Thrombolysis Therapy in Pulmonary Embolism UHL Guideline

University Hospitals of Leicester NHS
NHS Trust

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1. Introduction / Scope

All Patients with pulmonary embolism (PE) require rapid risk stratification. This guideline applies to all health professionals required to undertake a risk / benefit analysis for patients in whom the diagnosis of PE has ideally been confirmed. The adverse effects of thrombolytic therapy can be devastating and the indications and potential benefits need to be carefully weighed against the risk of adverse effects.

2. Background

PE accounts for 10% of patients admitted with non-traumatic sudden death and 50% of those arriving with electromechanical dissociation or asystole on ECG[1]

Thrombolytic agents activate plasminogen to form plasmin. This results in the accelerated lysis of thrombi. The efficacy, indications, contraindications and adverse effects of thrombolytic therapy in pulmonary embolus are summarised below:

2.1 Thrombolytic Therapy

- The decision to treat with thrombolysis should be taken at consultant level.
- This decision should be based upon the assessed clinical severity and prognosis of the pulmonary embolus, the bleeding risk and wherever possible after confirmation of the diagnosis by appropriate imaging
- Before treatment with thrombolysis, stop heparin.

The severity of pulmonary embolus may be assessed from the following predictor of 30-day mortality after PE, based upon routinely available clinical parameters[2]

Variable	Points
Age	1/year
Male sex	10
Cancer	30
Heart failure	10
Chronic lung disease	10
Heart rate >110/min	20
Systolic blood pressure <100 mmHg	30
Respiratory rate ≥30/min	20
Body temperature <36°C	20
Disorientation, lethargy, stupor, coma	60
SaO_2 <90%	20

Data are from reference 214.
Risk categories (30-day all-cause mortality, %): class I, <65 points (0%); class II, 66–85 points (1%); class III, 86–105 points (3.1%); class IV, 106–125 points (10.4%); class, V >125 points (24.4%). Low risk = classes I and II (0–1%).
SaO_2 = pulsoximetry.

2.2	Thrombolytic therapy - Pulmonary Embolus
Efficacy of Thrombolysis	**Thrombolytic therapy** • accelerates clot lysis • is associated with short term physiological benefits[3-5] • HAS NOT BEEN PROVEN TO IMPROVE MORTALITY [7,8] • No effect on recurrence of PE[7]
Indications for thrombolysis	**Massive PE** Acute massive PE is defined by the presence of haemodynamic instability not the physical size of the clot • Persistent hypotension (systolic BP less than 90mmHg for 15 minutes) (GRADE 1B evidence)[9] UNLESS there are major contraindications owing to the bleeding risk (see below) **Submassive PE** Acute PE without systemic hypotension but with either RV dysfunction or myocardial necrosis.The value of thrombolysis is uncertain and must be determined on a case by case basis with consultant decision. Consider administration of thrombolytic therapy in selected high-risk patients without hypotension who are judged to have a low risk of bleeding (Grade 2B evidence).Poor prognostic indicators include the following[9]: • Patients who appear ill, with marked dyspnoea, anxiety and severe hypoxaemia • Elevated troponin • Right ventricular dysfunction on echocardiography • Right ventricular enlargement on CTPA or cardiac echo • Other factors to consider are free-floating right ventricular thrombus, extensive thrombus load on CTPA or large perfusion defect, or the patient is known to have a patent foramen ovale
Contraindications	**Absolute** • History of haemorrhagic stroke • Active intracranial neoplasm • Recent (less than 2 months) intracranial surgery or trauma • Active or recent internal bleeding n the prior 6 months **Relative** • Bleeding diathesis • Uncontrolled severe hypertension (systolic BP greater than

	200mmHg or diastolic greater than 110mmHg) • Non-haemorrhagic stroke within the prior 2 months • Surgery within the previous 10 days • Thrombocytopaenia – platelets less than 100x109/l

2.3 Drug Regimen

Drug	Origin	Half Life (mins)	Antigenicity	Dose by peripheral infusion
t-PA-Alteplase **preferred option**	**Recombinant**	**5**	**No**	***Over 65Kg – 10mg iv bolus followed by 90mg iv infusion over 2 hours*** ***Under 65kg – 10mg iv bolus then max infusion dose should not exceed 1.5mg/kg*** **If cardiac arrest imminent - 50mg bolus**
Streptokinase (consider no previous administration)	Bacterial	20	Yes • Allergic reactions, anaphylaxis • Asthma • Antibody formation	Accelerated regimen: 1.5 million units over 2 hours 250,000 unit dose over 30 minutes
Urokinase	Cell structure	15	No	2000 unit/kg loading dose followed by 2000 unit/kg/hour

The 8th ACCP guidelines recommend that thrombolytic treatment be administered via a peripheral vein rather than placing a pulmonary catheter (grade 1B evidence) and that in patients with acute PE being treated with thrombolytic therapy regimens with short infusion times (eg a 2hour infusion) are used over those with prolonged infusion times (eg a 24 hour infusion) (grade 1B evidence)[9]

After treatment with thrombolysis,use heparin 18U/kg/hour as a continuous infusion as soon as the APTT is less than twice the upper limit of normal.

APTT monitoring is required 6 hourly after any dose change and at least daily. Heparin is continued until warfarin is in the therapeutic range (usually INR 2-3) for at least 2 days. The patient should have a minimum of 5 days of heparin treatment.

2.4 Catheter-directed thrombolysis

- **Intrapulmonary infusion**

There is no evidence that direct infusion of thrombolytics into the pulmonary artery via a pulmonary arterial catheter confers greater benefit than peripheral vein infusion.

- **Intraembolic infusion**

This delivers the thrombolytic directly into the embolus and is associated with increased thrombolysis in animal models

2.5 Adverse effects to thrombolysis

Bleeding

Bleeding is the most common adverse effect associated with thrombolysis but there are also some thrombolytic agent specific adverse reactions.

Accelerated fibrinolysis is not limited to the symptomatic thrombus but acts on all fibrin deposits. Bleeding occurs most commonly at sites of invasive procedures but there may also be pathological lesions within the brain, gastrointestinal tract or genitourinary tract. Thrombolysis in PE has a reported 3% risk of intracranial haemorrhage[12]. Fibrinolytic agents have an effect on platelets, fibrinogen and other plasma proteins. Some of these patients may also be on concurrent anticoagulant and antiplatelet agents.

2.6 Treatment of thrombolytic bleeding

If intracranial bleeding is suspected, stop infusion of the thrombolytic agent immediately, obtain imaging, consult neurosurgery and correct haemostasis as below.

For intracranial haemorrhage and other life threatening bleeding:

- Discontinue antiplatelet, anticoagulant and thrombolytic drugs.
- Send diagnostic tests – aPTT, INR, FBC and fibrinogen
- Tranexamic acid 1g iv over 15 minutes
- Give fresh frozen plasma and cryoprecipitate guided by clotting results : 10-15mls/kg FFP and 1 adult therapeutic dose (ATD ~ 330mls) of cryoprecipitate
- Repeat fibrinogen if patient still bleeding and fibrinogen is less than 1.0g/L transfuse an additional ATD of cryoprecipitate

If on-going bleeding despite the above measures tranexamic acid can be repeated at 8 hourly intervals.

2.7 Agent specific adverse effects

- Streptokinase is associated with allergic reactions. Hydrocortisone should be given with streptokinase to reduce the incidence of allergic reactions. It is antigenic and can cause immunological sensitization and allergic reactions especially with repeat administration. Its use on one occasion precludes its use in subsequent episodes because it is highly antigenic. Anti–streptokinase antibodies remain elevated for up to 7.5 years after treatment and this may result in a suboptimal response and/or allergic reaction if streptokinase is administered years later.

- Hypotension may occur during streptokinase infusion. It usually responds to slowing of the infusion, intravenous fluids or vasopressors.

2.8 Location of administration of thrombolytics

These should be administered in high dependency/CCU or intensive care unit unless cardiac arrest is imminent

2.9 Further information

Management of probable massive pulmonary embolism – summary from BTS guidelines for the management of suspected acute pulmonary embolism[1]: ***comments***

1. Massive PE is highly likely if:

   Collapse/hypotension, and

   Unexplained hypoxia, and

   Engorged neck veins, and

   Right ventricular gallop (often)

2. In stable patients where massive PE has confirmed, iv dose of alteplase is 100mg in 90 min (ie accelerated myocardial infarction regimen).

3. Thrombolysis is followed by unfractionated heparin after 3 hours, preferably weight adjusted.

4. A few units have facilities for clot fragmentation via pulmonary artery catheter. Elsewhere, contraindications to thrombolysis should be ignored in life threatening PE.

5. 'Blue light' patients with out-of-hospital cardiac arrest due to PE rarely recover

2.9 Alternatives to thrombolysis

EMBOLECTOMY

Embolectomy (ie, removal of the embolus) can be performed using catheters or surgically. It should be considered when a patient's presentation is severe enough (eg, persistent hypotension due to PE) to warrant thrombolysis and thrombolysis either fails or is contraindicated.

Catheter embolectomy

Case series using these techniques are small, and none of the techniques has been compared with other forms of therapy in randomized, controlled studies.

The 8th ACCP guidelines recommendation[9] :

- For most patients with PE, we recommend against use of interventional catheterization techniques (grade 1C evidence). In selected highly compromised patients who are unable to receive thrombolytic therapy because of bleeding risk or whose critical status does not allow sufficient time for systemic thrombolytic therapy to be effective, we suggest the use of interventional catherization techniques if appropriate expertise is available. (Grade 2C).

Surgical embolectomy:

Indications

1. Systemic hypotension due to PE in a patient in whom thrombolysis is contraindicated

2. echocardiographic evidence of an embolus trapped within a patent foramen ovale, the right atrium, or the right ventricle .

Surgical embolectomy has been compared to repeat thrombolysis in patients who failed initial thrombolysis. In a small observational cohort study, patients who underwent surgical embolectomy had fewer recurrent PE. There were fewer deaths and fewer major bleeding complications among the surgical embolectomy group, although these differences did not achieve statistical significance. Surgical embolectomy has not been compared to catheter embolectomy or primary thrombolytic therapy

The 8th ACCP guidelines recommendation[9] :

In selected highly compromised patients who are unable to receive thrombolytic therapy because of bleeding risk or whose critical status does not allow sufficient time for systemic thrombolytic therapy to be effective, we suggest that pulmonary embolectomy may be used if appropriate expertise is available. (Grade 2C).

IF CONSIDERING EMBOLECTOMY DISCUSS WITH CARDIOTHORACIC TEAM

3. References

1 British Thoracic Society Standards of Care Committee Pulmonary Embolism Development Group. British thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax 2003;58:470-484

2. ESC Guideline 2008 Aujesky D, Roy PM, Le Manach CP, Verschuren F, Meyer G, Obrosky DS et al.

Validation of a model to predict adverse outcomes in patients with pulmonary embolism. Eur Heart J 2006;27:476–481.

3 Konstantinides S, Tiede N, Geibel A et al Comparison of alteplase versus heparin for resolution of major pulmonary embolism Am J Cardiol 1998; 82:966

4 Sharma GVRK, Burleson VA, Sasahara AA Effect of thrombolytic therapy on pulmonary-capillary blod volume in patients with pulmonary embolism NEngl J Med 1980; 303:842

5 Come PC Echocardiographic evaluation of pulmonary embolism and its response to therapeutic interventions. Chest 1992; 101:151S

6 Sharma GVRK, Folland ED, McIntyre KM et al Longterm hemodynamic benefit of thrombolytoc therapy in pulmonary embolic disease (abstract) J Am Coll Cardiol 1990 ; 15:65A

7 Thabut G, Thabut D, Myers RP et al Thrombolytic therapy of pulmonary embolism: a meta-analysis. J Am Coll Cardiol 2002; 40:1660

8 Goldhaber SZ, Haire WD, Feldstein ML et al Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right ventricular function and pulmonary perfusion Lancet 1993; 341:507

9 Kearon C, Kahn SR, Agnelli G et al Anti thrombotic therapy for venous thromboembolic disease: American college of Chest Physicians Evidence-based Clinical Practice guidelines (8th edition) Chest 2008; 133:(6suppl)

10 Goldhaber SZ, Buring JE Lipnick RJ et al Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented deep vein thrombosis Am J Med 1984;76:393

11 Rogers LQ, Lutcher CL Streptokinase therapy for deep vein thrombosis: A comprehensive review of the literature. Am J Med 1990;88:389

12 Kucher N, Rossi E, De Rosa M, et al. Massive pulmonary embolism. Circulation 2006; 113:577–582

4. Legal Liability Guideline Statement

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