THE USE OF THROMBOLYTICS IN THE INTENSIVE CARE UNIT FOR PULMONARY EMBOLISM

SUMMARY
The role of thrombolytic agents in the management of massive pulmonary embolism (PE) is not well established. Alteplase (recombinant tissue-plasminogen activator; rt-PA), streptokinase, and urokinase effectively restore pulmonary blood flow when administered by the intravenous or intrapulmonary route. They have not been shown to improve mortality or long-term outcome and are associated with a significant risk of bleeding. Thrombolytics should be reserved for patients with massive PE and evidence of cardiac dysfunction who have a low risk of bleeding. Intrapulmonary administration has not been consistently shown to be superior to intravenous dosing. Administration of thrombolytics in the intensive care unit setting should be reserved for patients who are not stable for transport to the interventional radiology suite. Given the allergic reactions associated with streptokinase and long infusion duration of both streptokinase and urokinase, rt-PA is a reasonable first-line thrombolytic.

RECOMMENDATIONS

Level 1
- Heparin is the drug of choice for PE (regardless of whether thrombolytics are used) if:
  - No contraindications are present AND
  - The anticipated benefit outweighs the risk in patients at high risk for bleeding

Level 2
- End-tidal carbon dioxide (ET\textsubscript{CO2}) measurements may be used to assess the efficacy of thrombolytic therapy.

Level 3
- Consider intrapulmonary thrombolytics when urgent restoration of pulmonary blood flow is necessary.
- Reserve administration of ICU thrombolytics for patients who meet the following criteria:
  - Massive PE (obstruction of blood flow to a lobe or multiple segments of the lungs) AND
  - Evidence of cardiac dysfunction AND
  - Low bleeding risk AND
  - Transfer to interventional radiology is not feasible
- Consider consultation with interventional radiology for mechanical intervention and/or possible thrombolysis.
- Fibrinogen levels may be used to monitor thrombolytic therapy.

INTRODUCTION
The role of thrombolytic agents in the treatment of PE is not well established. Thrombolytics clearly restore pulmonary perfusion more rapidly than heparin alone and are associated with early hemodynamic improvement and reversal of right ventricular dysfunction. Improvements in mortality and long-term pulmonary artery patency, however, have not been consistently demonstrated. The major disadvantage of thrombolytic therapy is serious bleeding, including intracranial hemorrhage. Heparin remains the cornerstone of therapy and thrombolytics are generally reserved for patients who are hemodynamically unstable and have a low risk of bleeding (1). Intravenous administration is the FDA-approved route of drug delivery for rt-PA, streptokinase, and urokinase. Intrapulmonary infusion of these agents has been evaluated in several studies. The theoretical benefits of local administration include rapid achievement of peak concentrations at the thrombus and a decreased risk of systemic bleeding complications.
The safety and efficacy of intravenous versus intrapulmonary rt-PA were evaluated in a multicenter European study of patients with massive bilateral PE (2). After diagnosis was confirmed by pulmonary angiography, intravenous (n=15) or intrapulmonary (n=19) rt-PA was given as a 10mg bolus followed by 20mg/hour over the first 2 hours. All patients received an intravenous bolus of 5000 IU heparin followed by a continuous infusion of 1000 IU/hour. Follow-up pulmonary angiography was performed at the end of the 2-hour infusion period. If massive PE was present, a second infusion of 50mg rt-PA was given over 5 hours by the same route. Following rt-PA infusion, both groups had significant improvements in mean pulmonary arterial pressure and pulmonary angiographic severity score. Intrapulmonary infusion did not offer a significant benefit over the intravenous route of administration. Forty-seven percent (16/34) developed some degree of bleeding, primarily at puncture and/or surgical sites. (Class I)

Clot fragmentation combined with local fibrinolysis was performed in five patients with massive PE (3). All were fully heparinized during and after angiography. Local thrombolysis was achieved with an initial dose of 50-100mg rt-PA (a bolus of 14-20mg via the pulmonary artery after clot fragmentation, followed by an intrapulmonary infusion over 2-5 hours through a pigtail catheter). Pulmonary artery pressure significantly decreased following clot fragmentation and fibrinolysis. All patients survived and clinical improvement was noted within 24 hours. Bleeding complications occurred in 4/5 patients. Two experienced minor bleeding at the puncture site and 2 developed groin and retroperitoneal hematomas. Anticoagulation with heparin followed by coumadin was continued. (Class III)

Four patients with massive PE were treated by thrombus fragmentation followed by local administration of rt-PA (4). One patient received a low-dose regimen and is not discussed further. Following thrombus fragmentation, a bolus dose of 10-50mg was administered into the main pulmonary artery or into the major branches of the right and left pulmonary arteries. A continuous infusion of 10mg/hr was then initiated for 14-18 hours via the main pulmonary artery. Heparin was administered at 1000 U/hr throughout thrombus fragmentation, rt-PA infusion, and until full anticoagulation with warfarin was achieved. All patients survived and their clinical condition was improved at the 24-hour assessment point. There were no hemorrhagic complications during or after rt-PA infusion. (Class III)

The use of continuous end-tidal carbon dioxide tension (ET\textsubscript{CO2}) monitoring to assess the efficacy of thrombolytic therapy for acute massive PE was evaluated (5). Twelve consecutive patients with confirmed PE requiring mechanical ventilation and thrombolytic therapy were included. ET\textsubscript{CO2} levels were lower in nonsurvivors than survivors (12.3 ± 1.3 versus 20 ± 5.3 mmHg; p=0.08). There were significant increases in cardiac index and P\textsubscript{O2}/F\textsubscript{IO2} and significant decreases in MPAP and AD\textsubscript{CO2} in the ten survivors following thrombolytic therapy. When individual patients were analyzed, the change in ET\textsubscript{CO2} was highly correlated with changes in MPAP (r\textsuperscript{2}=0.79-0.98; p<0.001) and AD\textsubscript{CO2} (r\textsuperscript{2}=0.77-0.98; p<0.001). (Class II)

The effects of heparin plus alteplase versus heparin plus placebo for the treatment of acute submassive PE were evaluated in a prospective, randomized trial (6). Two hundred fifty six patients with right ventricular dysfunction or pulmonary hypertension, without hemodynamic instability, were included. Alteplase was administered as a 10mg bolus, followed by 90mg intravenously over 2 hours. The incidence of the combined primary endpoint (in-hospital mortality plus clinical deterioration requiring escalation of treatment) was significantly higher in the heparin/placebo group (24.6% versus 11%; p=0.006). However, when assessed individually, there was no significant difference in in-hospital mortality between groups. No significant difference in the secondary endpoints of recurrent PE, major bleeding, or ischemic stroke were found. Of note, the trial has been critiqued due to the low incidence of major bleeding in the heparin/ alteplase group (0.8%) (7). (Class I)
### Table I: Dosing Information

<table>
<thead>
<tr>
<th>Thrombolytic Regimens for the Treatment of Pulmonary Embolism</th>
<th>Thrombolytic</th>
<th>IV</th>
<th>Intrapulmonary (Not FDA-approved)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase (Recombinant tissue-plasminogen activator; rt-PA; Activase®)</td>
<td>100mg over 2 hours</td>
<td>10mg bolus over 10 minutes and re-evaluate need for continuation; may proceed with 20 mg/hr for 2 hours if necessary (2,8)</td>
<td></td>
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<tr>
<td>Streptokinase (Streptase®)</td>
<td>250,000 units over 30 minutes, followed by 100,000 units/hour for 24 hours</td>
<td>100,000 units/hr (9-11)</td>
<td></td>
</tr>
<tr>
<td>Urokinase (Abbokinase®)</td>
<td>4,400 units/kg over 10 minutes, followed by 4,400 units/kg/hour for 12 hours</td>
<td>Variable</td>
<td></td>
</tr>
</tbody>
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### Table II: Absolute Contraindications to rt-PA
- Active internal bleeding
- History of cerebrovascular accident
- Intracranial or intraspinal surgery or trauma (<2 months)
- Intracranial neoplasm
- Arteriovenous malformation or aneurysm
- Bleeding diathesis
- Severe uncontrolled hypertension

### Table III: Relative Contraindications to rt-PA
- The following conditions may increase the risk of bleeding and must be weighed against the anticipated benefits:
  - Recent (<10 days) major surgery
  - Cerebrovascular disease
  - Recent (<10 days) GI or GU bleeding
  - Recent (<10 days) trauma
  - Hypertension: >180 mmHg systolic or >110 mmHg diastolic
  - Likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation)
  - Acute pericarditis
  - Subacute bacterial endocarditis
  - Hemostatic defects secondary to severe hepatic or renal disease
  - Significant liver dysfunction
  - Pregnancy
  - Diabetic hemorrhagic retinopathy or other ophthalmic hemorrhaging
  - Septic thrombophlebitis or occluded AV cannula at seriously infected site
  - Advanced age (e.g., >75 years old)
  - Patients currently receiving oral anticoagulants
  - Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location
Table IV: Contraindications/Precautions to Heparin Therapy

- Hypersensitivity to heparin
- Active bleeding
- Severe thrombocytopenia
- Increased risk of hemorrhage, such as:
  - Selected traumatic injuries (i.e., severe liver laceration, intracranial hemorrhage, spinal cord injury)
  - Dissecting aneurysm
  - Treatment with drotrecogin alfa (activated) (Xigris®)
  - Hemophilia or other blood disorders
  - Epidural catheter
  - Subacute bacterial endocarditis
  - Uncontrolled hypertension

REFERENCES
THE USE OF THROMBOLYTICS IN THE ICU FOR PULMONARY EMBOLISM (PE)

Assess for PE

Does patient have a PE?

Yes

Are there contraindications to anticoagulation?

Yes

Consult Vascular Surgery or Interventional Radiology for mechanical extraction of clot, possible IVC filter

No

Start Heparin infusion

Is the PE massive?*

Yes

Consider Vascular Surgery or Interventional Radiology consultation for thrombotic therapy, mechanical extraction of clot, possible IVC filter

No

Evidence of cardiac dysfunction?

Yes

Is patient stable for transport to Interventional Radiology?

No

Are thrombolytics still contraindicated?

Yes

Consider bedside IVC filter placement

No

Are thrombolytics contraindicated?

Yes

Continue Heparin infusion

No

Administer thrombolytics in ICU

END

END

* - Massive PE = obstruction of blood flow to a lobe or multiple segments of the lungs