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REVIEW ARTICLE

Fibrinolytic therapy in pulmonary embolism

William J. Brady

Seth Althoff. Virginia Medical Centre. EE.UU.

Correspondence:
William J. Brady
Seth Althoff Virginia
Medical Centre. EE.UU.
E-mail: wjbrady@virginia.edu

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There is reasonable evidence that suggests that fibrinolytic therapy accelerates the resolution of PE while simultaneously reducing the recurrence of pulmonary embolism; it can also improve other parameters, such as pulmonary blood flow, lung perfusion, and right ventricular dysfunction. Unfortunately, conclusive evidence demonstrating a mortality reduction is not found in the literature, particularly in those patients who are clinically stable with intermediate to low risk of death. The clinician should assess the mortality risk of the PE relative to both the potential benefits and the adverse effects of fibrinolytic therapy for cardiac arrest and the various risk group presentations. In cardiac arrest related to PE, there are no contraindications to medical fibrinolysis; fibrinolytic therapy likely offers the reasonable chance at survival. In those patients not in cardiac arrest, a categorization into high, intermediate, and low risk groups will aid in decision making. In the absence of significant bleeding risk, those patients who are hemodynamically unstable or have signs of right ventricular dysfunction would likely benefit from fibrinolytic agents – i.e., the high risk group. Intermediate risk presentations demonstrate less benefit such that the consideration of complications not infrequently outweighs fibrinolytic advantage. The literature is mixed, however, in its recommendations for the intermediate group. And, lastly, the low risk group does not benefit from fibrinolysis. Despite this categorization, the decision to administer a fibrinolytic agent remains challenging; the clinician must consider the risks of PE coupled with the risks of fibrinolysis, as compared with this medication's potential benefit. The decision to administer a fibrinolytic agent in the setting of PE remains highly individual and is most appropriately addressed by the clinician at the bedside. [Emergencias 2011;23:319-323]

Key words: Pulmonary embolism. Fibrinolitic therapy. Pulmonary embolism.

Introduction

Pulmonary Embolism (PE) is estimated to occur in approximately 600,000 patients annually in the United States[1-4]. Mortality estimates for PE range from 1% to 95% depending on the clinical presentation and burden of disease[5,6]. PE may also contribute to as much as 15% of all in-hospital deaths[2,7,8]. As noted, there is a broad spectrum of disease presentation from asymptomatic to cardiac arrest. In the past, PE has been categorized as massive, sub-massive, and non-massive. Recent European guidelines, however, are recommending that PE be categorized based upon the patient's estimate of early pulmonary-embolism related death -- in essence, in-hospital or 30 day mortality[9]. This approach categorizes patients into high and non-high risk. Non-high risk patients can be further stratified into intermediate and low risk categories based on markers of right ventricular dysfunction and cardiac injury; this risk stratification is outlined in Table 1[9].

High risk patients, previously categorized as massive PE, present with acute right ventricular failure that results in shock defined as systolic blood pressure less than 90 mmHg or a sustained pressure drop of greater than 40 mmHg for at least 15 minutes. The three month mortality for these patients is approximately 50% with most deaths occurring within the first few days of presentation[5,11,12]. Intermediate risk patients have a mortality of roughly 3-15% and low risk patients typically less than 1%[10]. In this article, we will review current fibrinolytic agents and their indications from the perspective of PE mortality risk.

Table 1. Risk stratification of pulmonary embolism

Pulmonary embolism-related mortality risk		Risk Markers		
		Hemodynamic instability (systolic bp < 90 mmhg or pressure drop of > 49 mmhg over 15 mins)	Right ventricular dysfunction (BNP, NT-ProBNP, hypokinesis on echocardiography)	Myocardial injury (Troponin I or T)
High Risk (> 15%)		+	+	+
Non high risk	Intermediate (3-15%)	–	+	+
		–	–	+
		–	+	–
	Low (< 1%)	–	–	–

Adapted from 9.

Fibrinolytic agents

Fibrinolytic agents convert plasminogen to plasmin, which in turn breaks down the fibrinogen and fibrin in a clot, thereby actively reducing the size of the clot. Anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) only prevents the extension of the thrombus. There are various fibrinolytic agents on the market, but only three streptokinase, urokinase, and recombinant tissue plasminogen activator (rtPA) are approved in the treatment of PE. The current dosing regimens can be found in Table 2.

Multiple studies have demonstrated similar safety profiles for the three fibrinolytic agents in patients with PE[13-15]. Several studies have also compared various infusion times. Most of these studies demonstrated improved cardiac and pulmonary function initially, yet when compared at later times, found no significant differences in the various outcome parameters. These studies also found that there were no increased rates of major hemorrhage or mortality with the 2-hour infusion protocols as compared with 12 or 24-hour infusions[14-18]. Several studies have also compared bolus dosing, rather than continuous infusions[19-21]. Levine et al randomized 58 patients with PE to receive rtPA (0.6 mg/kg over two minutes) plus heparin or placebo plus heparin. Those receiving rt-PA initially had greater than 50% clot resolution and increased perfusion within 24 hours, but no difference was found at 7 days. This study found no major bleeding occurrences in either group[22]. The same 0.6 mg/kg of rtPA over 15 minutes demonstrated a trend towards a lower risk of bleeding when compared to the usual 100 mg infused over 2-hours, but was not statistically significant[19,20]. Thus, current evidence suggests that fibrinolytic therapy, if given, should be infused through a peripheral vein using the 2-hour infusion protocols in patients with sustained, though compromised, systemic perfusion.

Several small nonrandomized studies have also investigated catheter-directed thrombolysis[23-26]. Verstraete et al compared intrapulmonary thrombolysis to rt-PA 2-hour infusion. No significant differences were found between the two groups[27]. Theoretically, catheter-directed thrombolysis would have several potential benefits. Because the drug is being delivered directly to the clot, one would expect lower doses would be needed for similar clot lysis, more rapid clot lysis would occur, and less bleeding complications would be observed. However, given the limited data with this therapy, it is currently not recommended[28].

As with all therapies in medicine, the risks and benefits need to be considered before treatment is initiated. The major risk of fibrinolytic therapy is hemorrhage[29]. A meta analysis of 11 randomized controlled trials of patients with PE managed with fibrinolysis demonstrated severe bleeding in 13% of patients and a 1.8% risk of intracranial or fatal hemorrhage[6]. Bleeding most commonly occurs at

Table 2. Fibrinolytic dosing regimenes in PE

1. Alteplase
   a. 15 mg IV bolus followed by 85-mg IV infusion over 2 h.
   b. Accelerated 90-min regimen recommended total dose based upon patient weight, not to exceed 100 mg.
      < 67 Kg: drug administered as 15-mg IV bolus, followed by 0.75 mg/kg infused over next 30 min (not to exceed 50 mg) and then 0.50 mg/kg over next 60 min *not to exceed 35 mg).
      > 67 Kg: 100 mg given as 15-mg IV bolus followed by 50 mg infused over next 30 min and then 35 mg infused over next 60 min.
2. Reteplace
   a. 10-U IV bolus followed in 30 min by another 10-U IV bolus.
3. Urokinase
   a. 4400 IU/KG loading dose over 10 min followed by 4400 IU/Kg/h over 12-24 h
   b. 3 million IU infused over 2 h.
4. Streptokinase
   a. 250,000 IU as loading dose over 30 min, followed by 100,00 IU/h over 12-24 h.
   b. 1.5 million IU over 2 h.
5. Tenecteplace
   a. 0.5 mg/Kg IV bolus (max 50 mg)

Adapted from 9, 35.

venous access sites, but spontaneous hemorrhage may occur in the gastrointestinal tract, retroperitoneal area, and central nervous system[30,31]. One study sought to identify specific independent risk factors for increased bleeding risk and found the co-administration of catacholamines to be the greatest predictor, followed by the presence of malignancy, diabetes, and coagulopathy[32]. Other complications include fever, allergic reactions, urticaria, and hypotension.

Fibrinolytic therapy indications

Approximately 5% of patients will present in shock and be categorized as experiencing a massive PE or demonstrating a high-risk presentaton[33]. As previously discussed, these patients have the highest mortality and are currently the only group in which fibrinolytic agents can be considered. Jerjes-Sanchez et al reported that medical fibrinolysis reduced mortality in patients who were hemodynamically unstable[34]. This observation was confirmed by a meta-analysis including five randomized studies in which a 55% reduction in recurrent pulmonary embolism or death was associated with fibrinolytic therapy compared to heparin alone[6]. The high risk category of PE patients can be considered for firbrinolytic agent administration; given the unfavorable prognosis with this group, contraindications to fibrinolysis are largely relative[35].

All other patients would be defined as non-high risk either intermediate or low risk for PE-related mortality. Non-high risk patients can be further stratified based on any of the following abnormal clinical parameters: brain natriuretic peptide (BNP), N-terminal-proBNP (NT-proBNP), elevated cardiac troponin T or I, and/or right ventricular dilatation or hypokinesis on echocardiography. A positive finding from this list, in a hemodynamically stable patient, indicates the intermediate risk category; negative findings coupled with clinical stability suggest low mortality risk.

It is in this intermediate risk group of PE patients that the greatest therapeutic controversy exists regarding medical fibrinolysis. In patients managed with and without fibrinolysis, Goldhaber et al initially demonstrated that significant PE only recurred in those patients with baseline right ventricular hypokinesis. The overall rate of recurrence was low and no statistical difference was demonstrated between treatment groups; in other words, fibrinolysis did not reduce the rate of recurrence in this intermediate risk group[36]. In contrast to this study, the Management Strategy and Prognosis of Pulmonary Embolism Registry reported that a significantly higher recurrence rate of PE and death was noted in the subset of patients with right ventricular dysfunction who did not receive fibrinolytic agents. An improvement in right ventricular function was observed in 89% of those patients in the intermediate risk group who received fibrinolytic agents at 24 hours. This improved function was associated with a 58% reduction in in-hospital mortality[37]. Although these data are promising, these findings were not confirmed in the largest randomized control trial to date. Konstantinides et al enrolled 256 patients with a PE complicated by pulmonary hypertension or right ventricular dysfunction to be randomized to receive intravenous heparin plus placebo or intravenous heparin plus alteplase. No significant difference in mortality was demonstrated; there was an increased need for the escalation of treatment in the placebo group. The protocol permitted the breaking of the randomization code in deteriorating patients, of whom a portion received "rescue" fibrinolytic agent[38]. Because of this protocol allowance, this trial has been criticized. Thus, conclusive data in the intermediate risk group suggesting the use of fibrinolytic therapy does not yet exist. In 2007, a European trial began that will further investigate this subset of patients; its results are pending at this time.

Low risk patients do not benefit from medical fibrinolysis. This final category of patients demonstrates the most optimal outcome and is considered low risk; these patients are defined by hemodynamic stability and the absence of any signs of right ventricular dysfunction or myocardial injury. Such patients have a low mortality risk and the risks of fibrinolytic agents outweigh the benefits in this subset of patients.

The current American College of Chest Physicians guidelines recommend fibrinolytic therapy in those patients with the following features: 1. hemodynamic instability and 2. hemodynamic stability yet identified as higher risk. "Higher risk" indicators include patients with the following: ill appearing, significantly dyspneic, low oxygen sat urations, elevated troponins, right ventricular dysnfunction on echocardiography or right ventricular enlargement on chest CT. If these patients are at low risk of bleeding, meaning they have the absence of intracranial disease, uncontrolled hypertension or recent major surgery or trauma, then fibrinolytic agents can be beneficial according to this guideline[39].

Both the European and ACCP guidelines are in partial agreement on which patients may benefit the most from fibrinolytic therapy; however, they categorize these patients differently. The hemodynamically unstable patients described in the ACCP guidelines correspond to the European high risk categorization. These patient demonstrate the greatest benefit from firbrinolysis. The ACCP subset of higher risk, hemodynamically stable patients corresponds to the European intermediate risk group. This patient subgroup does not consistently demonstrate benefit from medical fibrinolysis; in these patients, an individual review of the clinical features and potential risk will guide therapeutic decisions.

The last area to consider is cardiac arrest. A significant minority of patients with PE will present in cardiac arrest. Of course, the diagnosis of PE must be confirmed or strongly considered in this setting a difficult task in and of itself. With a mortality rate approaching 95%[40], the use of fibrinolytic therapy offers a clear risk - benefit ratio; furthermore, it has no absolute contraindications in this particular presentation. In fact, according to the British Thoracic Society recommendations, the immediate use of 50 mg IV rtPA can be lifesaving for patients in cardiac arrest resulting from PE[41]. While it is unclear if treatment with fibrinolysis ultimately alters long-term outcome, the low rate of bleeding complications and the improvement in ROSC warrants consideration in this group that has dismal survival without aggressive management. If one considers the use of fibrinolysis in cardiac arrest of all cause, outcomes with fibrinolysis are dismal; the empiric use of fibrinolytic agents in all patients with cardiac arrest of uncertain origin is not recommended due to futility.

References

1 Coon WW, Willis PW. Deep venous thrombosis and pulmonary embolism: prediction, prevention and treatment. Am J Cardiol. 1959;4:611-21.
2 Dalen JE, Alpert JS. Natural history of pulmonary embolism. Prog Cardiovasc Dis. 1975;17:259-70.
3 Bell WR, Simon TL. Current status of pulnoary thrombo-embolic disease: pathophysiology, diagnosis, prevention and treatment. Am Heart J. 1982;103:239-62.
4 Lilienfeld DE, Chan E, Ehland J, Godbold JM, Landrigam PJ, Marsh G. Mortality from pulmonary embolism in the United States: 1962 to 1984. Chest. 1990;98:1067-72.
5 Kasper W, Konstantinides S, Geibel A, Olschewiski M, Heinrich F, Grosser KD, et al. Management Strategies and Determinants of Outcome in Acute Major Pulmonary Embolism; results of a multicenter registry(MAPPET). J Am Coll Cardiol. 1997;30:1165-71.
6 Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation. 2004;110:744-9.
7 Morrell MT. Dunnill MS. The post-mortem incidence of pulmonary embolism in a hospital population. Br J Surg. 1968;55:347-52.
8 Uhland H, Goldberg LM. Pulmonary embolism: a commonly missed clinical entity. Dis Chest. 1964;45:533-6.
9 Meneveau N. Therapy for acute high-risk pulmonary embolism: fibrinolytic therapy and embolectomy. Curr Opin Cardiol. 2010;25:560-7.
10 Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. Eur Heart J. 2008;29:2276-315.
11 Kucher N, Rossi E, DeRosa M, Goldhaber SZ. Massive pulmonary embolism. Circulation. 2006;113:577-82.
12 Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. Chest. 1995;108:978-81.
13 Urokinase-streptokinase embolism trial. Phase 2 results. A cooperative study. JAMA. 1974;229:1606-13.
14 Godlhaber SZ, Kessler CM, Heit J, Warkis J, Sharma GV, Dawley D, et al. Randomized controlled trial of recombinant tissue plasminogen activator versus urokinase in acute pulmonary embolism. Lancet. 1988;2:293-8.
15 Meyer G, Sors H, Charbonnier B, Kasper W, Bassand JP, Kerr IM, et al. Effects of intravenous urokinase versus alteplase on total pulmonary resistance in acute massive pulmonary embolism: a European multicenter double-blinded trial. The European Cooperative Study Group for Pulmonary Embolism. J Am Coll Cardiol. 1992;19:239-45.
16 Godlhaber SZ, Kessler CM, Heit J, Elliot CG, Friedenbery WR, Heisselman DE, et al. Recombinant tissue plasminogen activator versus urokinase in acute pulmonary embolism. a randomized controlled multicenter trial. J Am Coll Cardiol. 1992;20:24-30.
17 Meneveau N, Schiele F, Vuillemenot A, Valette B, Grollier G, Bernard Y, et al. Streptokinase vs alteplase in massive pulmonary embolism: a randomized trial assessing right heart hemodynamics and pulmonary vascular obstruction. Eu Heart J. 1997;18:1141-8.
18 Meneveau N, Schiele F, Metz D, Valette B, Attali P, Willemenot A, et al. Comparative efficacy of a two-hour regimen of streptokinase versus alteplase in acute massive pulmonary embolism: immediate clinical and hemodynamic outcome and one-year follow-up. J Am Coll Cardiol. 1998;31:1057-63.
19 Sors H, Pacouret G, Azarian R, Meyer G, Chazbomier B, Simaneau G. Hemodynamic effects of bolus vs 2-h infusion of alteplase in acute massive pulmonary embolism. A randomized controlled multicenter trial. Chest. 1994;106:712-7.
20 Goldhaber SZ, Agneli G, Levine MN. Reduced dose bolus alteplase vs conventional alteplase infusion for pulmonary embolism thrombolysis. An international multicenter randomized trial. The Bolus Alteplase Pulmonary Embolism Group. Chest. 1994;106:718-24.
21 Goldhaber SZ, Feldstein ML, Sors H. Two trials of reduced bolus alteplase in the treatment of pulmonary embolism: an overview. Chest. 1994;106:725-6.
22 Levine M, Hirsh J, Weitz J, Cruickshank M, Neemeh J, Turpie AG, et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. Chest. 1990;98:1473.
23 Leeper KV, Jr, Popovich J, JR, Lesser BA, Adams D, Froelich JW, Burke MW, et al. Treatment of massive acute pulmonary embolism. The use of low doses of intrapulmonary arterial streptokinase combined with full doses of systemic heparin. Chest. 1988;93:234-40.
24 Barberena J. Intraarterial infusion of urokinase in the treatment of acute pulmonary thromboembolism; preliminary observations. Am J Roentgenol. 1983;140:883.
25 Schwarz F, Stehr H, Zimmermann R, Zimmermann R, Manthey J, Kübler W. Sustained improvement of pulmonary hemodynamics in patients at rest and during exercise after fibrinolytic treatment of massive pulmonary embolism. Circulation. 1985;71:117-23.
26 The UKEP study: multicentre clinical trial on two local regimens of urokinase in massive pulmonary embolism. The UKEP Study Research Group. Eur Heart J. 1987;8:2.
27 Verstraete M, Miller GA, Bounameaux H, Charbonier B, Colle JP, Lecorj G, et al. Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. Circulation. 1988;77:353-60.
28 Arcasoy SM, Kreit JW. Fibrinolytic Therapy of Pulmonary Embolism: A comprehensive review of current evidence. Chest. 1999;115:1695-707.
29 Levine MN, Goldhaber SZ, Gore JM, Hirsh J, Califf RM. Hemorrhagic complications of fibrinolytic therapy in the treatment of myocardial infarction and venous thromboembolism. Chest. 1995;108(suppl);291S-301S.
30 Meyer G, Gisselbrecth M, Diehl JL, Jurnois D, Sors H. Incidence and predictors of major hemorrhagic complications from fibrinolytic therapy in patients with massive pulmonary embolism. Am J Med. 1998;105:472-7.
31 Gore JM. Prevention of severe neurologic events in the fibrinolytic era. Chest. 1992;101:124S.

32 Fiumara K, Kucher N, Fanikos J, Goldhaber SZ. Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism. Am J Cardiol. 2006;97:127-9.
33 Goldhaber SZ, Visani L, De la Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353:1386-9.
34 Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. J Thromb Thrombolyisis. 1995;2:227-9.
35 Fengler BT, Brady WJ. Fibrinolytic therapy in pulmonary embolism: an evidence-based treatment algorithm. Am J Emerg Med. 2009;27:84-95.
36 Goldhaber SZ, Haire WD, Feldstein ML, Muller M, Tolzis R, Smith JL, et al. Alteplase versus heparin in acute pulmonary embolism: randomized trial assessing right-ventricular function and pulmonary perfusion. Lancet. 1993;341:507-11.
37 Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser K, Rauber K, et al. Association between fibrinolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. Circulation. 1997;96:882-8.
38 Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002;347:1143-50.
39 Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ, et al. Antithrombotic Therapy for Venous Thromboembolic Disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest. 2008;133:546S-592S.
40 British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax. 2003;58:470-84.

Tratamiento fibrinolítico en la embolia de pulmón

Brady WJ

Existe una evidencia razonable que el tratamiento fibrinolítico acelera la resolución de la embolia pulmonar (EP) mientras que simultáneamente reduce su recurrencia. También puede mejorar otros parámetros, como el flujo sanguíneo pulmonar, la perfusión pulmonar y la disfunción del ventrículo derecho. Desafortunadamente, en la literatura no se ha encontrado evidencia concluyente que demuestre una disminución de la mortalidad, particularmente en aquellos pacientes que están clínicamente estables con riesgo de mortalidad bajo o intermedio. Los clínicos deberían valorar el riesgo de mortalidad de la EP y los potenciales beneficios y efectos adversos del tratamiento fibrinolítico tanto para la parada cardiorrespiratoria como en los distintos grupos de riesgo de presentación. En la parada cardiorrespiratoria secundaria a EP, no existen contraindicaciones para la fibrinolisis médica, que ofrecería una oportunidad razonable de supervivencia. En aquellos pacientes sin parada cardiorrespiratoria, clasificar en grupos de alto, intermedio y bajo riesgo ayudará en la toma de decisiones. En la ausencia de riesgo significativo de sangrado, aquellos pacientes que están hemodinámicamente inestables o tienen signos de disfunción del ventrículo derecho probablemente se beneficiarían de agentes fibrinolíticos –como por ejemplo el grupo de alto riesgo–. Las presentaciones de riesgo intermedio demuestran menor beneficio ya que no es infrecuente que las complicaciones superen las ventajas de la fibrinolisis. La literatura, sin embargo, es controvertida para las recomendaciones del grupo intermedio. Y por último, el grupo de bajo riesgo no se beneficia de la fibrinolisis. A pesar de esta clasificación, la decisión de administrar el agente fibrinolítico es compleja; el clínico debe considerar los riesgos de la EP conjuntamente con los riesgos de la fibrinolisis; y comparar el beneficio potencial de este fármaco. La decisión de administrar un agente fibrinolítico en la EP continúa siendo muy individualizada, y lo más adecuado es que sea tomada por el clínico a la cabecera del enfermo. [Emergencias 2011;23:319-323]

Palabras clave: Embolia de pulmón. Tratamiento fibrinolítico. Embolismo pulmonar.