Thrombolytic therapy of pulmonary embolism: a meta-analysis

Authors’ objectives
To assess the safety and efficacy of thrombolytic treatment in people with acute pulmonary embolism (PE).

Searching
MEDLINE (from 1967 to 2000), EMBASE (from 1974 to 2000) and Current Contents were searched. In addition, the reference lists from identified studies and reviews were checked. Articles published in any language as an abstract or full publications were eligible. Investigators in the field and the manufacturers of thrombolytic agents were also contacted for missing or unpublished studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Retrospective, non-randomised and quasi-randomised studies were excluded.

Specific interventions included in the review
Studies that compared thrombolytic therapy using urokinase, streptokinase or recombinant tissue-type plasminogen activator (rt-PA) with heparin were eligible for inclusion. Studies comparing two thrombolytic agents were excluded.

The treatment regimens in the included studies were as follows.

For urokinase: 2,000 U/lb bolus then 2,000 U/lb per hour intravenously (i.v.) for 12 hours; 800,000 U/day i.v. for 72 hours; and 3,300,000 U i.v. for 12 hours.

For streptokinase: intrapulmonary, 600,000 U bolus then 100,000 U/hour for 72 hours; 250,000 U bolus then 100,000 U/hour for 72 hours; and 1,500,000 U i.v. over one hour.

For rt-PA: 40 to 80 mg i.v. over 90 minutes plus heparin; 0.6 mg/kg i.v. over 2 minutes; and 100 mg i.v. over 2 hours.

Participants included in the review
Studies of patients with acute PE were eligible for inclusion. All of the included studies excluded patients with contraindications to thrombolytic therapy. In all of the included studies, the patients had experienced symptoms consistent with acute PE at least 15 days previously. Some studies excluded patients in shock, while other studies did not; overall, only 5.2% of the participants presented in shock. Some studies only included patients with a study-defined extent of vascular obstruction. The participants ranged in age from 47 to 66 years and the proportion of males ranged from 27 to 100%.

Outcomes assessed in the review
Studies that assessed at least one of the following outcomes were eligible for inclusion: mortality, recurrence of PE, or major haemorrhage. Recurrence of PE had to be confirmed by a perfusion lung scan, pulmonary angiography or postmortem examination. Major haemorrhage was defined as intracranial or retroperitoneal haemorrhage or other bleeding requiring blood transfusion or surgery. The outcomes were assessed at the end of follow-up for each study. The duration of follow-up ranged from 3 to 14 days (median 7).

How were decisions on the relevance of primary studies made?
Two authors independently conducted the searches and selected the studies. Any disagreements were resolved through discussion with a third author.

Assessment of study quality
Validity was assessed and scored using the 5-point Jadad scale, which considers randomisation, blinding and withdrawals (see Other Publications of Related Interest). Two reviewers independently assessed validity and resolved any disagreements by consensus.

**Data extraction**

Two reviewers independently extracted the data using a structured form and resolved any disagreements through discussion. The data extracted were: inclusion and exclusion criteria; method of diagnosis; severity assessment of vascular obstruction; treatment regimen and follow-up. The data were extracted on an intention-to-treat basis. The relative risk (RR) was calculated for each RCT for each outcome.

**Methods of synthesis**

**How were the studies combined?**

The pooled RR and 95% confidence intervals (CIs) were calculated using the fixed-effect method (Mantel-Haenszel) in the absence of significant heterogeneity and the random-effects model (DerSimonian and Laird) when significant heterogeneity was found. Where a statistically-significant difference between the treatments was found, the number-needed-to-treat to prevent death or recurrent PE or the number-needed-to-harm (NNH) to prevent a major haemorrhage were calculated. The possibility of publication bias was explored using a funnel plot.

**How were differences between studies investigated?**

Statistical heterogeneity was assessed using the chi-squared statistic. Sensitivity analyses were used to explore the influence of several factors on the results: type of thrombolytic therapy was investigated by limiting the analysis to RCTs of rt-PA only; severity of PE was investigated using a post-hoc analysis limited to studies including patients in shock, and another analysis that was limited to RCTs requiring a specific extent of pulmonary vascular obstruction; validity was explored by excluding RCTs with a Jadad score of 2 or less.

**Results of the review**

Nine RCTs (461 patients) were included.

The median validity score was 2 (range: 1 to 3). Three RCTs were double-blinded; the remainder were unblinded. The funnel plot showed no evidence for publication bias.

Mortality (9 RCTs, 461 patients).

There was no significant difference in mortality between thrombolytic agents and heparin; the mortality rates were 4.6% and 7.7% in the thrombolytic and heparin groups, respectively (RR 0.63, 95% CI: 0.32, 1.23). No significant statistical heterogeneity was found (P=0.77). There was no significant difference in mortality between treatments according to the type of thrombolytic agent, the clinical severity of PE, the radiologic severity of pulmonary vascular obstruction, or validity.

Recurrence of PE (7 RCTs, 428 patients).

There was no significant difference in recurrent PE between thrombolytic agents and heparin; the mean rates of recurrent PE were 4.9% and 9.3% thrombolytic and heparin groups, respectively (RR 0.59, 95% CI: 0.30, 1.18). No significant statistical heterogeneity was found (P=0.58). There was no significant difference in the recurrence of PE between treatments according to the type of thrombolytic agent, the clinical severity of PE, the radiologic severity of pulmonary vascular obstruction, or validity.

Major haemorrhage (9 RCTs, 461 patients).

Thrombolytic therapy significantly increased the risk of major haemorrhage compared with heparin: 13.7% versus 7.7% (RR 1.76, 95% CI: 1.04, 2.98). No significant statistical heterogeneity was found (P=1.0); the NNH was 17 (95% CI: 7, 325). In the sensitivity analyses, the difference was significant only for RCTs that randomised patients in shock (RR 1.82, 95% CI: 1.01, 3.26) and for high-quality RCTs (RR 1.90, 95% CI: 1.03, 3.50). There was no significant
difference in major haemorrhage for RCTs of rt-PA or for RCTs that required a specific severity of PE.

Authors’ conclusions
Thrombolytic therapy increased the risk of major haemorrhage in patients with PE, but there was no significant difference in recurrent PE or mortality. The lack of statistical significance may be due to the small number of patients in the included trials.

CRD commentary
This was a well-conducted and clearly presented review. The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched, no language limitations were applied, and attempts were made to locate unpublished studies. However, the search terms were not reported. Two reviewers independently selected the studies, assessed validity and extracted the data; this reduced the potential for bias and errors. Validity was assessed using validated criteria and relevant information on the included studies was tabulated. The data were appropriately combined in a meta-analysis and statistical heterogeneity was assessed. Sensitivity analyses were used to explore the influence on the results of the type of thrombolytic agent, the severity of PE and validity. Limitations of the review and potential reasons for the lack of statistical significance of some of the results were discussed in the text.

The evidence presented appears to support the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that large prospective RCTs are required to determine the usefulness of thrombolytic therapy in patients with PE.

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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.