. George I. M. Georgescu" Cardiovascular Diseases Institute Iaşi, Romania
[2] "Grigore T. Popa" University of Medicine and Pharmacy Iaşi, Romania
[3] Pneumology Clinic of Pneumoftiziology Hospital Iasi, Romania

Corresponding Author:
Liviu Macovei, "Prof. Dr. George I. M. Georgescu" Cardiovascular Diseases Institute, 50th Carol I Avenue, Iaşi, Romania.
Email: liviughemacovei@yahoo.com

Materials and Methods

The patients with high-risk PE were assigned in 2 groups of thrombolytic treatment: the administration directly in the PA (in situ) for 37 patients and systemic (intravenous) for 36 patients.

The inclusion criteria were the diagnosis of high-risk PE, with an onset of symptoms less than 14 days. Exclusion criteria for thrombolysis were represented by intermediate and low-risk PE, a history of hemorrhagic stroke, ischemic stroke in the last 6 months, lesions or cerebral cancer, major trauma, surgery or recent cranial trauma (in the last 3 weeks), gastrointestinal bleeding in the last month, known bleeding, recent untreated malignancy, and pregnancy.

This is an observational study during 13 years. The study was conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee and all patients signed informed consent.

We used the European Society of Cardiology criteria for risk stratification. High-risk PE was defined as acute PE with sustained systemic arterial hypotension with right ventricle (RV) dysfunction.[19] The initial stratification of the risk was made according to the presence of the cardiogenic shock (defined by sustained low blood pressure with tissue hypoperfusion despite adequate left ventricular filling pressure) or the hypotension (systolic arterial blood pressure <90 mm Hg or a decrease in systolic arterial blood pressure $\geq$40 mm Hg for minimum 15 minutes) in high-risk PE. The risk stratification was established after imaging studies. The high likelihood of this diagnosis was raised after echocardiographic evaluation, soon after intensive care unit (ICU) admission for all patients (right ventricle dilatation, hypokinesia of the right ventricle free wall, or abnormal movement of the interventricular septum, with or without tricuspid regurgitation) and clinical status stabilization. We confirmed invasively this diagnosis through an angiographic study of the pulmonary arteries for all the patients who gave informed consent for this procedure (48 patients—all patients treated with in situ thrombolysis and 11 patients treated with systemic thrombolysis). A computed tomography pulmonary angiogram (CTPA) or ventilation/perfusion lung scan (V/Q) was not available in our hospital.

All the angiographic studies had been made in the same laboratory of cardiac catheterization using the same contrast agent and the same protocol of angiographic diagnose.

After the diagnosis confirmation, the modality of giving the thrombolytic agent, systemic or intrapulmonary, was chosen by a multidisciplinary team (cardiologist, ICU physician, interventional cardiologist), depending on clinical status, hemorrhagic risk, patient desire, and accessibility to the catheterization laboratory, although we tried to make these 2 groups as similar as possible. The thrombolytic agent was SK, 250 000 UI/30 minutes followed by 50 000 to 100 000 UI/h. The adjuvant therapy that was used is represented by anticoagulants (unfractionated heparin, low-molecular-weight heparin). All patients admitted in the ICU required vasopressors/inotrope agents and volume repletion for stabilization, being in cardiogenic shock.

None required endotracheal intubation and mechanical ventilation at the time of admission (during the hospitalization, few patients required standard advance life support measures). Due to the fact that at the beginning of the study SK was the only fibrinolytic therapy available in our center, along with Acenocoumarol as an oral anticoagulant, we decided to use only these drugs for all patients with high-risk PE; new oral anticoagulants were also not used in this study.

The following parameters were monitored in the ICU, at the end of the thrombolytic treatment, and were also reassessed at a median follow-up period of 24 months, being grouped as follows: clinical features, hemodynamic, echocardiographic and angiographic parameters. The evolution of the mean pressure in the PA (mean PAP) at the end of in situ thrombolysis has been invasively determined.

Clinical evolution was evaluated by the presence of dyspnea, chest pain, and asymptomatic status at the end of the thrombolytic treatment. Hemodynamic parameters compared at the beginning and at the end of thrombolysis were systolic arterial blood pressure, peripheral oxygen saturation, and heart rate. The following echocardiographic parameters (during thrombolytic treatment and after 24-month follow-up) were end diastolic diameter of right ventricle (RVD_2), lateromedial diameter of right atrium (RA minor axis), pressure gradient between right ventricle and right atrium (P_{RV-RA}), diameter of the right branch of the pulmonary artery, the inferior vena cava's diameter (IVC) and systolic pulmonary artery pressure (SPAP)—estimated from the addition between the right atrium pressure based on IVC diameter and respirophasic changes to the pressure gradient between right ventricle and right atrium (P_{RV-RA}). We used *the American Society of Echocardiography recommendations for chamber quantification guidelines*, published in 2005 (available at the beginning of the study), throughout the study as well as for the follow-up for a more accurate assessment of the echocardiographic parameters.[20]

The efficiency and safety profile of the treatment has been evaluated by following: the severity of residual pulmonary hypertension (determined with echocardiography) and the mortality, the appearance of major bleeding complications (brain or gastrointestinal bleeding, massive hematoma on the puncture site or acute posthemorrhagic anemia and disseminated intravascular coagulation) or minor complications (minor bleeding, hematoma on the puncture site, transient ischemic attack), secondary to thrombolytic therapy. For stratification and reduction of hemorrhagic risk, we used our own protocol called "bleeding from 150 to 90." Thus, we determined from 6 to 6 hours, during SK thrombolysis, blood count, and fibrinogen. When platelet counts were below 150 000/mmc and/or fibrinogen were below 150 mg% we reduced the SK dose by half and when platelet levels were below 90 000/mmc and/or fibrinogen below 90 mg% we stopped the thrombolytic administration.

Statistical analyses were performed using SPSS Statistics version 17 (the level of statistical significance was .05).The centralization of the data was done nominally and numerically. Nominal data were characterized by absolute and relative frequency. Numerical data have been studied from the view of the

Table 1. Selected Baseline Characteristics of Patients

	Route of thrombolytic administration	
	In situ	Systemic vein
No. of patient in group	37	36
Men/women	19/18	17/19
Age (years, median [SD])	61 (13.6)	54 (13)
Predisposing factors for venous thromboembolism, n (%)		
Chronic heart failure	10 (27)	4 (11.1)
Oral contraceptive therapy	4 (10.8)	1 (2.8)
Malignancy	4 (10.8)	2 (5.6)
Previous VTE	11 (29.7)	17 (47.2)
Bed rest >3days	4 (10.8)	6 (16.7)
Obesity	22 (59.5)	17 (47.2)
Varicose veins	16 (43.2)	13 (36.1)
Clinical markers		
Dyspnea	37 (100)	34 (94.4)
Chest pain	23 (62.2)	19 (52.8)
Syncope	14 (37.8)	15 (41.7)

parameters of the central tendency (media and median) and the dispersion (standard deviation, minimum, maximum, rank, quartiles). Intergroup statistical data were analyzed through the nominal variables using Fisher exact test. In the case of numeric variables, the distribution of data was determined by using Shapiro-Wilk test. The non-normal distribution of data imposed the use of nonparametric Mann-Whitney U test.

Results

The average duration of treatment was 3 days (limits between 1 and 4 days) for in situ thrombolysis and 2 days (limits between 1 and 3 days) in systemic thrombolysis, having a high significant statistical difference ($P = .002$). According to the protocol described above, we reduced dose to 50 000 UI/h at 6 (16.2%) patients with in situ thrombolysis compared to 7 (19.4%) patients with systemic thrombolysis, without statistically significant difference ($P = .594$). Also, it was necessary to stop thrombolysis due to increased hemorrhagic risk in 4 (10.8%) patients with in situ thrombolysis, compared to 8 (22.2%) patients with systemic thrombolysis, without significant difference ($P = .159$).

The features of the patients in the initial moment of the study are represented in Table 1. The average follow-up period was 24 months, without significant statistical difference ($P = .061$).

Clinical Results

At the end of the thrombolysis, 4 (10.8%) patients with a systemic approach were asymptomatic, compared to 16 (44.4%) patients with in situ thrombolysis. Statistical analyses revealed a significant difference between the 2 groups ($P = .001$).

Table 2. Echocardiographic Parameters.

	Route of thrombolytic administration		
	In situ	P value	Systemic vein
RVD$_2$ (median)			
Before (mm)	45		40
After (mm)	36		36
Percentage difference (%)	15	.019	16
Follow-up (mm)	25		34
Follow-up (%)	36	.5[a]	16
RA minor axis (median)			
Before (mm)	46		52
After (mm)	43		45
Percentage difference (%)	16	.029	16
Follow-up (mm Hg)	37		46
Follow-up (%)	7.8	.5[a]	8.6
P$_{RV-RA}$(median)			
Before(mm Hg)	45		63
After(mm Hg)	15		25
Percentage difference (%)	54	.446	51
Follow-up(mm)	27		25
Follow-up (%)	60	.044	40
IVC (median)			
Before(mm)	20		22
After(mm)	15		20
Percentage difference (%)	25	.003	9.5
Follow-up (mm)	15		17
Follow-up (%)	0	.5[a]	15
RPA (median)			
Before (mm)	27		22
After (mm)	24		20
Percentage difference (%)	8	.226	14
Follow-up (mm)	20		22
Follow-up (%)	5.4	.667	4.5
SPAP (median)			
Before (mm Hg)	51		70
After (mm Hg)	15		37
Percentage difference (%)	66	.390	50
Follow-up (mm Hg)	70		25
Follow-up (%)	60	.023	40

Abbreviations: IVC, inferior vena cava; RPA, right pulmonary artery; RV, right ventricle; SPAP, systolic pulmonary artery pressure.
[a]Exact significance (2 tailed).

Hemodynamic Findings

The evaluation of hemodynamic parameters, before and after the fibrinolytic therapy, showed a different evolution in the 2 groups. Cardiogenic shock, which initially was found in 23 patients with local thrombolysis and in 28 patients with systemic thrombolysis, has totally remitted in the group with thrombolysis in situ, meanwhile, at the end of the systemic thrombolysis, remained in 8 (28.6%) patients, with important statistical difference ($P = .002$). The improvement in peripheral oxygen saturation (SO_2) was registered in both groups, but without any statistical difference. Heart rate dropped in both groups: in the arm with in situ thrombolysis from an average of 100 to 70 bpm (31%) and in systemic thrombolysis, from an average of 99 to 72 bpm (22%) without significant statistical difference.
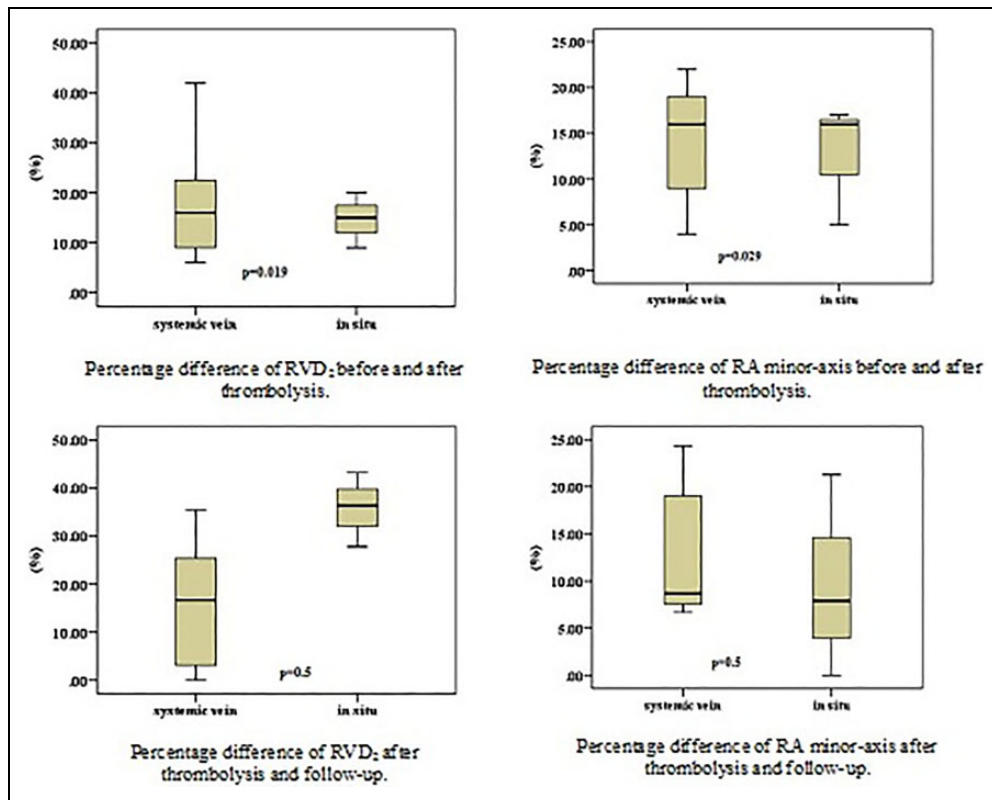
Figure 1. Percentage difference for RVD2 and RA minor axis before, after, and follow-up thrombolysis. Box plots express median, 25% and 75% quartiles, minimum and maximum.

Echocardiographic Results

Due to the fact that we registered a higher in-hospital mortality in the group of patients with systemic thrombolysis, we believe that the results of echocardiographic examination in this group was influenced by it, taking into consideration that for patients who died we could not register all the parameters regularly (Table 2). RVD_2, after local thrombolysis reduced from a maximum of 52 mm (range 16 mm) to a maximum of 44 mm (range 11 mm), the average decreased with 15%, representing a significant statistical difference, compared with systemic thrombolysis ($P = .019$). The 24 months follow-up showed a decrease in RVD_2 with 36.3% in the local thrombolysis group, compared with 16.6% in systemic thrombolysis, without significant statistical difference ($P = .5$; Figure 1).

RA minor axis reduced after both types of thrombolysis. Secondary to the in situ administration, the RA minor axis dropped from a maximum of 56 mm (range: 11 mm) to a maximum of 47 mm (range: 9 mm) and in systemic administration of SK, the RA minor axis has dropped from a maximum of 58 mm (range: 13 mm) to a maximum of 50 mm (range: 14 mm), representing a significant statistical difference ($P = .029$). The 24 months follow-up showed a decrease in RA minor-axis with 7.8% in thrombolysis in situ compared with 8.6% in systemic thrombolysis, without significant statistical difference ($P = .5$; Figure 1).

P_{RV-RA} had different variations. In the case of thrombolysis in situ, the maximum dropped from 75 mm Hg (range: 39 mm Hg) to 34 mm Hg (range: 19 mm Hg), compared to the systemic thrombolysis where the maximum dropped from 100 mm Hg (range: 68 mm Hg) to 55 mm Hg (range: 37 mm Hg). The analysis of percentage reduction of P_{RV-RA} in function by the modality of administration of thrombolytic agent, showed a drop of 54% in the group with in situ thrombolysis and of 51% in the group with systemic thrombolysis, without significant statistical difference ($P = .446$). The 24 months follow-up revealed a decrease of P_{RV-RA} with 60% in thrombolysis in situ compared with 40% in systemic thrombolysis, with significant statistical difference ($P = .044$; Figure 2).

After thrombolytic therapy, decreasing of IVC diameter was registered in both groups. The administration of in situ thrombolytic therapy determined a reduction in IVC diameter from a maximum of 23 mm (range: 8 mm) to 20 mm (range: 10 mm), versus the systemic administration, in which IVC decreased from a maximum of 28 mm (range: 12 mm) to 24 mm (range: 9 mm). Median IVC diameter presented a decrease of 25% secondary to local thrombolysis versus a decrease of 9.5% secondary to systemic thrombolysis, having significant statistical difference ($P = .003$). After 24 months follow-up, IVC diameter has remained the same in the arm with in situ thrombolysis, compared with systemic thrombolysis ($P = .5$; Figure 2).
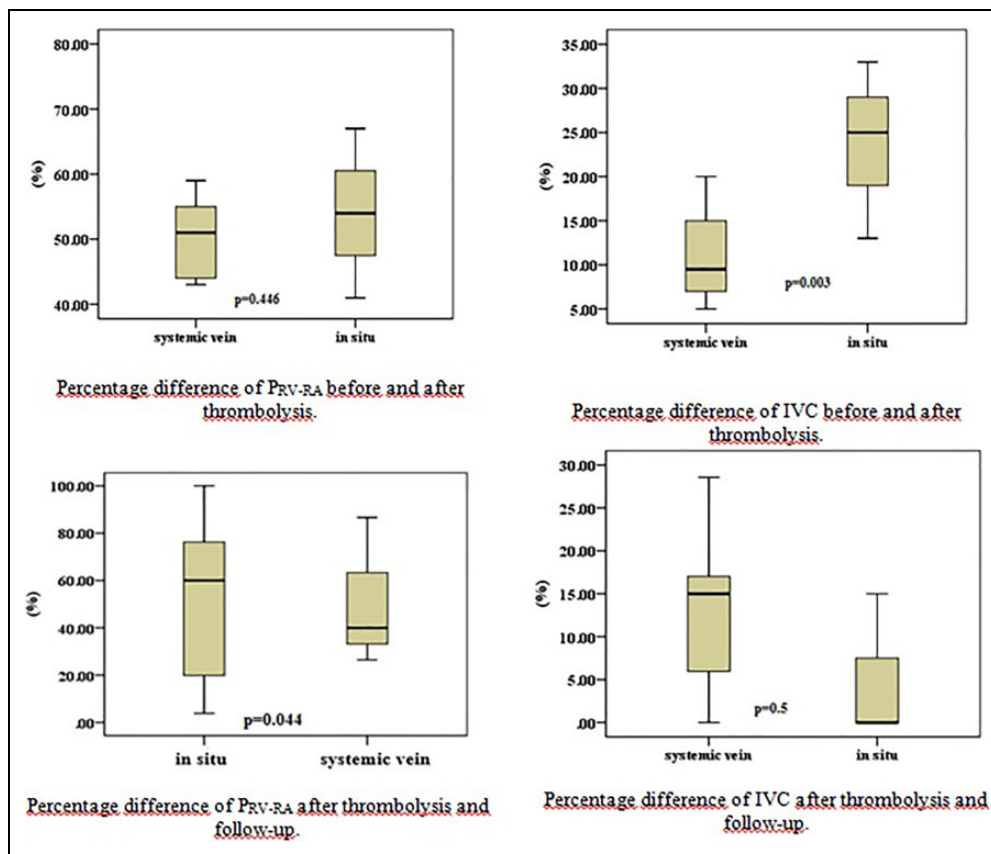
Figure 2. Percentage difference for P_{RV-RA} and inferior vena cava (IVC) before, after, and follow-up thrombolysis. Box plots express median, 25% and 75% quartiles, minimum and maximum.

Systolic pulmonary artery pressure had different variations. In the case of in situ thrombolysis, the maximum dropped from 75 (range: 30 mm Hg) to 34 mm Hg (range: 19 mm Hg), compared to the systemic thrombolysis where the maximum dropped from 115 (range: 83 mm Hg) to 55 mm Hg (range: 37 mm Hg). The anslsis of percentage reduction of SPAP in function by the modality of administration of thrombolytic agent, showed a drop of 66% in the group with local thrombolysis and of 50% in the group with systemic thrombolysis, without significant statistical difference ($P = .390$). The 24 months follow-up showed a decrease of SPAP with 60% in thrombolysis in situ compared with 40% in systemic thrombolysis, with significant statistical difference ($P = .023$; Figure 3).

Angiographic Findings

The evolution of mean PAP was dependent on the way of administration of the thrombolytic agent. In situ thrombolysis reduced the mean PAP from a maximum of 68 mm Hg (range: 44 mm Hg) to 45 mm Hg (range: 35 mm Hg), the average reducing by 41%, after thrombolysis. When compared with systemic administration of SK (number of patients = 11), the maximum value of the mean PAP, remained the same (52 mm

Hg, range: 36 mm Hg), with the average reducing insignificantly from 50 to 48 mm Hg ($P = .003$; Figure 4).

Safety Profile

The safety of the thrombolytic treatment was evaluated by analyzing the development of complications. Major bleeding occurred in 4 (10.8%) patients with in situ therapy, compared to 8 (22.2%) patients in the group with systemic thrombolysis, without significant difference ($P = .159$). Minor bleeding complications were seen in 6 (16.2%) patients with in situ thrombolysis, compared with 7 (19.4%) patients in the group with systemic thrombolysis, also without statistical significance ($P = .594$). Disseminated intravascular coagulation developed in one patient with systemic thrombolysis (2.7%, $P = .253$).

Adjuvant Therapy

The therapeutic management was represented (except for the thrombolysis), by a series of adjuvant treatment like the anticoagulant therapy. The unfractionated heparin was used in 34 (91.8%) patients with in situ thrombolysis and in 33 (91.6%) patients with systemic thrombolysis, and low-molecular-weight heparin was administrated in 3 (8.1%) patients with
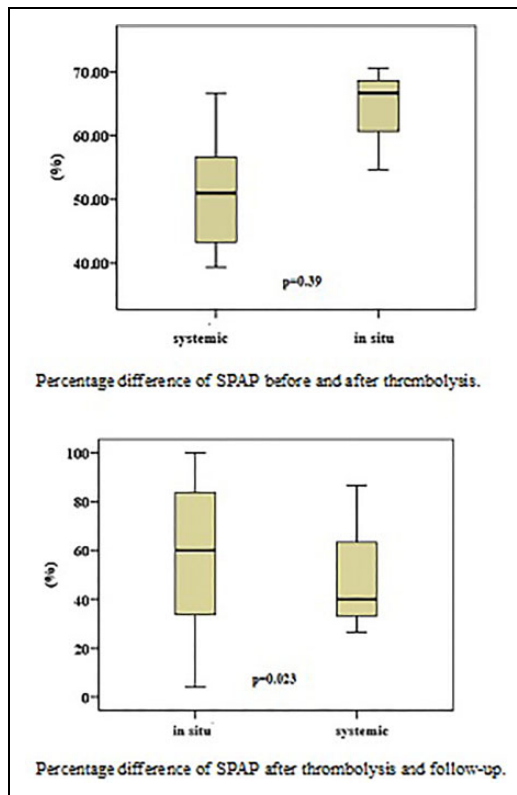
Figure 3. Percentage difference for systolic pulmonary artery pressure (SPAP) before, after, and follow-up thrombolysis. Box plots express median, 25% and 75% quartiles, minimum and maximum.

local thrombolysis and in 3 (8.3%) patients in the group with systemic thrombolysis, without significant statistical difference. There is no significant statistical differences in the duration of chronic treatment with antivitamin K therapy in the 2 groups ($P = .591$).

Mortality

Throughout the study 18 deaths were registered: 14 patients in the group with systemic thrombolysis and 4 from in situ group, with a mortality rate significantly higher in the patients with systemic SK administration ($P = .006$). The in-hospital mortality was 27.8% (10 patients) in the group with systemic thrombolysis and significantly lower, 2.7% (1 patient) in the group with in situ thrombolysis ($P = .003$), all patients having the immediate cause the PE, none from major bleedings. After discharge, in the next 24 months follow-up, the mortality was 15.4% (4 patients from the 26 patients who survived to the acute episode) in the group with systemic thrombolysis and 8.3% (3 patients from 36 patients discharged), in the group with local administration, without statistical significance, but with unknown death causes. All other patients—22 from the group with systemic thrombolysis and 33 from the group with in situ thrombolysis presented regularly at follow-up ($P = .285$; Figure 5).

Discussions

The European Society of Cardiology and the American Heart Association recommend consideration of fibrinolytic therapy for high-risk PE.[19,21] The main debate is related to the way of administration of thrombolytic agent. There are very few studies that compare long-term efficacy of systemic to local thrombolysis, mostly from small case series.[12]

In our study, cardiogenic shock has been totally remitted in the group with local thrombolysis and in only 71.4% patients with systemic thrombolysis, with an important significant statistical difference. A recent study, which specifically evaluated the cardiac output via invasive measurement in patients with acute intermediate high-risk PE demonstrated that right ventricular outflow tract velocity time integral (RVOT VTI) was an important predictor of low cardiac index, and a low RVOT VTI was clearly associated with increased PE-related mortality, even with normotension.[22]

Regression of right ventricular overload after local thrombolysis in high-risk PE is associated with reduced morbidity and mortality.[10,16,23] On the other side, Yujiro et al reported in their study that right ventricular overload was not significantly different before and immediately after local thrombolysis.[16]

In our study, the decrease in RVD_2 and RA minor axis was significantly higher immediately after intra-arterial thrombolysis compared to systemic thrombolysis. These results do not maintain at 24-month follow-up, when no longer significant differences regarding the evolution of RVD_2 and RA minor axis were registered.

P_{RV-RA} decreased with 54% after thrombolysis in situ and with 51% in systemic thrombolysis, without significant statistical difference. The 24 months follow-up revealed a decrease in P_{RV-RA} with 60% in thrombolysis in situ compared with 40% in systemic thrombolysis, with significant statistical difference.

A meta-analysis of 15 trials involving 2057 patients proved that thrombolysis is more frequently associated with major bleedings and fatal or intracranial bleeding than anticoagulation treatment alone.[1,7] The same results were registered in the International Cooperative Pulmonary Embolism Registry, Pulmonary Embolism International Thrombolysis trial, and in Management Strategies and Prognosis of Pulmonary Embolism trial.[7,16,24-27]

In our study, major bleedings occurred in 4 (10.8%) patients with in situ thrombolysis, compared with 8 (22.2%) patients in the group with systemic thrombolysis, without significant difference. Also, minor bleeding complications were not significantly frequent in systemic thrombolysis group. There was no intracranial bleeding in our study. Disseminated intravascular coagulation occurred in one patient with systemic thrombolysis.

Data obtained from US Nationwide Inpatient Sample during the 8-year period showed that in-hospital mortality with PE decreased from 12.3% to 8.2%, largely due to an early and correct diagnosis.[7]

Our study showed impressive results regarding the survival, which is superior to those registered by Goldhaber et al (1999)
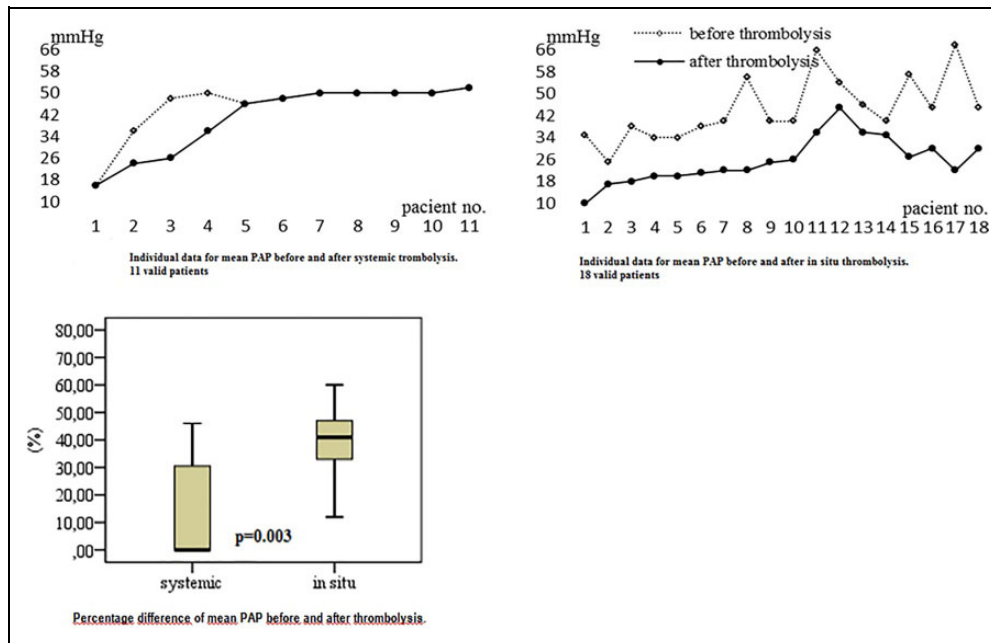
Figure 4. Individual data and percentage difference for mean PAP before and after thrombolysis (angiographic evaluated). Individual data are ordered ascending. Box plots express median, 25% and 75% quartiles, minimum and maximum.
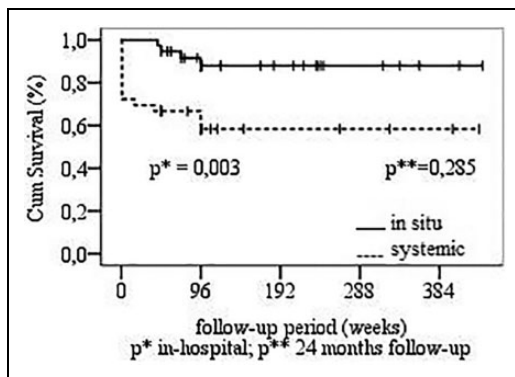

Figure 5. Kaplan Meier survival curve.

and Yujiro et al (2010) and comparable with the results of Macovei et al (2015).[10,16] The total mortality, at the end of 24 months of follow-up, was 38.9% in the group with systemic thrombolysis and significantly lower in patients with local thrombolysis (10.8%). The in-hospital mortality was significantly lower in the group with local thrombolysis (2.7% vs 27.8%, $P < .003$). We believe that this major difference between these 2 groups for mortality rate is due to the more potent effect of local thrombolysis by faster degradation of the local thrombus with a "mechanical" effect, along with a higher local concentration of SK; because this study is an observational one, we cannot fully eliminate a selection bias. After hospitalization, in the 24 months of follow-up, the survival does not significantly increase in the patients with local thrombolysis (8.3%) compared to the systemic thrombolysis (15.4%), stating the known idea that if a patient survives this major

cardiovascular event in the acute phase, late mortality is no longer influenced by the in-hospital treatment.

Strengths and Limitations

This study has several limitations. First of all, it is an observational study with a limited number of patients, from a single institution, and the results may not be generalizable. Second, none of the patients had other therapeutic options than thrombolysis such as surgical or catheter embolectomy, and for this reason we were not be able to compare the effects of alternative therapy options. Third, we did not have available a CTPA or V/Q lung scan, imaging studies that are now mandatory and might also had adverse effects on outcome.

On the other hand, we think that our study has some strengths. Our cohort consisted of very severe PE patients, and the results of this study give important insights to the most severe clinical presentation of PE. Literature data for this subgroup of patients are scarce and it has been shown that ICU admissions for PE showed a huge variation between hospitals.

Conclusions

Local thrombolysis was associated during the hospitalization with significant improvement in clinical and hemodynamic parameters and most important with a significantly lower mortality rate comparing to the systemic thrombolysis. The evaluation after 24 months showed that the evolution of residual pulmonary hypertension was significantly better after in situ thrombolysis, with a comparable survival rate in both groups.

Declaration of Conflicting Interests

Funding

ORCID iD

Robert Magopet https://orcid.org/0000-0003-0264-7724
Cristina Prisecariu https://orcid.org/0000-0003-0369-5816

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