Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials

Wan S, Quinlan DJ, Agnelli G, Eikelboom JW

CRD summary
This review concluded that evidence for a benefit of thrombolytic therapy compared with heparin for the initial treatment of patients with acute pulmonary embolism was lacking; there may be a benefit in high-risk patients. Given the limitations of the evidence available, the reliability and applicability of the overall estimates and conclusions are uncertain.

Authors' objectives
To compare the efficacy and safety of thrombolytic therapy with heparin in patients with acute pulmonary embolism (blood clot in the pulmonary artery).

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from 1980 up to January 2003; search terms were reported. Bibliographies of included articles and abstracts from major international meetings (not specified) were also searched.

Study selection
Randomised controlled trials (RCTs) that compared thrombolysis with heparin for the initial treatment of patients with objectively diagnosed symptomatic pulmonary embolism were eligible for inclusion. Trials had to report objectively measured outcomes; the primary outcome was a composite of recurrent pulmonary embolism or death.

The thrombolysis treatments evaluated in the included RCTs were tissue plasminogen activator (two minute bolus dose to two hours), streptokinase (two to 72 hours), and urokinase (12 hours or three days). All trials used warfarin for subsequent anticoagulation and most also used heparin; the proportion of patients in the RCTs using these subsequent therapies was not reported. All the trials recruited patients with acute pulmonary embolism; some trials restricted inclusion to patients with major/life-threatening pulmonary embolism. Duration of symptoms ranged from less than five days to 14 days or longer, where reported.

Two reviewers independently selected studies for the review; disagreements were resolved by discussion.

Assessment of study quality
Trial quality was assessed using sequence generation, allocation concealment, blinding, and completeness of follow-up. RCTs had to report the use of an appropriate randomisation procedure to be included.

It seemed that two reviewers independently assessed study quality.

Data extraction
Two reviewers independently extracted data on the incidence of recurrent pulmonary embolism/death, recurrent pulmonary embolism, death, major bleeding, non-major bleeding, and intracranial haemorrhage, from which odds ratios and 95% confidence intervals were calculated.

Methods of synthesis
Pooled odds ratios with 95% confidence intervals were calculated using a Mantel-Haenszel fixed-effect model; a random-effects model was conducted as a sensitivity analysis. The number needed to treat or harm was also calculated. Heterogeneity was assessed using the X² test.

Subgroup analyses were used to investigate the impact of RCTs that included patients with haemodynamically unstable pulmonary embolism. Sensitivity analyses were used to investigate trial quality and the impact of each trial (by excluding them one at a time).
Publication bias for the primary outcome was assessed using a funnel plot.

**Results of the review**

Eleven RCTs (748 patients, range 8 to 256) were included in the review. Three RCTs reported using random number tables or computer generation. Five RCTs reported appropriate methods to conceal allocation. Three RCTs reported blinding patients and investigators. None of the RCTs reported losses to follow-up. The duration of follow-up ranged from ‘in hospital’ to 30 days.

Compared with heparin, thrombolytic therapy resulted in a non-statistically significant reduction in recurrent pulmonary embolism/death (OR 0.67, 95% CI 0.40 to 1.12; 11 RCTs); no publication bias was observed. When restricted to RCTs that included patients with haemodynamically unstable pulmonary embolism, the risk of recurrent pulmonary embolism/death was significantly reduced with thrombolytic therapy (OR 0.45, 95% CI 0.22 to 0.92; NNT=10; five RCTs), but there were no difference when restricted to RCTs that excluded these patients (six RCTs).

Compared with heparin, thrombolytic therapy did not produce any statistically significant difference for recurrent pulmonary embolism (OR 0.67, 95% CI 0.33 to 1.37; 11 RCTs), death (OR 0.70, 95% CI 0.37 to 1.30; 11 RCTs), or major bleeding (OR 1.42, 95% CI 0.81 to 2.46; 11 RCTs). There was a statistically significant increase in non-major bleeding (OR 2.63, 95% CI 1.53 to 4.54; eight RCTs; NNH=8).

Results for further subgroup and sensitivity analyses were reported. No statistically significant heterogeneity was observed for any outcome.

**Authors’ conclusions**

Available data provided no evidence for a benefit of thrombolytic therapy compared with heparin for the initial treatment of unselected patients with acute pulmonary embolism. A benefit was suggested in patients at the highest risk of recurrence or death (especially those with haemodynamic instability).

**CRD commentary**

The review addressed a clear question supported by reproducible inclusion criteria. Relevant sources were searched for published and unpublished studies. It was unclear whether language restrictions were applied, so the potential for language bias could not be assessed. Each stage of the review was conducted in duplicate, which reduced the risk of reviewer error and bias.

Appropriate criteria were used to assess trial quality. Although inclusion was stated as being restricted to RCTs with appropriate randomisation procedures, it seemed that only three of the 11 RCTs included reported using such methods. Most of the included RCTs seemed to be at a high risk of bias. Details of moderating factors (such as treatment regimens and the age and gender of patients) were not reported and were not investigated in the analyses. Despite apparent clinical heterogeneity, a fixed-effect model was used to produce pooled estimates; the authors stated that the results of random-effects models were similar, although the results were not presented, so the difference in precision of the pooled estimate could not be assessed. The number of patients and events included in the meta-analyses was small; this was decreased further in the subgroup analyses, which reduced the reliability of the results obtained.

Given the clinical diversity across the trials, the small sample size, the high risk of bias of the included RCTs, and the imprecision of the results from most of the included trials (for the analysis where this could be determined), the reliability and generalisability of the overall pooled estimates is uncertain. Consequently, the authors’ conclusions seem overly strong and the recommendation for further research in only high risk patients premature.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that the available RCTs were small and further evaluation of the efficacy and safety of thrombolytic therapy for the treatment of high-risk patients with acute pulmonary embolism appeared warranted.

**Funding**

Not reported.
Bibliographic details

PubMedID
15262836

DOI
10.1161/01.CIR.0000137826.09715.9C

Original Paper URL
http://circ.ahajournals.org/content/110/6/744.abstract

Additional Data URL

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Disease; Anticoagulants /adverse effects /therapeutic use; Fibrinolytic Agents /adverse effects /therapeutic use; Hemorrhage /chemically induced /epidemiology; Heparin /adverse effects /therapeutic use; Humans; Pulmonary Embolism /drug therapy; Randomized Controlled Trials as Topic /statistics & numerical data; Recurrence; Research Design; Risk; Thrombolytic Therapy; Treatment Outcome

AccessionNumber
12004001502

Date bibliographic record published
08/10/2004

Date abstract record published
14/05/2013

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.