Do iodinated contrast agents impair fibrinolysis in acute stroke? A systematic review

Dani KA, Muir KW

CRD summary
The authors concluded that recanalisation rates were not significantly different in patients undergoing thrombolysis for acute stroke who received iodinated contrast agents versus those who did not. The limited search, potential for reviewer error and bias, and lack of direct comparison between groups exposed and not exposed to contrast agents mean that review findings may not be reliable.

Authors' objectives
To evaluate the effect of iodinated contrast media on rates of recanalisation of an occluded artery after an acute ischaemic stroke treated with thrombolytic drugs.

Searching
MEDLINE and EMBASE were searched from inception to 2006 (week 40) for studies published in English. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) and observational studies of male and female patients of any age with an acute anterior circulation stroke were eligible for inclusion. Studies had to report the absolute number of patients with documented occlusion who recanalised after intravenous thrombolytic therapy; recanalisation had to be shown on imaging and could be partial or complete.

The review compared recanalisation rates for studies that used iodinated contrast media with studies that did not use iodinated contrast media.

Included studies evaluated recanalisation using transcranial Doppler sonography, magnetic resonance angiography, computed tomographic angiography and digital subtraction angiography. Most studies used the recombinant tissue plasminogen activation regimen in the National Institute of Neurological Disorders and Stroke protocol. Timing of recanalisation assessment ranged from immediately post-thrombolysis to seven days. Occlusion sites varied; most were in the M1, M2 branch of the middle cerebral artery.

One reviewer selected studies.

Assessment of study quality
One reviewer assessed validity using fourteen criteria from a validated checklist. The criteria included: adequate description of study question; sample characteristics; randomisation; appropriate and clearly described study design and sample selection methods; blinding of investigators and patients; well defined outcome and exposure measures; appropriate sample size; appropriate and clearly reported analysis; variance reported; control for confounders; adequate reporting of results; and results supported by conclusions.

Data extraction
One reviewer extracted the absolute numbers and proportions of patients who recanalised for studies using and studies not using iodinated contrast media. Some authors provided additional information. Vessel occlusion graded 0 or 1 (on the Thrombolysis in Myocardial Infarction or Brain Ischaemia scales) were classified as failed recanalisation. Where upper time limits for thrombolysis were unclear, these were estimated as the mean time plus two standard deviations.

Methods of synthesis
Weighted pooled proportions of patients who recanalised were calculated for studies using and studies not using iodinated contrast media, using a random-effects DerSimonian and Laird model. Statistical heterogeneity was assessed using the I² statistic, with values of more than 75% considered to indicate high heterogeneity.
Subgroup analyses were conducted on patients with site of occlusion in the M1 or M2 segment of the middle cerebral artery, patients with recanalisation evaluated at late time points (defined as 24 hours or later), and cohort studies. Results for the analysis of cohort studies were not reported.

Random-effects meta-regression and unrestricted maximum likelihood estimates for between study variance were used to examine the influence of differences in the upper time limit of thrombolysis.

Results of the review

Eighteen studies were included in the review (n=765 patients reported in table). These included four randomised controlled trials (RCTs, n=63 patients), one non randomised controlled trial (n=26 patients), nine prospective cohort studies (n=543 patients), three retrospective cohort studies (n=109 patients) and one case-control study (n=24 patients). The number of relevant patients per study ranged from three to 219. Eight studies were considered to meet all quality criteria; six studies failed to meet just one criterion.

None of the RCTs directly compared iodinated contrast media with no iodinated contrast media. Six studies used iodinated contrast media (n=143 patients) and 12 did not use iodinated contrast media (n=622 patients).

Pooled proportions of recanalisation were 53% (95% CI 36 to 70) for iodinated contrast media groups and 61% (95% CI 52 to 71) for groups without iodinated contrast media. No significant statistical heterogeneity was found.

Pooled proportions for middle cerebral artery occlusions (M1 and M2) were 66% (95% CI 49 to 82%; three studies) for iodinated contrast media groups and 63% (95% CI 52 to 74; significant statistical heterogeneity was found, I²=83%; nine studies) for groups without iodinated contrast media.

Pooled proportions for studies assessing late recanalisation (24 hours or later) were 66% (95% CI 54 to 77; four studies) for iodinated contrast media groups and 67% (95% CI 51 to 82; significant statistical heterogeneity was found, I²=85%; eight studies) for groups without iodinated contrast media.

Meta-regression found no significant effect of the upper time limit for thrombolysis.

Authors’ conclusions

Recanalisation rates were not significantly different in patients undergoing thrombolysis for acute stroke who received iodinated contrast agents compared with those who had not received contrast agents.

CRD commentary

The review question was clearly stated and inclusion criteria were appropriately defined. Limiting the search to English language reports listed in two databases increased the potential for missing studies and that for publication and language bias; the potential for language bias was acknowledged by the authors. Only one reviewer selected studies, extracted data and assessed validity, leaving review processes open to reviewer error and bias.

Study quality was assessed and the results were reported. Results for studies using and not using contrast agents were summarised by pooling heterogeneous data; such summary estimates do not reflect the wide range of values in individual studies. The authors acknowledged that the use of indirect evidence and heterogeneity meant that review findings should be regarded with caution.

The limited search, potential for reviewer error and bias, differences between studies, and the lack of direct comparison between groups exposed and not exposed to contrast agents mean that review findings may not be reliable.

Implications of the review for practice and research

Practice: The authors stated that, based on review findings, they could not recommend not using contrast agents when they were considered to be clinically useful.

Research: The authors stated that for any adequately powered study to directly compare recanalisation rates with and
without iodinated contrast media, a large number of patients would probably be needed (estimated at between 240 and 10,000 to detect a 3% to 16% difference in recanalisation rates with a power of 80% and significance level of 0.05).

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