Meta-analysis of randomized intra-arterial thrombolytic trials for the treatment of acute stroke due to middle cerebral artery occlusion

Fields JD, Khatri P, Nesbit GM, Liu KC, Barnwell SL, Lutsep HL, Clark WM, Lansberg MG

CRD summary
The review concluded that intra-arterial thromboloytic treatment within six hours of symptom onset substantially improved all functional outcomes after acute stroke from middle cerebral artery blockage. Despite an increased risk of symptomatic intracerebral haemorrhage, there was no effect on mortality. The review process and reporting had limitations, so the authors' conclusions should not be considered as likely to be reliable.

Authors' objectives
To estimate the benefit of intra-arterial administration of thromboloytics for the treatment of acute stroke due to middle cerebral artery occlusion.

Searching
PubMed was searched. Bibliographic references were scanned. This was supplemented by the authors' knowledge of the literature.

Study selection
Randomised controlled trials (RCTs) of intra-arterial administration of thromboloytics versus placebo for the treatment of acute stroke due to middle cerebral artery occlusion were eligible for inclusion.

All included trials treated patients within six hours of symptom onset. The thrombolytic drugs used were urokinase (600,000U maximum) and recombinant pro-urokinase (6 or 9mg); heparin doses varied. Mean patient ages ranged from 64 to 68 years. Different definitions for symptomatic intracranial haemorrhage were used across trials.

The authors did not state how many reviewers selected studies.

Assessment of study quality
The authors did not report an assessment of trial quality (although level of blinding was reported).

Data extraction
Intention-to-treat data were extracted (where possible) to calculate odd ratios (OR) with 95% confidence intervals (CI).

The authors did not state how many reviewers extracted data.

Methods of synthesis
Meta-analyses were performed to calculate pooled odds ratios, using a fixed-effect model. Heterogeneity was assessed using $I^2$. Absolute risk reductions (ARR) were also calculated.

Results of the review
All results were from pooling the three included RCTs (334 patients). One trial was reported as being double-blind and two were single-blind (where only follow-up assessment was blinded).

At 90 days' follow-up, patients treated with intra-arterial administration of thromboloytics were significantly more likely to have a modified Rankin scale score of 1 or under (OR 2.0, 95% CI 1.2 to 3.4; ARR 10.9%), a modified Rankin scale score of 2 or under (OR 1.9, 95% CI 1.2 to 3.0; ARR 12.4%) and a National Institutes of Health Stroke Scale score of 0 or 1 (OR 2.4, 95% CI 1.3 to 4.4; ARR 10.7%). The risk of symptomatic intracranial haemorrhage was increased with intra-arterial administration of thromboloytics (OR 4.6, 95% CI 1.3 to 16; absolute risk increase 8.1%). There was no significant difference between treatments for mortality at 90 days.

None of the major outcome variables showed evidence of heterogeneity ($I^2=0\%$).
Authors' conclusions
Intra-arterial administration of thrombolotics within six hours of symptom onset substantially improved all standard measures of functional outcome after acute stroke. Despite an increased risk of symptomatic intracerebral haemorrhage there was no effect on mortality.

CRD commentary
The review question and inclusion criteria were clear, although placebo was used in only one trial, despite being pre-specified in the review inclusion criteria. Only one database was searched, which meant relevant studies may have been missed. Search strategy details were not reported, so it was not possible to evaluate how comprehensive the PubMed search was. It was also possible that the review may have been subject to language and/or publication bias (relevant details were not reported). The authors did not report using methods which could minimise the risk of reviewer error and bias during the review process (such as independent duplicate study selection and data extraction).

Trial quality was not appraised, so it was not possible to fully evaluate the reliability of the trial evidence (although the lack of blinding of patients and care-providers may have resulted in performance bias affecting those trials). Appropriate methods were used to pool data and assess heterogeneity.

In light of the limitations in the conduct and reporting of the review, the authors' conclusions should not be considered as likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the review provided stronger evidence that intra-arterial administration of thrombolotics was likely to be safe and effective within six hours of stroke due to middle cerebral artery occlusion in patients ineligible for intravenous recombinant tissue plasminogen activator.

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

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