Intravenous recombinant tissue plasminogen activator administered after 3 h following onset of ischaemic stroke: a metaanalysis

Maiser SJ, Georgiadis AL, Suri MF, Vazquez G, Lakshminarayan K, Qureshi AI

CRD summary
The review found that treatment with intravenous recombinant tissue plasminogen activator (IV rtPA) administered three to 4.5 hours following onset of an ischaemic stroke was associated with a higher rate of favourable outcomes at 90 days. Limitations of the review process and the limited evidence base mean that the findings should be interpreted with caution.

Authors' objectives
To assess the efficacy and safety of intravenous recombinant tissue plasminogen activator (IV rtPA) administered three to six hours following the onset of an ischaemic stroke on functional outcome and mortality.

Searching
MEDLINE, BIOSIS, The Cochrane Library and Stroke Trials Registry were searched from inception to October 2008. No language restrictions were applied. Search terms were listed in the review. A further search of Stroke and Cardiovascular Trials databases was performed. Bibliographies of identified studies and review articles were searched. Proceedings of neurology and cerebrovascular disease related conferences were searched.

Study selection
Randomised controlled trials (RCTs) of 0.9mg/kg IV rtPA given three to six hours following onset of an acute ischaemic stroke were eligible for inclusion. To be eligible, the control group had to receive a pharmacological placebo. Trials had to have emergent neuroimaging and exclude patients with intracranial haemorrhage. Definitions of intracranial haemorrhage differed in each trial and were reported in the review. Studies needed to have data available on onset to treatment time (OTT), baseline National Institutes of Health Stroke Scale Score (NIHSS), functional outcome and mortality at three months follow-up.

In the included studies (performed between 1993 and 2007), mean/median age ranged from 64.9 to 72.2 years, the proportion of men ranged from 53% to 63.6%, mean/median baseline NIHSS score ranged from 10 to 14 and the mean/median OTT ranged from 238 to 328 minutes. The imaging test used was either computed tomography (CT) or CT/magnetic resonance imaging (MRI).

One reviewer performed the study selection, which was verified by a second reviewer.

Assessment of study quality
The authors did not state that they assessed validity, but they reported on randomisation and use of intention-to-treat analyses.

Data extraction
Data from intention-to-treat analyses were extracted where these did not include patients treated with rtPA less than three hours following stroke onset or where studies were based on such patients, data relevant to the review were extracted. Follow-up was defined as 90 days (also refered to in the review as three to six months).

One reviewer performed the data extraction, which was verified by a second reviewer.

Methods of synthesis
The studies were combined using a random-effects meta-analysis based on DerSimonian and Laird's method to estimate pooled odds ratio (OR) and 95% confidence intervals (CI). Heterogeneity between studies was assessed using the $I^2$ statistic. A subgroup analysis was performed to investigate whether the timing of treatment (three to 4.5 hours or 4.5 to
Results of the review

Four trials (2,104 patients) were included in the review. Sample sizes ranged from 100 to 821. The trim-and-fill method to assess publication bias suggested that one RCT might have been missed from the review. The funnel plot was not presented in the review.

Compared to placebo, patients who received IV rtPA three to six hours following onset of ischaemic stroke had a higher chance of favourable neurological outcome at follow-up (OR 1.24, 95% CI 1.04 to 1.47; four trials), with no evidence of heterogeneity. There was no difference in terms of mortality between the IV rtPA and placebo groups. There was no evidence of statistical heterogeneity between the studies and no difference in effect according to the timing of treatment.

The beneficial effect of IV rtPA on neurological outcome was greater when given three to 4.5 hours post onset (OR 1.27, 95% CI 1.01 to 1.60; three trials) and not significantly different from placebo when given at 4.5 to six hours (two trials). However, the test of effect modification between the two time periods was not significant (p=0.42).

Symptomatic intracranial haemorrhage was higher in patients who received IV rtPA compared to those who received placebo (OR 3.01, 95% CI 1.99 to 4.55; four trials), with no evidence of statistical heterogeneity between studies.

Authors’ conclusions

Treatment with IV rtPA three to 4.5 hours post stroke onset was associated with a higher rate of favourable neurological outcomes at 90 days, but there was no beneficial effect with IV rtPA treatment given between 4.5 and six hours post stroke onset.

CRD commentary

The study question was clear. Eligibility criteria were well defined and appropriate. The search covered several databases and was likely to have identified most relevant published studies. Publication bias was assessed, but as so few studies were included the reliability of the findings was questionable.

Definition of intracranial haemorrhage varied between studies and was assessed by CT in two studies and CT/MRI in two others. Duration of follow-up in the included studies was not clear, as it was defined in the review as 90 days and as three to six months. The evidence base was limited by the identification and inclusion of only four studies.

No validity assessment was performed, so the quality of the included studies was unclear. The meta-analysis was appropriate. The authors based their conclusions on a subgroup analysis, despite the test for significance between subgroups not being significant. The authors did not comment on the observation that symptomatic intracranial haemorrhage was more common in patients who received IV rtPA compared to placebo.

Limitations of the review process and the limited evidence base mean that the findings should be interpreted with caution.

Implications of the review for practice and research

Practice: The authors stated that patients who presented three to 4.5 hours after stroke symptom onset can benefit from IV rtPA, but data do not support treatment of those who presented 4.5 to six hours after onset.

Research: The authors stated that improved imaging techniques and clinical selection criteria were required in further studies.

Funding

None stated.
Bibliographic details

PubMedID
21205237

DOI
10.1111/j.1747-4949.2010.00537.x

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Adult; Aged; Aged, 80 and over; Brain Ischemia /complications /drug therapy /mortality; Clinical Trials as Topic; Female; Fibrinolytic Agents /administration & dosage /therapeutic use; Humans; Injections, Intravenous; Magnetic Resonance Imaging; Male; Middle Aged; Nervous System Diseases /etiology /prevention & control; Plasminogen Activators /administration & dosage /therapeutic use; Randomized Controlled Trials as Topic; Stroke /drug therapy /etiology /mortality; Time Factors; Tissue Plasminogen Activator /administration & dosage /therapeutic use; Tomography, X-Ray Computed; Treatment Outcome; Young Adult

AccessionNumber
12011000932

Date bibliographic record published
11/05/2011

Date abstract record published
02/11/2011

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.