Thrombolytic therapy of pulmonary embolism: a comprehensive review of current evidence

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Authors' objectives
To provide a comprehensive and systematic review of studies evaluating thrombolytic therapy of patients with pulmonary embolism (PE). Seven objectives were identified:

1. What are the proven advantages of thrombolytic therapy?
2. How do available thrombolytic agents compare with regard to efficacy and safety?
3. Should thrombolytic therapy be administered systemically or locally?
4. What is the role of bolus thrombolytic therapy?
5. What is the optimum time window for PE thrombolysis?
6. What are the complications of thrombolytic therapy?
7. What are the indications for thrombolytic therapy of PE?

Searching
MEDLINE was searched from 1966 to 1998. The following search terms were used as MeSH terms and textwords: thrombolytic therapy, thrombolysis, fibrinolyses, urokinase (UK), streptokinase (SK), recombinant tissue-type plasminogen activator (rt-PA), and pulmonary embolism. The reference lists of all articles were examined to identify additional studies. No attempt was made to evaluate unpublished data.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) are the focus of the review, but non-randomised, uncontrolled trials and case series are also discussed.

Specific interventions included in the review
Thrombolytic therapy including streptokinase (SK), urokinase (UK) and recombinant tissue-plasminogen activator (rt-PA) with heparin as comparator.

Participants included in the review
Patients with PE. Definition of PE, or required diagnostic evidence of PE not stated.

Outcomes assessed in the review
Mortality, recurrent PE, and haemorrhage (major and intracranial).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The levels of evidence assigned were those of the Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy (see Other Publications of Related Interest no.1). Level 1 = large randomised trials or meta-analyses with sufficient power to detect or reliably exclude a difference between groups. Level II are randomised
studies or meta-analyses with insufficient power to detect or reliably exclude a difference between groups. Levels III - V are non-randomised, uncontrolled trials or case-series. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
Studies are combined in a narrative summary.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Not clearly stated. From tables and text it appears that there were 9 randomised trials (461 patients) of efficacy (comparing thrombolytic to heparin), 6 randomised trials (481 patients) comparing efficacy and safety of one thrombolytic versus another.

1. What are the proven advantages of thrombolytic therapy?

Thrombolytic therapy results in more rapid clot resolution than treatment with heparin alone. Within 5 to 7 days, both treatments produce similar improvements in pulmonary perfusion, as assessed by perfusion scan (Level I and II evidence).

Based on data from a small randomised study, thrombolytic therapy appears to reduce mortality in patients with shock due to massive PE (level II evidence).

In haemodynamically stable patients, thrombolysis has not been proven to reduce mortality or the risk of recurrence of PE (level I and II evidence).

In the subset of patients with normal systemic arterial pressure and right ventricular dysfunction, thrombolytic therapy may decrease both mortality and recurrent thromboembolism (level II and III evidence). Based on one level II study, thrombolytic therapy may enhance the resolution of small peripheral emboli and improve the hemodynamic response to exercise.

2. How do available thrombolytic agents compare with regard to efficacy and safety?

The three thrombolytic agents appear to be equally effective and safe when equivalent doses are delivered at the same rate over a short period of time (level II evidence).

A 2-hour infusion of rt-PA results in more rapid clot lysis when compared with the 12 or 24-hour regimens of UK and SK (level II evidence).

3. Should thrombolytic therapy be administered systemically or locally?

The limited available data do not support the use of intrapulmonary thrombolytic therapy (level II and V evidence).

4. What is the role of bolus thrombolytic therapy?

Bolus dose rt-PA therapy is not safer or more effective that the approved 2-hour regimen (level II evidence).
5. What is the optimum time window for PE thrombolysis?

Thrombolytic therapy is most effective when administered soon after PE but benefit may extend up to 14 days after symptom onset. (Level I and II evidence).

6. What are the complications of thrombolytic therapy?

Thrombolytic therapy is accompanied by a significantly greater risk of major haemorrhage than is treatment with heparin alone. There is also a small but clinically important risk of intracranial hemorrhage. (Level I and II evidence).

7. What are the indications for thrombolytic therapy of PE?

Patients with hypotension or other signs of systemic hypoperfusion caused by PE should be treated with thrombolytic therapy (level II evidence).

Additional information is needed to determine whether right ventricular dysfunction and/or large clot burden are, by themselves, indications for PE thrombolysis.

Authors' conclusions
Unquestionably, thrombolytic therapy leads to much more rapid improvement in pulmonary vascular obstruction and hemodynamic abnormalities than treatment with anticoagulation alone. Despite many randomised-controlled trials performed during the past three decades, however, it has not been proven that this benefit translates into a reduction in morbidity or mortality. In patients with shock due to massive PE, the potential benefits of thrombolysis almost certainly outweigh the risk of significant hemorrhage. In those with small emboli that produce no hemodynamic disturbances, the risk of thrombolytic therapy is clearly not warranted.

CRD commentary
The review included all reports, including uncontrolled case series, but was based primarily on randomised trials. The search strategy included only one electronic database (MEDLINE) and did not contact authors or search for unpublished information. Therefore, considering the limited information found, it is possible that important information could have been missed. The validity assessment was simply stratifying the studies into levels of evidence, but further examination within levels was not done. Therefore, the strength of the evidence within each level is not fully known. The findings and conclusions are handled in a narrative format, emphasising level I and II studies, but differences between studies and their impact on the findings are not discussed. The authors' conclusions do seem to follow from the research findings, but the strength of the evidence may be over-emphasised.

Implications of the review for practice and research
The authors recommend that additional information is required to assess the most appropriate therapy for patients who fall between the two extremes of shock and no hemodynamic disturbances. In particular, future research must determine whether thrombolytic therapy reduces morbidity or mortality in patients with a large clot burden and/or right ventricular dysfunction who have no clinical signs of systemic hypoperfusion.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.