Is Thrombolytic Therapy Effective for Pulmonary Embolism?

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Pulmonary embolism is a disorder that is associated with significant morbidity and mortality. Right-sided heart failure and recurrent pulmonary embolism are the main causes of death associated with pulmonary embolism in the first two weeks after the embolic event. Thrombolysis is a potentially lifesaving therapy when used in conjunction with standard anticoagulation. However, it has significant side effects and must therefore be used with caution. Indications for thrombolysis are not well defined and are thus controversial. The only current absolute indication is massive pulmonary embolism with hypotension. Other potential indications include right heart dysfunction, recurrent pulmonary embolism and the prevention of pulmonary hypertension. However, no evidence exists to show benefit of thrombolytic therapy over standard anticoagulation therapy for recurrent pulmonary embolism, mortality or chronic complications. Bleeding is the most common complication of thrombolysis and may be fatal. (Am Fam Physician 2002;65:1097-102. Copyright© 2002 American Academy of Family Physicians.)

Pulmonary embolism (PE) is a common disorder that is associated with significant morbidity and mortality. The primary cause of death in fatal PE is right-sided heart failure. The most serious long-term complication of PE is pulmonary hypertension.

Earlier studies[1] have reported that the mortality rate associated with pulmonary embolism has remained the same for the last 40 years. A more recent study,[2] however, found a significant decline in mortality from 1979 to 1996. Anticoagulation remains the standard of treatment for PE and has clearly been shown to reduce mortality and the rate of recurrent PE.[3] Anticoagulation does not directly contribute to clot lysis. It prevents the propagation of the thrombus while allowing endogenous fibrinolytic activity to dissolve the clot. The lytic process may take several days to several months to develop, and in many patients it is incomplete and may lead to the occurrence of pulmonary hypertension.

Clinical Trials of Thrombolysis

Beginning in the early 1970s, several trials compared the efficacy of thrombolysis and anticoagulation. The first large prospective randomized trial was the Urokinase Pulmonary Embolism Trial (UPET).[4] A total of 160 patients with angiographically documented PE were divided into two groups, each of which received standard heparin or urokinase. Lung scans, pulmonary angiograms and measurements of right heart pressures and blood flow dynamics performed at 24 hours showed significant improvement only in the urokinase group. However, lung scans performed seven days, 14 days, three months and six months later showed no difference between the two groups.

The phase II Urokinase-Streptokinase Pulmonary Embolism Trial (USET)[5] followed four years later and compared both urokinase and streptokinase with standard anticoagulation. A total of 167 patients were divided into groups receiving heparin only, streptokinase and heparin, or urokinase and heparin. The effects on lung scans were similar between the streptokinase/heparin group and urokinase/heparin only group. Again, compared with the heparin group, improvement occurred only within the first 24 hours; over a longer period of time, no differences were apparent between the groups.

More recently, Levine and associates[6] divided 58 patients with PE into two groups; 33 received thrombolysis and 25 received standard anticoagulation with heparin. Lung scans performed 24 hours, seven days and

No evidence from clinical trials proves that thrombolytic therapy reduces the recurrence rate of pulmonary embolism or affects mortality in hemodynamically stable patients.

30 days later showed that while at 24 hours there was greater improvement in the thrombolysis group than in the heparin group (37 percent versus 19 percent), at seven days and 30 days, the extent of PE resolution did not differ between the two groups.

Finally, the randomized Plasminogen Activator Italian Multicenter Study 2 (PAIMS 2)[7] divided 36 patients with angiographically proved PE into two groups, each receiving either tissue plasminogen activator (tPA) or heparin. Angiography was repeated two hours later, and a Miller Index score (measure of vascular obstruction: 0 = no obstruction, 33 = complete obstruction) was given for all patients before and after therapy. The thrombolysis group had an average decrease of 12.4 percent in the Miller score, while the heparin group had only a 0.4 percent decrease. Pulmonary arterial pressures were also measured and showed a mean decrease from 30.2 mm Hg to 21.4 mm Hg in the thrombolysis group, compared with a change from 22.3 mm Hg to 24.8 mm Hg in the heparin group. In view of these objective changes, however, no clinical benefit was seen in the thrombolysis group compared with the heparin group.

In summary, what these studies have shown is that, although there is a more rapid improvement in pulmonary pressures, Miller index and scintigraphic findings in PE patients receiving thrombolysis than in those receiving heparin, there is no difference in clinical benefit between the two therapies after the first 24 to 48 hours. Furthermore, although the number of patients involved in individual studies was small, no significant difference was seen in rates of mortality or recurrent PE.

Confirmation of Diagnosis Before Thrombolysis

The potentially catastrophic complications of thrombolytic therapy mandate confirmation of the diagnosis of PE before administration *(Table 1)*. Hemodynamically unstable patients with PE should be considered for thrombolysis, but their instability and the urgency of intervention will preclude them from undergoing lung perfusion scans, pulmonary angiograms or other diagnostic tests quickly. Therefore, confirming PE would be difficult in these patients. A bedside echocardiogram that shows right ventricular strain or dysfunction is sufficient to warrant thrombolysis in a patient with a history typical of PE and hypotension. In the absence of an echocardiogram, classic symptomatology and typical clinical examination findings of PE in a setting of significant risk factors would be enough to consider thrombolysis if the patient is hemodynamically unstable and clinically deteriorating.

TABLE 1
Indications for Pulmonary Embolism Thrombolysis

Absolute
Massive pulmonary embolism with hypotension or systemic hypoperfusion
Relative
Right ventricular dysfunction
Pulmonary hypertension
Presence of extensive deep venous thrombosis
Prevention of recurrent pulmonary embolism

In a stable patient, the accepted methods of ventilation-perfusion lung scanning or helical computed tomography to confirm PE would provide sufficient evidence to institute or avoid thrombolysis.[8,9] If the diagnosis is still in doubt based on these test results in the setting of a high clinical index of suspicion for PE, then pulmonary angiography should be performed to confirm the diagnosis before starting thrombolysis.

Goals of Thrombolytic Therapy

The rationale behind thrombolysis is that, in conjunction with anticoagulation, it may reduce the rate of clinically important endpoints such as death, recurrent PE and pulmonary hypertension. Its goals, therefore, include the following:

- More rapid clot lysis and quicker reperfusion of lung tissue.
- Elimination of the source of the clot, thus decreasing the incidence of recurrent PE.
- Prevention of chronic complications of PE by producing more complete clot lysis.
- Reduction of morbidity and mortality, especially by reversal of right-sided heart failure.

TABLE 2
Thrombolytic Agents Approved for the Treatment of Pulmonary Embolism

Drug	*Dosage*	*Year of approval*
Streptokinase (Streptase)	250,000 U over 30 minutes, then 100,000 U per hour for 24 hours	1977
Urokinase (Abbokinase)	4,400 U per kg over 10 minutes, then 4,400 U per kg per hour for 12 or 24 hours	1978
rtPA	100 mg over 2 hours	1990

rtPA = recombinant tissue plasminogen activator.

Mechanism of Action

Currently, three agents are approved by the U.S. Food and Drug Administration (FDA) for use in PE thrombolysis *(Table 2)*: streptokinase (Streptase), urokinase (Abbokinase) and recombinant tissue plasminogen activator (rtPA). All of these agents convert plasminogen to plasmin, which in turn breaks down fibrin and promotes clot lysis. However, these agents also cause systemic plasminogen activation. By cleaving and inactivating fibrinogen and clotting factors II, V and VIII, they interfere with blood coagulation and produce a systemic hypocoagulable state. Furthermore, elevated serum fibrin and fibrinogen degradation products inhibit the conversion of fibrinogen to fibrin by negative feedback; and therefore interfere with fibrin polymerization. There is also a direct neurohormonal effect on pulmonary vasoconstriction and bronchoconstriction; substances such as serotonin and thromboxane A_2 are released in the presence of PE and promote local vasoconstriction and bronchoconstriction. Finally, thrombolysis may cause platelet dysfunction by affecting platelet surface receptors GpIb and GpIIb.

Differences Between Thrombolytic Agents

USET[5] was the first trial comparing two thrombolytic agents, and no difference in efficacy between urokinase and streptokinase was apparent. Further studies by Goldhaber and associates[10] and the European Cooperative study[11] compared rtPA and urokinase and found that, although rtPA initially produced a faster resolution of the clot, results were the same after 24 hours.

Administration of Thrombolytic Agents

Thrombolytics are given according to regimens approved by the FDA *(Table 2)*. During administration, laboratory monitoring is unnecessary. However, after the infusion is given, partial thromboplastin time (PTT) should be measured. If it is less than 2.5 times the control value, a heparin infusion should be started and adjusted to maintain a PTT of 1.5 to 2.5 times the control. If the PTT initially is greater than 2.5 times the control it should be checked every four hours, and heparin should be started if the PTT drops below this level.

In contrast to thrombolysis for myocardial infarction and stroke, thrombolysis for PE has a longer time window of opportunity. One group[12] compared data for 308 patients from five PE thrombolysis trials and followed the improvement based on lung scans and angiograms up to 14 days after initial presentation with a PE. These data showed a persistent but attenuated benefit from thrombolysis when given up to 14 days later: 86 percent of patients improved an average of 16 percent when thrombolytics were given within the first 24 hours, whereas 69 percent of patients improved an average of 8 percent when treated seven to 14 days after a PE. Therefore, although benefit from thrombolysis for PE may be seen when given up to 14 days after the initial diagnosis of a PE, it is most beneficial when given as early as possible.

Finally, little evidence supports the concept of local administration or bolus dosing of thrombolytic therapy.[13-15]

The goal of thrombolytic therapy is rapid clot lysis, which hastens reperfusion of lung tissue and prevents chronic complications of pulmonary embolism such as pulmonary hypertension.

TABLE 3
Randomized Clinical Trials Comparing Thrombolysis and Heparin Therapy

Study	Number of patients	Treatment regimen	Number of deaths (%)	Number of cases of recurrent PE (%)
UPET (1970)[4]	78	Heparin	7 (8.9)	15 (19)
	82	Urokinase (12 hours)	6 (7.3)	12 (15)
PIOPED (1990)[18]	4	Heparin	0	NA
	9	rtPA	1 (11.1)	
Levine, et al. (1990)[6]	25	Heparin	0	0
	33	rtPA	1 (3)	0
PAIMS 2 (1992)[7]	16	Heparin	1 (6.3)	3 (18.8)
	20	rtPA	2 (10)	1 (5)
Goldhaber (1993)[17]	55	Heparin	2 (3.6)	5 (9.1)
	46	rtPA	0	0

PE = pulmonary embolism; UPET = Urokinase Pulmonary Embolism Trial; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis Trial; rtPA = recombinant tissue plasminogen activator; NA = no data available; PAIMS = Plasminogen Activator Italian Multicenter Study.

Information from references 4, 6, 7, 17 and 18.

Outcomes of Therapy

MORTALITY

More than 80 percent of patients with massive PE die within the first two hours after onset, mainly from right-sided heart failure.[16] To decrease the mortality associated with acute PE, the thrombus must be broken down quickly and the obstruction resolved rapidly to preclude right ventricular dysfunction. Furthermore, the rate of recurrence of PE must be reduced. The first trial to look at the effect of thrombolysis on mortality was the USET study.[5] The mortality rate among the 167 patients studied was 7.3 percent in the thrombolytic group and 8.9 percent in the heparin group. Other studies *(Table 3)*[4,6,7,17,18] involving both clinically stable and unstable patients showed similar mortality rates, ranging from 3 to 11 percent. Therefore, no evidence suggests that thrombolytic therapy reduces mortality.

RECURRENT PULMONARY EMBOLISM

The rate of recurrent PE in patients who develop an initial PE and are treated with heparin is 10 percent over two weeks.[3] It is the primary cause of death in these patients who are hemodynamically stable initially. The rate of recurrence in the UPET trial[4] was 15 percent in the thrombolytic group and 19 percent in the heparin group. Data from other recent randomized clinical trials *(Table 3)*[4,6,7,17,18] have shown similar results between groups treated with heparin and those treated with thrombolytic therapy. Therefore, no evidence exists to prove that thrombolysis decreases the rate of recurrent PE.

RIGHT VENTRICULAR DYSFUNCTION

Approximately 40 to 50 percent of echocardiograms performed in patients with acute PE show evidence of right ventricular (RV) dysfunction.[19] The acute vascular obstruction and associated neurohormonal effects cause increased pulmonary artery pressures, and therefore increased RV afterload. This leads to RV dilatation, dysfunction and ischemia, and possible interventricular septal shift. Decreased cardiac output ensues, reducing systemic and coronary perfusion and eventually causing hemodynamic collapse.

A 1993 study by Goldhaber and colleagues[17] provides the most evidence of benefit of thrombolytic therapy for RV dysfunction. Echocardiography performed in 101 hemodynamically stable patients who were randomly assigned to treatment with heparin or thrombolysis showed 39 percent improvement in RV function in the thrombolytic therapy group versus 17 percent improvement in the heparin group. In addition, pulmonary perfusion improved 14 percent in the thrombolytic therapy group versus 1.5 percent in the heparin group. Two of the 55 patients in the

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TABLE 4
Contraindications to Pulmonary Embolism Thrombolysis

Cerebrovascular accident, intracranial trauma or surgery within past two months
Active intracranial disease (neoplasm, aneurysm, vascular malformations)
Major internal bleeding within past six months
Uncontrolled hypertension (systolic blood pressure > 200 mm Hg, diastolic blood pressure > 110 mm Hg)
Bleeding diathesis/coagulopathies
Recent major surgery, organ biopsy or obstetric delivery (within 10 days)
Recent trauma
Infective endocarditis/pericarditis
Pregnancy
Aortic aneurysm
Hemorrhagic retinopathy

heparin group died, while none of the 46 patients in the thrombolysis group died. Unfortunately, other studies failed to confirm these results or to show any benefit from thrombolysis of hemodynamically stable patients with evidence of RV dysfunction. Therefore, no evidence at this time supports the efficacy of thrombolysis in these patients.

Complications of Thrombolysis

The major complication of thrombolytic therapy is bleeding. The rate of bleeding in earlier trials ranged from 22 to 45 percent, mainly because of the use of larger doses and an increased rate of venous cutdowns.[4,5] More recent studies show an overall bleeding rate of 20 to 25 percent, with a rate of 5 to 10 percent for major bleeding.[7,10,11,17,18] Rates of bleeding are similar among all the thrombolytic agents, and bleeding mostly occurs at catheter sites, in the gastrointestinal tract and in the retroperitoneal area. The most critical bleeding is intracranial bleeding, which occurs at the rate of 2.1 percent.[20] One half of all cases of intracranial bleeding prove fatal. Risk factors for bleeding include invasive procedures, dose and length of time of thrombolytic therapy, increased body mass index, hypertension and age over 70 years.[20] Treatment involves stopping thrombolysis, compression and transfusion of blood products as needed. Several other contraindications preclude the use of thrombolytic therapy *(Table 4)*.

Because most patients with massive pulmonary embolism die within two hours of symptom onset, thrombolytic therapy may be most beneficial in hospitalized patients in whom the diagnosis and therapy can be achieved more quickly.

Thrombolysis vs. Surgical Therapy

Very little data are available on the benefits of thrombolysis versus surgical therapy for pulmonary embolism. The largest study to date to compare these therapies examined 37 patients with massive PE and shock who were randomized to receive one of the two interventions.[21] It showed that patients treated with thrombolytic therapy had a higher death rate, increased risk of major hemorrhage and an increased rate of PE recurrence when compared with patients treated surgically with embolectomy. However, the disadvantage of embolectomy is that it requires more hospital resources and may not always be available.

Final Comment

Despite the theoretic advantages of thrombolysis over standard therapy, little data support its widespread use except in situations where it is truly indicated *(Table 1)*. Hemodynamic instability is the only absolute indication. No firm evidence exists to show benefit over standard therapy for recurrent PE, mortality or chronic complications. Because most patients with hypotensive massive PE die within two hours of the onset of symptoms, the use of thrombolytic therapy may be more beneficial and practical in hospitalized patients who develop PE because diagnosis and therapy are able to proceed quicker. This therapy may be used to save lives of patients who present with classic symptoms and risk factors for PE. However, little data currently exist to support this type of therapy.[22] The risks and costs of thrombolysis also must be seriously considered. In most situations, reliable confirmation of the diagnosis of PE must be made before this therapy is utilized *(Table 5)*.

TABLE 5

Approach to Pulmonary Embolism Thrombolysis in Selected Patients

Take a careful neurologic and hematologic history.
Confirm the diagnosis of pulmonary embolism, preferably with noninvasive means; in unstable patients, diagnosis may be based on echocardiography or a right-sided heart catheterization in addition to clinical examination and the presence of risk factors.
Type and screen blood; obtain a complete blood count.
Minimize invasive tests (e.g., phlebotomy) and physical handling of the patient.
Infuse thrombolytic agent peripherally, using one of the three regimens approved by the U.S. Food and Drug Administration.
Anticoagulate with heparin (and eventually warfarin) immediately after thrombolytic agent is completely infused; do not administer heparin concomitantly; check PTT every 6 hours until therapeutic (1.5 to 2 times value of upper limit of normal).
Do not draw blood for laboratory tests during thrombolytic infusion.
If bleeding occurs, stop thrombolytic infusion and give blood products as needed.
Patients should preferably be in a closely monitored setting (i.e., intensive care unit).

PTT = partial thromboplastin time.

PE thrombolysis has come a long way since the UPET and USET trials. Today, complications are fewer, the window of opportunity is longer, the route of administration is peripheral and laboratory tests are fewer. Nevertheless, more data based on larger prospective, randomized clinical trials are needed to clarify indications and clinical benefits of thrombolysis, its long-term effects and its advantages over surgical therapies.

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