Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischemic stroke. Where do we go from here: a cumulative meta-analysis

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CRD summary
This review assessed whether new data published since 1995 strengthen or weaken the existing evidence for recombinant tissue plasminogen activator (rtPA) for acute ischemic stroke. The authors concluded that, despite the volume of data having doubled since 1995, the magnitude of the risks and benefits of rtPA remains imprecise. This was a well-conducted systematic review.

Authors' objectives
To assess whether new data published since 1995 strengthen or weaken the existing evidence for recombinant tissue plasminogen activator (rtPA) for acute ischemic stroke.

Searching
The authors stated that the search methods were described in a related Cochrane Review (see Other Publications of Related Interest). The sources searched in the Cochrane Review were the Cochrane Stroke Group's Specialised Register and EMBASE (from inception). The review also reported that additional trials were sought by contacting principal researchers in the field and 321 pharmaceutical companies, attending relevant conferences, and handsearching reference lists and four Japanese journals.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies of thrombolytic agents started within 6 hours after stroke were eligible for inclusion in the review.

Participants included in the review
Studies of patients with imaging-confirmed non-haemorrhagic stroke were eligible for inclusion in the review.

Outcomes assessed in the review
The outcomes of interest were the number of patients who developed symptomatic or fatal intracranial haemorrhage within the first 7 to 10 days, and the number of patients who either died or were dependent on others in activities of daily living by the end of follow-up (usually 3 to 6 months). 'Dependent' was defined as a score of 3 to 5 on the modified Rankin Scale, or a score of 60 or less on the Barthel index.

How were decisions on the relevance of primary studies made?
The authors stated that the search methods were described in a related Cochrane Review (see Other Publications of Related Interest). The Cochrane Review reported that one reviewer applied the inclusion criteria, after seeking additional unpublished information from the principal investigators of all potentially relevant trials.

Assessment of study quality
The authors stated that the data verification methods were described in a related Cochrane Review (see Other Publications of Related Interest). The Cochrane Review reported that the validity of the primary studies was assessed on the basis of the following criteria: the method of randomisation, blinding of treatment administration, blinding of outcome assessment, and whether an intention-to-treat analysis was conducted or was possible. The authors stated that the data verification methods were reported in a related Cochrane Review (see Other Publications of Related Interest).
The Cochrane Review reported that one reviewer extracted the data, which were then tabulated, cross-checked and verified with the principal investigator of each trial. Any errors were corrected.

Data extraction
The authors stated that the data extraction methods were described in a related Cochrane Review (see Other Publications of Related Interest). The Cochrane Review reported that one reviewer extracted the data, which were then tabulated, cross-checked and verified with the principal investigator of each trial. Any errors were corrected. Data were extracted on the number of patients randomised to the intervention or control groups, the number of patients who developed symptomatic or fatal intracranial haemorrhage within the first 7 to 10 days, and the number of patients who either died or were dependent on others in activities of daily living by the end of follow-up.

Methods of synthesis
How were the studies combined?
The authors performed a separate analysis for each year in which new data emerged, starting with 1992. This method was used to show the impact of new data on the existing point estimates of treatment effect, the increase in precision of treatment effect and temporal trends. The results were reported as odds ratios (ORs) with 95% confidence intervals (CIs), calculated by fixed-effect and random-effects methods. The analyses were conducted on an intention-to-treat basis.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test.

Results of the review
Fourteen RCTs were included in the review. Of these, 8 (2,955 participants) were of rtPA.

Death or dependency at the end of follow-up.

Trials published between 1995 and 2000 showed that the use of rtPA started within 6 hours after stroke statistically significantly reduced the proportion of patients who were dead or dependent at the end of follow-up. One trial published in 1992 had a non statistically significant result (OR 0.32, 95% CI: 0.07, 1.48). The pooled OR was 0.69 (95% CI: 0.56, 0.87) for 3 trials (1,275 patients) published by 1995, 0.70 (95% CI: 0.59, 0.84) for 4 trials (2075 patients) published by 1998, and 0.80 (95% CI: 0.69, 0.93) for 6 trials (2,830 patients) published by 2000. For 1,000 patients treated with rtPA up to 6 hours after stroke, 55 (95% CI: 18, 92) fewer patients would be dead or dependent at the end of follow-up. However, there was significant heterogeneity between trials (P=0.02), but not between time points (P=0.45).

Death alone at the end of follow-up.

Trials published between 1995 and 2000 showed that the use of rtPA resulted in a non statistically significant trend for an increase in death alone at the end of follow-up. The pooled OR of 8 trials (2,955 patients) published by 2000 was 1.16 (95% CI: 0.95, 1.43). Again, there was significant heterogeneity between trials (P=0.04), but not between time points (P=0.69).

Intracranial haemorrhage within 7 to 10 days.

Trials published between 1995 and 2000 showed that the use of rtPA statistically significantly increased the proportion of patients who developed symptomatic or fatal intracranial haemorrhage within 7 to 10 days. For symptomatic intracranial haemorrhage, the pooled OR of 8 trials (2,955 patients) published by 2000 was 3.13 (95% CI: 2.34, 4.19). For fatal intracranial haemorrhage, the pooled OR was 3.6 (95% CI: 2.3, 5.7). There was no significant heterogeneity between trials (P=0.11) or between time points (P=0.26).

Consistency of effects of rtPA and other thrombolytic agents.
Trials of other thrombolytic agents that provided a similar amount of data to trials of rtPA (12 trials, 4,342 patients) had similar results. The pooled OR was 0.82 (95% CI: 0.75, 0.96) for death or dependency, with borderline significant heterogeneity between trials (P=0.07), but no significant heterogeneity between time points (P=0.72). Thrombolytic agents statistically significantly increased the proportion of patients who died; there were 40 more deaths per 1,000 patients treated (95% CI: 20, 70). Again, there was significant heterogeneity between trials (P=0.0009), but not between time points (P=0.72).

Effects in subgroups of patients.

There was a trend towards higher case fatality with more frequent and earlier use of antithrombotic agents.

There was a trend towards thrombolysis being associated with more deaths in patients with more severe strokes at baseline.

There was no statistically significant difference in the risk of death between patients treated in under 3 hours compared with those treated between 3 and 6 hours.

Thrombolysis (all agents) started within 3 hours after stroke resulted in a larger reduction in the proportion of patients who were dead or dependent at the end of follow-up (OR: 0.66, 95% CI: 0.52, 0.82). There was no evidence of heterogeneity between trials (P=0.61).

There was no statistically significant difference in the risk of death between trials using different types of thrombolytic agents or between low-dose or high-dose rtPA.

Authors’ conclusions
Despite the volume of data having doubled since 1995, the magnitude of the risks and benefits of rtPA remains imprecise. New trials are needed to fill this gap in knowledge, which may be hindering the clinical use of rtPA.

CRD commentary
The review question was clear in terms of the study designs, participants, interventions and outcomes of interest. The search strategy was adequate, with unpublished data sought from various sources, and no language restrictions appear to have been applied. It is therefore less likely that bias due to publication or language was introduced into the review. One reviewer assessed the relevance of studies for the review; assessment in duplicate would have been preferable to reduce the potential for reviewer bias or error. However, the data extraction and validity assessment were carried out by one reviewer, but cross-checked and verified with the principal investigator of each trial, thus reducing the potential for reviewer bias or error. The criteria used for assessing validity were appropriate.

No details of the individual studies were given, although the authors referred readers to a related Cochrane Review for further information. The methods used to combine the trials appear to have been appropriate. Statistical heterogeneity was assessed and subgroup analyses were performed. This was a well-conducted systematic review and the authors' conclusions are supported by their findings.

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

Research: The authors stated that the evidence to date on rtPA in stroke is encouraging, but not persuasive, and that further large-scale trials are required.

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