Is thrombolytic therapy associated with increased mortality: meta-analysis of randomized controlled trials

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CRD summary
This review compared the effectiveness of thrombolytic therapy with placebo in patients with acute ischaemic stroke and concluded that there was no increase in all-cause mortality. Limitations in the reporting of aspects of the review methodology and the included studies mean that it is not possible to comment on the reliability of this conclusion.

Authors' objectives
To determine the all-cause mortality risk of certain thrombolytic agents used in the treatment of acute ischaemic stroke.

Searching
MEDLINE and the Cochrane CENTRAL Register were searched from 1966 to 2003 for articles in the English language. The reference lists of relevant studies and reviews were searched, as were the proceedings of pertinent conferences. In addition, relevant websites were reviewed and experts in the field were contacted.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of thrombolytic agents compared with placebo were eligible for inclusion. Studies that compared thrombolytic agents with another agent were excluded. Most of the included studies evaluated recombinant tissue plasminogen activator (rt-PA); others evaluated prourokinase or ancrod. Studies of prourokinase used heparin as a control. With the exception of the prourokinase studies, therapy was administered intravenously. The treatments were given between 3 and 6 hours post stroke.

Participants included in the review
Studies of participants with acute ischaemic stroke were eligible for inclusion. The included studies evaluated patients with all types of ischaemic stroke, the carotid territory, or the internal carotid artery or middle cerebral artery.

Outcomes assessed in the review
Studies that reported all-cause mortality were eligible for inclusion.

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 validity of each included study was assessed using a validated scale that considered the use of blinding, randomisation and statistical analysis.

Two reviewers independently determined the validity of each included study.

Data extraction
Two reviewers independently extracted the data. Mortality rates were extracted from each included study, and were used to derive an odds ratio (OR) with 95% confidence intervals (CIs) and an absolute risk difference.
Methods of synthesis
How were the studies combined?
The results from individual studies were combined using a random-effects meta-analysis to give a pooled OR with 95% CI. A pooled risk difference and number-needed-to-harm (NNH) were also calculated, along with 95% CIs. Funnel plots were used to assess publication bias.

How were differences between studies investigated?
The authors tested the homogeneity of the results between studies using the DerSimonian and Laird Q test statistic. Sensitivity analyses were performed on the following: mortality within 1 month of thrombolytic therapy; the exclusion of ancrod trials; rt-PA therapy studies alone; and rt-PA therapy administration within 3 hours.

Results of the review
Eleven RCTs (n=3,709) were included in the review. Nine of the included studies were placebo-controlled and two used an active comparator. The duration of follow-up ranged from 1 to 12 months.

Thrombolytic therapy was associated with a non-significant slight increase in mortality at the end of follow-up (OR 1.07, 95% CI: 0.8, 1.39, P=0.3; based on 11 RCTs). The absolute increased risk of mortality was 11 per 1,000 persons (95% CI: -24, 48, P=0.3) and the NNH was 84.

Similar results in mortality were shown when the analysis was based on thrombolytic therapy administered during the first month of therapy (OR 1.14, 95% CI: 0.75, 1.73, P=0.6; based on 9 RCTs), following the exclusion of ancrod studies (OR 1.13, 95% CI: 0.77, 1.68, P=0.2; based on 9 RCTs) and for studies of rt-PA therapy (OR 1.25, 95% CI: 0.87, 1.78, P=0.1; based on 7 RCTs). A non-significant slight decrease in mortality was shown for rt-PA therapy administration within 3 hours (OR 0.98, 95% CI: 0.63, 1.53, P=0.8; based on 4 RCTs).

The funnel plots did not show any evidence of publication bias (data not reported).

Authors' conclusions
Thrombolytic therapy does not significantly increase all-cause mortality in patients with acute ischaemic stroke.

CRD commentary
The review addressed a clear research question and inclusion criteria were defined. Several sources were searched for relevant studies and attempts were made to minimise publication bias. However, the inclusion of only English language studies might have introduced language bias. The methods used to select studies for inclusion were not reported; this is of importance as the use of placebo control was an eligibility criterion, yet two of the included studies used heparin as a comparator. Two reviewers extracted the data and assessed validity. However, other than the level of blinding, the results of the validity assessment were not reported. Thus, it is not possible to comment on the reliability of the review’s findings.

The results of the homogeneity tests were not reported, although the authors performed several subgroup analyses to account for different thrombolytic therapy regimens and length of follow-up. There was limited data on the demographics of the participants, which means that it is difficult to generalise the results. The authors acknowledged the limitation of using all-cause mortality as an outcome, and commented that the included studies did not always report on the cause of death. This factor should be considered in the interpretation of the review findings. In summary, although the evidence presented appears to support the authors’ conclusion, limitations in the reporting of the review methodology and validity assessment mean that it is difficult to comment on the reliability of the conclusion.

Implications of the review for practice and research
Practice: The authors stated that thrombolytic therapy may be considered for ischaemic stroke patients who have the right indications.
Research: The authors stated that RCTs are needed to determine the effectiveness of thrombolytic therapy. They also stated that an individual patient data meta-analysis that details cause of mortality may be needed to determine the effect of thrombolytic therapy on cause-specific mortality.

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