Efficacy of thrombolytic agents in the treatment of pulmonary embolism

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CRD summary
This review assessed the use of alteplase, given as an infusion or a bolus injection, and streptokinase for the treatment of pulmonary embolism. The authors concluded that firm recommendations as to which thrombolytic regimen is preferable cannot be drawn from the insufficient evidence found; further research is needed. This conclusion is appropriate given the data presented.

Authors' objectives
To compare the effects of alteplase and streptokinase in the treatment of pulmonary embolism (PE).

Searching
MEDLINE (1966 to September 2003), EMBASE (1974 to September 2003), CINAHL (1950 to September 2003) and the Cochrane Library were searched; the search terms were given. The reference lists of relevant articles and reviews were checked for further published studies.

Study selection
Study designs of evaluations included in the review
The authors said that they looked for randomised controlled trials (RCTs). Prospective and retrospective studies and case studies were also included, owing to the small number of RCTs identified. Where stated, the duration of follow-up in the included studies ranged from 10 days to 1 year.

Specific interventions included in the review
Studies that assessed the use of alteplase, given as a 100-mg 2-hour infusion or a bolus regimen, or the use of streptokinase were eligible for inclusion. Details of the dosing regimens used in the included studies were given. Comparisons were made between drugs, with differing dosing regimens (alteplase bolus versus infusion), or with urokinase. Heparin was administered concomitantly (dosing regimens given in paper).

Participants included in the review
Studies on individuals with PE were eligible for inclusion. In the included studies people had massive PE or nonmassive PE. The diagnosis of PE was made using pulmonary angiography, scintigraphy, necroscopy or perfusion lung scan.

Outcomes assessed in the review
The outcomes of interest were thrombolysis, measured objectively (i.e. angiographic evidence of clot lysis, echocardiogram, or more than 50% improvement in perfusion lung scan), all-cause mortality, death from PE, death from major bleeding, death from recurrent PE, major bleeding episodes and recurrent PE.

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

Assessment of study quality
The quality of the included studies was assessed using the Jadad scoring system, which is based on method of randomisation, blinding, and handling of drop-outs and withdrawals. The scores ranged from 0 to 5, with 5 indicating the highest quality. The authors did not state how the validity assessment was performed.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data
The results were analysed on an intention-to-treat basis.

Methods of synthesis
How were the studies combined?
Data from the RCTs were pooled using a random-effects model where heterogeneity existed. The pooled relative risk (RR), odds ratio (OR) and 95% confidence intervals (CIs) were calculated. In addition, outcome data for all cohorts assessing a particular drug were summed to give a percentage effect. A risk ratio between treatments was then estimated using a chi-squared test. The number-needed-to-harm (NNH) and number-needed-to-treat (NNT) were calculated where appropriate.

How were differences between studies investigated?
Heterogeneity was assessed using the chi-squared test. Sensitivity analyses were conducted based on severity of disease (massive PE versus nonmassive PE), methodological quality (score 3+ versus less than 3) and results from RCTs only.

Results of the review
Twenty-six studies were included: 16 RCTs (1,284 participants), 7 prospective studies (274 participants), 2 retrospective studies (153 participants) and 1 case study (6 participants).

Thrombolysis was not assessed for alteplase intravenous infusion versus bolus dose (2 RCTs). No significant differences in any other outcomes were observed between the two treatment groups.

There was no difference in all-cause mortality between alteplase infusion and streptokinase (RR 1.00, 95% CI: 0.07, 15.12, p=1.0; 2 RCTs). When an additional retrospective study was included, alteplase was associated with a trend towards greater incidence of major bleeding (RR 2.07, 95% CI: 0.8, 5.3, p=0.13).

Alteplase infusion was more effective than urokinase for thrombolysis (RR 1.32, 95% CI: 1.05, 1.67, p=0.02; 2 RCTs). The pooled analysis showed that all-cause mortality was similar for alteplase infusion compared with all other treatments combined (RR 1.34, 95% CI: 0.57, 3.14, p=0.7; 8 studies).

When data from cohorts on the same drug were combined and the results compared with those from different studies, alteplase infusion achieved thrombolysis in more cases than bolus dose alteplase (RR 1.95 95% CI: 1.19, 3.2, p=0.008; NNT 3). Streptokinase achieved thrombolysis in more cases than alteplase bolus dose (RR 2.48, 95% CI: 1.52, 4.03, p=0.0003) and alteplase infusion (RR 1.27, 95% CI: 1.09, 1.47, p=0.002; NNT=6). Alteplase infusion had a lower mortality from initial PE than either bolus dose alteplase or streptokinase (RR 0.16, 95% CI: 0.05, 0.59, p=0.005 and RR 0.13, 95% CI: 0.04, 0.46, p=0.001, respectively).

Authors’ conclusions
The different thrombolytic regimens (alteplase infusion and bolus dose, and streptokinase) may have differing effects. A firm recommendation on which thrombolytic regimen is preferable for people with PE cannot be made on the strength of the available evidence.

CRD commentary
The aims of this review were only partially stated, in particular, although the authors said they looked for RCTs they included other study designs in the analysis. It was not clear whether they searched for, or included, all studies of these designs within the review. A number of relevant databases were searched and no mention was made of any language restrictions. Only published studies appear to have been included and it is possible that other studies might have been missed. Details of the methods of the review (study selection and data extraction) were not given, so it is possible for bias to have been introduced at these stages. The studies were assessed for quality, but the method used was one intended for RCTs; this might not have been appropriate for assessing the quality of the non-RCTs included.
In some analyses data from RCTs and other studies were pooled. In addition, some of the comparisons presented were based on indirect comparisons between studies. These methods are considered to be less reliable than within-study direct comparisons. However, as the authors' conclusions relate mainly to a lack of evidence, this was appropriate given the data presented.

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

Research: A large scale RCT is needed to compare the effects of thrombolysis with heparin alone in the treatment of PE. Alteplase infusion should be the drug regimen used in any trial.

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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.