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Regular Article

Short term effect of recombinant tissue plasminogen activator in patients with hemodynamically stable acute pulmonary embolism: Results of a meta-analysis involving 464 patients

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ABSTRACT

By considering studies where a mixing of patients with and without shock, with or without invasive procedure, treated with various thrombolytic agents through different ways of infusion, have been included, current meta-analyses on thrombolysis efficacy in Pulmonary embolism (PE) are of limited value. Modern management of PE includes the use of both non-invasive diagnostic methods and intravenous rt-PA as thrombolytic agent.

Methods: We performed a meta-analysis of all randomized trials comparing rt-PA with heparin in patients with hemodynamically stable pulmonary embolism. Only the events clearly identified as related with the venous thromboembolic disease or with the treatment were considered.

Results: Five studies involving 464 patients were included. The pooled estimate from all the trials revealed a non-statistically significant reduction in death related to PE or pulmonary recurrence for rt-PA compared with heparin (3.5% versus 4.6%; RR 0.97, 95% CI 0.38 to 2.51, P for heterogeneity among the studies = 0.73). Compared with heparin, rt-PA was not associated with a significant increase in major bleeding (4.9% versus 4.6%; RR 0.94, 95% CI 0.39 to 2.27). Similar results were found when only studies including patients with echocardiographic evidence of right ventricular dysfunction were considered.

Conclusion: Neither mortality due to pulmonary embolism nor objective pulmonary embolism recurrence are decreased by rt-PA compared with heparin in patients with hemodynamically stable pulmonary embolism. No benefit is suggested in studies including patients with right ventricular dysfunction alone.

To date, both the American and the European guidelines on the treatment of pulmonary embolism (PE) recommend the use of thrombolytic therapy only in patients with hemodynamically unstable PE [1,2]. Indeed, no significant statistical benefit of thrombolysis has been demonstrated in previous meta-analyses of randomized trials comparing thrombolytic therapy with heparin in patients with acute non-massive PE [3–5]. However, the interpretation of these meta-analyses, including studies realized from October 1968 to August 2001, appears to be somewhat limited. Indeed, in the oldest studies, invasive procedures for PE management, known to increase the hemorrhagic risk, were largely used. In addition, despite a very different prognosis, a mixing of patients with and without shock were included in these studies, making the effect of thrombolysis in terms of mortality invaluable. Moreover, in the oldest studies, heparin regimens were non adequate in most cases with doses adjusted to the results of the Lee-White clotting or with the infusion of heparin through an intrapulmonary catheter. Finally, various thrombolytic agents were used in the oldest studies with different dose regimen as well as different ways of infusion (intravenous, intrapulmonary). Because of the inclusion of these old studies, the results of the previous meta-analyses do no represent the current PE management. To date, a short intravenous infusion of recombinant tissue Plasminogen Activator (rt-PA) appears to be one of the best choices among the different thrombolytic agents and regimen modalities [1,2]. In order to clarify the potential role of thrombolytic therapy in PE, we performed an updated meta-analysis of randomized trials comparing intravenous rt-PA and heparin in the treatment of only hemodynamically stable acute PE. In addition, as patients with hemodynamically stable PE and echocardiographic evidence of right ventricular dysfunction (RVD) could have a higher mortality than those without RVD [6–8], the effect of rt-PA therapy compared to heparin, in this subset of patients was also studied.

Methods

Study identification

In order to identify all randomized clinical trials comparing thrombolysis and heparin or low-molecular-weight heparin for the treatment or pulmonary embolism, we searched electronic databases

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Table 1
Randomized clinical trials comparing thrombolytic and heparin in patients with acute PE.

Trial, Year (reference)	Inclusion	Randomized treatment	Number of patients			Follow up
			included	with pulmonary angiography	with echocardiographic signs of RVD	
Levine, 1990 [22]	Acute PE	rt-PA: 0.6 mg/kg for 2 minutes	33	67%	ND	10 days
	Symptoms ≤ 14 days	Heparin	25	72%	ND	
PIOPED, 1990 [23]	Acute PE	rt-PA: 40 à 80 mg for 40 to 90 minutes	9	100%	ND	7 days
	Symptoms ≤ 7 days	Heparin	4	100%	ND	
PAIMS, 1992 [24]	Acute PE	rt-PA: 100 mg for 2 h	20	100%	ND	30 days
	Symptoms ≤ 10 days	Heparin	16	100%	ND	
Goldhaber, 1993 [25]	Acute PE	rt-PA: 100 mg for 2 h	46	13%	50%	In hospital or 14 days♣
	Symptoms ≤ 14 days	Heparin	55	27%	42%	
Konstantinides, 2002 [26]	Acute PE	rt-PA: 100 mg for 2 h	118	16%	31%	In hospital or 30 days
	Symptoms ≤ 4 days	Heparin	138	17.4%	31%	

PIOPED: Prospective investigation of pulmonary embolism, diagnosis; PAIMS: Plasminogen activator Italian multicenter study; PE: pulmonary embolism; rt-PA: recombinant tissue-type plasminogen activator. ♣Major haemorrhage was taken into account only during the 72 hours following inclusion.

(Embase, Pascal and Medline) from January 1975 to June 2008 and the Cochrane library (2006, Issue 1) using the terms: humans, pulmonary embolism, thromboembolism, thrombolysis, fibrinolysis, recombinant tissue plasminogen activator, rt-PA, alteplase, randomized controlled trial, controlled clinical trials. Only studies with data accessible in the English, French or Spanish languages were considered.

Study selection

Two investigators (BT, CV) independently evaluated studies for inclusion. Discrepancy between the results obtained by the investigators was resolved by consensus. The criteria for inclusion were 1) randomization, 2) patients with objectively diagnosed acute pulmonary embolism, 3) comparison of intravenous rt-PA with intravenous heparin for the initial treatment of PE, 4) outcomes including death, PE recurrence and major haemorrhage.

Data extraction

Two investigators (BT, CV) independently extracted data on the study design and quality and on the safety and efficacy outcomes during hospitalisation or within 30 days. In the event of discrepancy between the results obtained by the investigators concerning data extraction, a third investigator (FZ) helped in the final decision. Efficacy outcomes included death related to PE and PE recurrence. Death related to PE was defined by death directly related to PE as reported by the authors or proven by autopsy. As the PE recurrence definitions in the original articles were heterogeneous, PE recurrence was taken into account only when it was reported as either proven by radiological investigations or proven by autopsy. Safety outcomes included major haemorrhage. As the major haemorrhage definitions in the original articles were heterogeneous, major haemorrhage was considered when it was reported as a "major haemorrhage episode" by the authors or when bleeding was pericardial, retroperitoneal or intracerebral or fatal or associated with either a decrease in the haemoglobin level of at least 2 g per decilitre or the need for transfusion of 2 or more units of red cells, or leading to surgery or permanent discontinuation of the drug. In addition to these efficacy and safety outcomes, the need for treatment escalation was also recorded in the event of subsequent development of shock or mechanical ventilation needed after thrombolysis or heparin failure. The treatment escalation was defined as the use of at least one of the following: secondary thrombolysis, surgical embolectomy and thrombus fragmentation by catheter.

Outcomes

The primary efficacy outcome was a composite of recurrent PE or death related to PE. Secondary outcomes were the individual components of the primary outcome, all-causes death and major haemorrhage.

Statistical analysis

Relative risks were combined using a fixed effect model and the EasyMA software. The level of statistical significance was set at alpha = 5%. We assessed the heterogeneity between studies with the Cochran Q test and took $p<0.05$ as the threshold of statistical significance for heterogeneity. Potential publication bias was evaluated using the funnel plot approach.

Results

Study selection

Our search identified 18 potentially eligible randomized controlled trials. Among them, six were excluded as they presented long term follow-up or sub-groups of patients previously reported [9–14]. Seven other studies were also excluded as the thrombolytic agent used was urokinase or streptokinase [15–21]. In addition, in 6 of these seven studies, patients with shock were not excluded [15–18,20]. So, 5 studies were included in the present meta-analysis [22–26] (Table 1). All these 5 studies included patients during the acute phase of a symptomatic PE proven using angiography or V/Q scan. Hemodynamically instable patients were not included in these 5 studies. Pulmonary angiography was performed in the vast majority of patients in three studies [22–24] while pulmonary angiography was performed in no more than one quarter of cases in the two most recent studies [25,26]. Baseline echocardiography was performed in nearly 100 per cent of cases in two studies [25,26] while echocardiography was not performed in the 3 other studies. A right ventricular dysfunction was found in 60 patients (36.5%) among the 164 who received rt-PA and in 66 patients (34%) among the 193 who were assigned to heparin. As in these studies the reported follow-up of patients did not exceed 30 days, only the short term effect of rt-PA versus heparin was analyzed. Among the 5 trials, a double blind design was used in only three studies [22,23,26]. In only one study, escalation of treatment was a pre-defined outcome [26]. A validation of outcomes by a central committee unaware of the treatment group was not used in any of the trials. The number of patients lost in follow-up was not reported in any of the trials. Overall, 464 patients were included in the analysis: 226 received thrombolytic therapy and 238 received heparin.

Efficacy outcomes

The binary endpoints summary is presented in Fig. 1. Data on the primary outcome (death related to PE or recurrent pulmonary embolism) and individual components of this primary outcome are presented in Table 2. The pooled estimate from all the trials revealed a non-statistically significant reduction in death related to PE or

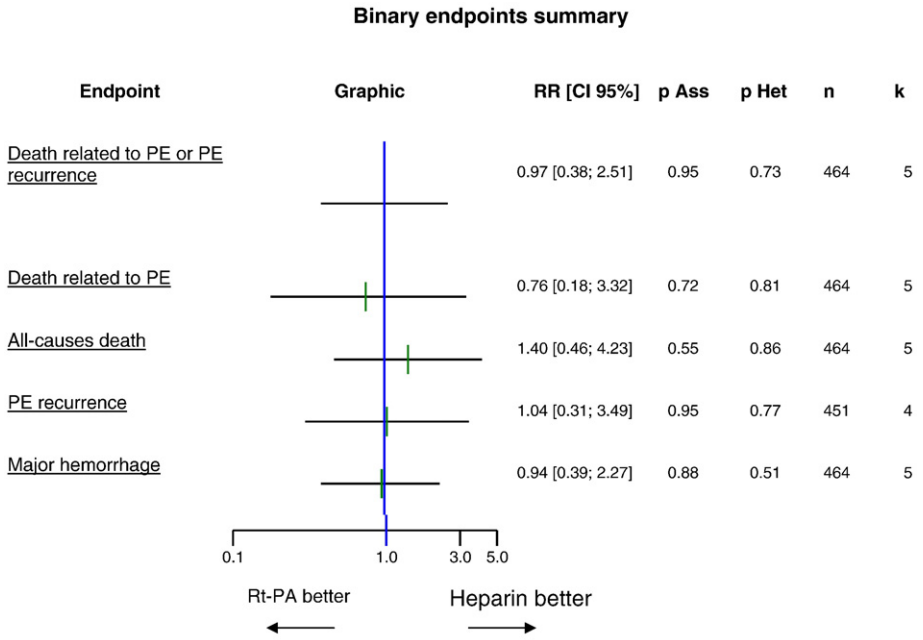

Fig. 1. Binary endpoints summary (all studies). pAss = p Association, p Het = p heterogeneity, n = number of patients, k = number of studies.

pulmonary recurrence for thrombolysis compared with heparin (3.5% versus 4.6%; RR 0.97, 95% CI 0.38 to 2.51) with no statistical evidence of heterogeneity among the studies (p = 0.73). A similar estimate of treatment effect was obtained for death related to PE (1.3% versus 2.1%; RR 0.76, 95% CI 0.18 to 3.32) (Heterogeneity test p = 0.81) while no effect was found when all-causes death was considered (Fig. 1 and Table 2). No statistical difference was found between treatments for PE recurrence (2.3% versus 2.6%; RR 1.04, 95% CI 0.31 to 3.49) (Heterogeneity test p = 0.98). Graphical analysis of the funnel plot did not suggest publication bias (data not shown).

In the two trials that included patients with echocardiographic RVD [25,26], compared with heparin, thrombolytic therapy was associated with a non-significant reduction in death related to PE or recurrent PE (3.6% versus 5.2%; RR 0.96, 95% CI 0.35 to 2.80) (Fig. 2). A similar estimate of treatment effect was obtained for death related to PE (1.2% versus 2.1%; RR 0.81, 95% CI 0.14 – 4.69) and for PE recurrence (2% versus 3.1%; RR 0.96, 95% CI 0.26 – 3.49) (Fig. 2).

Safety outcomes

Pooled and individual data of major hemorrhage outcomes are presented on Fig. 3. The pooled data do not reveal evidence of an increased risk of major hemorrhage with rt-PA compared with heparin (4.9% versus 4.6%; RR 0.94, 95% CI 0.39 to 2.27) (Heterogeneity test p = 0.61). Among a total of 22 episodes of major hemorrhage, pericardial effusion or perforation caused by the catheter used for angiography and bleeding at catheter venous sites were observed in 5 (22%) patients, who were treated with rt-PA in 4 cases and with heparin in 1 case. Major hemorrhage was fatal in a total of 3 (13.6%) patients, 2 treated with rt-PA and 1 with heparin. Intracranial hemorrhage was observed in only 2 (9%) patients both treated with rt-PA (given off protocol in 1 case) and was fatal in one case.

Escalation of treatment

During the follow-up period, the need for an escalation of treatment was observed in two studies [25,26], but using pre-defined criteria in only one study [26]. A total of 45 (9.6%) patients underwent an escalation of treatment including thrombolysis in 44 cases and surgical embolectomy in 1 case. Among these 45 patients with escalation of treatment, 42 (93%) (9 in the rt-PA group and 33 in the heparin group) were reported in the only study that used pre-defined criteria for escalation [26]. During the follow-up period of the 5 trials, an escalation of treatment was observed in 36 (15%) of the 238

Table 2
Adverse outcome events.

Study (reference)	Death related to PE or PE recurrence			Death related to PE			All-causes death			PE recurrence		
	rt-PA	UFH	RR 95% CI	rt-PA	UFH	RR 95% CI	rt-PA	UFH	RR 95% CI	rt-PA	UFH	RR 95% CI
Levine [22]	1 / 33	0 / 25	3.03 0.04–235.15	1 / 33	0 / 25	3.03 0.04–235.15	1 / 33	0 / 25	3.03 0.04-235.15	0 / 33	0 /25	0.76 0.00-188.93
PIOPED [23]	0 / 9	0 / 4	0.44 0.00–100.08	0 / 9	0 / 4	0.44 0.00-100.08	1 / 9	0 / 4	1.78 0.03-121.10			
PAIMS [24]	1 / 20	1 / 16	0.80 0.05 – 11.82	0 / 20	1 / 16	0.20 0.00 - 15.23	2 / 20	1 / 16	1.60 0.16 – 16.10	1 / 20	0/ 16	3.20 0.04–243.72
Goldhaber [25]	0 / 46	4 / 55	0.07 0.00 – 4.17	0 / 46	2 / 55	0.15 0.00 – 9.38	0 / 46	2 / 55	0.15 0.00 - 9.38	0 / 46	2 / 55	0.15 0.00 – 9.38
Konstantinides [26]	6 / 118	6 / 138	1.17 0.39 – 3.53	2 /118	2 /138	1.17 0.17 – 8.17	4 / 118	3 / 138	1.56 0.36 – 6.83	4 / 118	4 / 138	1.17 0.30 - 4.57
All studies	**8 / 226**	**11 / 238**	0.97 0.38 – 2.51	**3 / 226**	**5 / 238**	0.76 0.18 – 3.32	**8 / 226**	**6 / 238**	1.40 0.46 – 4.23	**5 / 217**	**6/234**	1.04 0.31 – 3.49

rt-PA: recombinant tissue plasminogen activator, HNF: unfractionated heparin; RR: relative risk; CI: confidence interval.

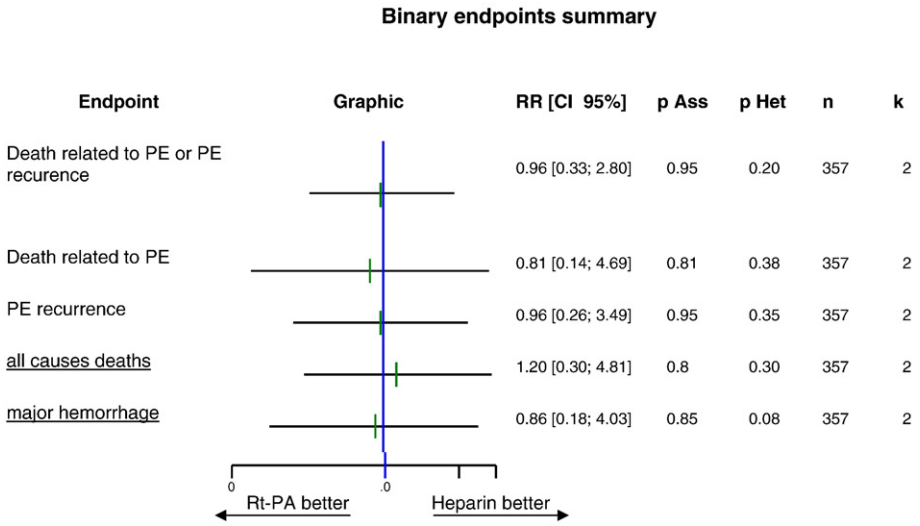

Fig. 2. Binary endpoints summary (studies that included patients with echographic right ventricular dysfonction). pAss = p Association, p Het = p heterogeneity, n = number of patients, k = number of studies.

patients initially treated with heparin alone and in 9 (4%) of the 226 patients initially treated with rt-PA. The objective reasons for escalation of treatment were hemodynamic instability or secondary cardiac shock (9 cases) or respiratory distress requiring mechanical ventilation (5 cases) giving a total of 14 (3%) among the 464 patients with hemodynamically stable PE.

Discussion

This meta-analysis of currently available randomized trials does not demonstrate any statistical significant benefit from rt-PA compared to heparin in the treatment of patients with hemodynamically stable acute PE. As the main cause of PE mortality is recurrent PE, the low mortality (under 3%) observed in both groups of patients is related to the low (under 3%) rate of PE recurrence whatever the treatment. These rates observed are in accordance with the rate of 3% of fatal and non fatal PE recurrence recently reported in an international randomized study in which 2213 patients with hemodynamically stable acute PE treated with unfractionated heparin or Fondaparinux were enrolled [27]. In the subgroup of studies including patients with RVD, the mortality related to PE under heparin therapy (2.1%) appears to be very similar to the mortality rate observed in the global population of patients with hemodynamically stable acute PE (2.1%). Rather to a non beneficial effect of rt-PA in such patients, these low mortality rates are most likely attributable to the low-risk nature of these patients. Indeed, the reliability of RVD alone as discriminating factor to identity high risk patients remains to be established. In a recent non-randomised study in which 64 patients treated by thrombolysis for PE were matched by echographic evidence of RVD with 64 patients treated with heparin, both mortality and PE

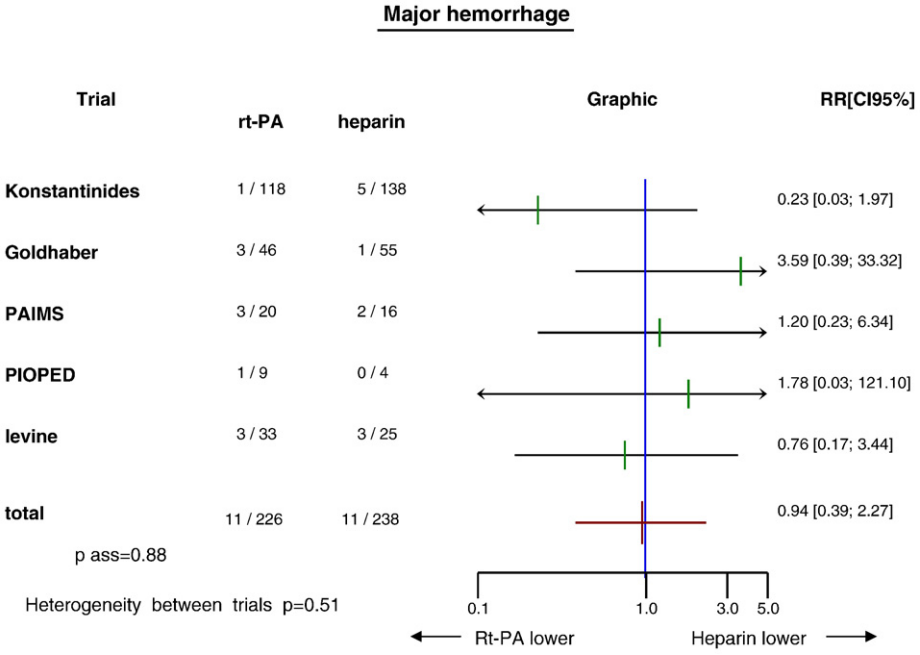

Fig. 3. Individual data of the secondary outcome of major hemorrhage. PAIMS: Plasminogen activator Italian multicenter study; PIOPED: Prospective investigation of pulmonary embolism, diagnosis.

recurrence rates were found to be similar [28]. The escalation of treatment related to objective criteria such as secondary hemodynamic instability or respiratory distress requiring mechanical ventilation appears to be a rare event (3%) in patients with hemodynamically stable PE. A similar rate (3.9%) of escalation of treatment is observed when only studies, that included patients with RVD, are considered. The criteria to identify patients with high risk of adverse clinical outcome, for which thrombolysis should decrease PE recurrence or secondary shock occurrence, remain to be found. To date, several biochemical markers, including troponin and B-type natriuretic peptides, which reflect myocardial microinfarction and myocardial stretch respectively, have been evaluated as predictive factors of adverse outcome in short series of patients with acute pulmonary embolism [29–32]. As increased levels of these markers seem to correlate with the mortality rate of such patients. These markers, in association or not with echocardiography, have been proposed to stratify patients for more aggressive therapies such as thrombolysis. On the other hand, despite the use of the largest criteria of major hemorrhage in our study compared with the previous meta-analyses [3–5], rt-PA therapy was not associated with a significant statistical increase of major hemorrhage risk. Moreover in this meta-analysis, fatal major hemorrhage as well as intracranial hemorrhage occurred in less than 1% of patients treated with rt-PA. The observed rate of 4.8% of major hemorrhage with rt-PA therapy is less than twofold those reported in the previous meta-analysis. Even if short infusion of rt-PA could induce less major hemorrhage than prolonged infusion of urokinase [1,2], the current management with a better selection of patients and less invasive investigations are probably the main causes of such an observation. Currently, a randomised trial is conducted in Europe in patients with hemodynamically stable PE and both elevated troponin levels and echographic right ventricular enlargement. This trial will randomise approximatively 1 000 patients to thrombolysis with a bolus of tenecteplase plus heparin versus heparin alone.

The present study has several potential limitations. First, by limiting our meta-analysis to studies comparing rt-PA with heparin in patients with hemodynamically stable PE, the total number of patients randomised and the number of outcome events are low. Consequently, the present study has a limited statistical power. However, compared to previous meta-analyses, this study is a better representation of current management of PE. Secondly, the present meta-analysis failed to identify patients with high risk of adverse outcome events. Patients with echocardiographic evidence of RVD were included in only 2 randomised trials without stratification of treatment depending on the existence or not of echocardiographic signs of RVD. However, with these limits, the analysis of the subgroup of studies in which patients with RVD were included did not show evidence for a difference in incidence of adverse outcome events. Finally, in contrast with previous meta-analyses, our choice to consider only events related to venous thromboembolism may be debatable. However, the design of most of the studies included was to compare the effect of thrombolysis and heparin therapy on the rate and the speed of lung reperfusion. In most of these studies, the clinical characteristics of patients on inclusion were not comparable between the two groups of treatment. So, reporting global mortality rather than mortality related to PE could introduce, in our opinion, a major bias in the analysis.

To conclude, the current data available do not show evidence of a benefit of rt-PA in patients with hemodynamically stable PE. However, in selected high risk patients with both RVD and elevated cardiac biomarkers, rt-PA could be beneficial. With well selected patients and invasive procedures avoided, major hemorrhage related to rt-PA treatment is not frequent.

Conflict of interest statement

None declared.

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