Efficacy of intra-arterial fibrinolysis for acute ischemic stroke: meta-analysis of randomized controlled trials

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CRD summary
This review found that intra-arterial fibrinolysis significantly increased re-canalisation rates and the attainment of good and excellent clinical outcomes in patients with acute ischaemic stroke; the increased frequency of haemorrhage was not associated with an increase in mortality. The review was well conducted and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To evaluate the use of intra-arterial fibrinolysis in the treatment of acute ischaemic stroke

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were searched to August 2009 for relevant studies; search terms were reported. The World Health Organisation and the Internet Stroke Center were searched for ongoing clinical trials. There were no language restrictions. Reference lists of all relevant trials and review articles were checked to identify additional studies.

Study selection
Randomised controlled trials (RCTs) that evaluated the use of intra-arterial fibrinolysis in patients with ischaemic stroke were eligible for inclusion. Eligible trials had to report on clinical outcomes using a modified Rankin Scale at 90 days or at the trial end point. Patients were included who received additional intravenous fibrinolysis but trials were excluded if the control group received an active therapy not used in the treatment group.

The primary outcomes were the achievement of good clinical outcomes (mRS score from 0 to 2 or nearest equivalent) and excellent (mRS scores between 0 and 1 or nearest equivalent) at 90 days or at the trial end point.

The mean age of included patients ranged from 61 to 68 years; the percentage of females ranged from 37.5 to 64.9% of the populations in the trials. All but one of the trials enrolled patients with anterior circulation ischaemic stroke with a treatment time window of within six hours; the remaining trial enrolled patients with posterior circulation ischaemic stroke with a treatment time window of within 24 hours. The baseline median or mean National Institutes of Health Stroke scales ranged from 14 to 25. The fibrinolytic agents used in the included trials were pro-urokinase and tissue plasminogen activator. Four trials compared intra-arterial fibrinolysis with controls; one trial compared intra-arterial combined with intravenous fibrinolysis.

Two reviewers independently selected the studies for inclusion in the review.

Assessment of study quality
Methodological quality of the included trials was evaluated by two reviewers using a 100-point scale used by Liebeskind et al, which assessed randomisation, outcome, inclusion and exclusion criteria, the description of the therapeutic regimen, and the use of statistical analyses.

Data extraction
Two reviewers independently extracted data for the outcomes to calculate odds ratios (OR) and 95% confidence intervals (CI). The data were assessed by the reviewers using intention-to-treat analyses. Any discrepancies were resolved by discussion with a third reviewer.

Methods of synthesis
Pooled odds ratios and 95% confidence intervals were calculated using a Peto fixed-effects model. Statistical heterogeneity was assessed using the χ² and I² tests. The results from the fixed-effects model were compared with
random-effects models for the same outcomes. Numbers-needed-to-treat (NNT) for each outcome were also calculated for the primary outcomes.

Sensitivity analyses were performed to examine the influence of each trial.

**Results of the review**

Five RCTs (n=395 patients) were included in the review. Sample sizes ranged from 16 to 180 patients. Allocation concealment and randomisation were reported in four trials. Trial quality scores ranged between 43 to 86 out of 100. Four trials reported adequate allocation concealment. Follow-up durations across the trials ranged from 90 days to 12 months. The results reported below are for fixed-effects models, but the results of random-effects models were similar.

There were statistically significant benefits observed with intra-arterial fibrinolysis in the attainment of increased "good" clinical outcomes (OR 2.05, 95% CI 1.33 to 3.14; NNT=6.8) and attainment of "excellent" clinical outcomes (OR 2.14, 95% CI 1.31 to 3.51; NNT=7.7). In the analysis that excluded the trial combining intra-arterial and intravenous fibrinolysis, there were similar benefits observed compared with control treatment (OR 1.83, 95% CI 1.14 to 2.92).

Additional significant benefits observed with intra-arterial fibrinolysis were higher frequencies of minimal neurological deficit (OR 2.24, 95% CI 1.27 to 3.95), minimal impairment of activities of daily living (OR 1.60, 95% CI 1.01 to 2.51), partial or incomplete re-canalisation (OR 6.42, 95% CI 3.67 to 11.24) and complete re-canalisation (OR 4.62, 95% CI 2.02 to 10.56).

Compared with control treatment, with intra-arterial fibrinolysis was associated with increased radiological intracerebral haemorrhage (OR 3.37, 95% CI 1.90 to 5.95) and symptomatic intracerebral haemorrhage (OR 2.87, 95% CI 1.21 to 6.83), but there were no differences in mortality between the groups.

There was no statistically significant heterogeneity observed across the trials for the outcomes examined.

The results of the sensitivity analyses did not differ from those of the overall analysis for the outcomes.

**Authors' conclusions**

Intra-arterial fibrinolysis significantly increased re-canalisation rates and the attainment of good and excellent clinical outcomes in patients with acute ischaemic stroke; the increased frequency of haemorrhage was not associated with an increase in mortality.

**CRD commentary**

The review addressed a clear question. Criteria for the inclusion of studies were clearly stipulated. Appropriate databases were searched, with no language restrictions; unpublished studies were sought. Steps were taken to minimise errors and bias at each stage of the review process.

The decision to combine the results in a meta-analysis appeared to be justified, particularly given the lack of statistical heterogeneity across the trials.

The review was well conducted and the authors' conclusions are likely to be reliable.

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

The authors did not state any implications for research or practice.

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