Short term effect of recombinant tissue plasminogen activator in patients with hemodynamically stable acute pulmonary embolism: results of a meta-analysis involving 464 patients

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CRD summary
This review found that in patients with haemodynamically stable pulmonary embolus, recombinant tissue plasminogen activator did not reduce rates of objective recurrent pulmonary embolism or pulmonary embolism-related mortality compared to heparin. The review was limited by the small amount of evidence available and questionable study quality. The authors’ conclusions may require cautious interpretation.

Authors' objectives
To assess the use of recombinant tissue plasminogen activator (rt-PA) compared to heparin for treating haemodynamically stable acute pulmonary embolism.

Searching
EMBASE, Pascal, MEDLINE (all from 1975 to June 2008) and The Cochrane Library (Issue 1, 2006) were searched. Search terms were reported. The search was limited to articles in English, French or Spanish.

Study selection
Randomised controlled trials (RCTs) that compared intravenous rt-PA versus intravenous heparin for the initial treatment of patients with objectively diagnosed haemodynamically stable acute pulmonary embolism were eligible for inclusion. The primary review outcome was composite: radiologically confirmed recurrent pulmonary embolism or pulmonary embolism-related death (reported by the authors or noted at autopsy). Other review outcomes were recurrent pulmonary embolism, pulmonary embolism-related death, all-cause death, major haemorrhage (secondary outcomes) and treatment escalation. These outcomes were defined in the review.

Participants in the included studies had acute symptomatic pulmonary embolism confirmed by angiography or ventilation/perfusion scan. Maximum duration of symptoms ranged from four to 14 days. The proportion of participants who received pulmonary angiography ranged from 13% to 100% across studies. In a minority of studies, all participants received echocardiography; in these studies 31% to 50% of each group had right ventricular dysfunction (RVD); however, the studies did not report separate data for the RVD groups. Studies varied with respect to treatment regimen for rt-PA and definition of outcomes. Duration of follow-up ranged from seven to 30 days or while in hospital.

Two reviewers independently selected the studies. Disagreements were resolved by consensus.

Assessment of study quality
Components of study design and quality were appraised; these included blinding, reporting of losses to follow up and outcomes assessment.

Two reviewers independently conducted the assessment. Disagreements were resolved by discussion with a third reviewer.

Data extraction
Relative risks (RRs) were extracted or calculated with 95% confidence intervals (CIs).

Two reviewers independently extracted data. Disagreements were resolved by discussion with a third reviewer.
Methods of synthesis
Studies were combined to calculate pooled relative risks and 95% CIs using a fixed-effect model. Heterogeneity was assessed with the \( \chi^2 \) test. Publication bias was assessed with funnel plots. Subgroup analysis restricted studies to those that included participants with right ventricular dysfunction confirmed by echocardiography.

Results of the review
Five RCTs were included in the review (n=464, range 13 to 256). Three studies were double-blinded. No studies reported rates of loss to follow-up and none used a central committee to validate outcomes.

There was no statistically significant difference between the groups for the composite outcome of pulmonary embolism-related death or recurrent pulmonary embolism (five RCTs), pulmonary embolism-related death (five RCTs), recurrent pulmonary embolism (four RCTs), all-cause death (five RCTs) and major haemorrhage (five RCTs). There was no significant statistical heterogeneity for any analysis.

The findings of the subgroup analysis were similar to the main results. Findings for escalation of treatment were reported in the review; this was a prespecified outcome in only one RCT.

Authors' conclusions
In patients with haemodynamically stable pulmonary embolism, rt-PA did not reduce rates of objective recurrent pulmonary embolism or pulmonary embolism-related mortality compared to heparin.

CRD commentary
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies. The search was restricted by language, which risked language bias. It was unclear whether the search was restricted by publication status. Funnel testing was not suggestive of publication bias, but the power of this test is low when applied to so few studies. It was unclear why only short-term outcomes were reported in the review, as reports of long-term follow up were apparently available for some of the included studies. Steps were taken to minimise risks of reviewer bias and error by having more than one reviewer select studies, assess validity and extract data. The process used for validity assessment was not systematically described and some relevant details of study validity were not reported in the review (for example, randomisation and allocation concealment methods), which made it difficult to assess the reliability of study findings. Appropriate statistical techniques were used to combine the studies and assess and explore potential heterogeneity. As the authors noted, the review was limited by the small number of studies and low sample sizes.

Although findings were consistent across studies, the review was limited by the small amount of evidence available and questionable study quality, so the authors' conclusions may require cautious interpretation.

Implications of the review for practice and research

Practice: The authors stated that rt-PA might be of benefit to selected high-risk patients with both RVD and elevated cardiac biomarkers; this suggestion was not well supported by the evidence presented in the review. The authors also noted that if patients were selected carefully and invasive procedures were avoided, rt-PA treatment was not frequently associated with major haemorrhage.

Research: The authors did not state any implications for further research.

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Bibliographic details
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.