A systematic review of intra-arterial thrombolytic therapy for lower-limb ischaemia

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Authors' objectives
To determine the relative effectiveness of intra-arterial thrombolysis compared to surgery for the treatment of lower-limb ischaemia.

Searching
A search of the MEDLINE from 1980 to 1998, EMBASE, CINAHL, Biological Abstracts, Science Citation Index and The Cochrane Library (years not stated) was carried out to identify randomised controlled trials of intra-arterial thrombolytic therapy in the treatment of limb ischaemia. Details of the keywords used are provided in an appendix. In addition, key journals were handsearched (names of journals not provided) and citations were also reviewed. The search was limited to English language articles, or those that provided a sufficiently detailed English summary, and to articles published after 1980.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs).

Specific interventions included in the review
Intra-arterial thrombolysis (streptokinase, urokinase, and tissue plasminogen activator ((r)t-PA)) compared to surgery. Some studies also compared different doses/modes of administration of (r)t-PA, or different types of thrombolysis.

Participants included in the review
People with lower-limb ischaemia. In the individual studies, inclusion criteria were people who had lower-limb ischaemia of less than six months duration or patients with acute lower limb peripheral artery occlusion of less than 14 - 30 days duration.

Outcomes assessed in the review
Adverse events such as death/major amputation and post-intervention wound complications. Also mortality, amputation ischaemia, and life-threatening haemorrhage. Mean length of hospital stay and duration of ischaemia was also evaluated in some studies.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The quality of the included studies was determined using a proforma based on the CONSORT statement (see Other Publications of Related Interest nos.1-2) and Cochrane Collaboration checklists. The proforma graded studies for inclusion by assessment of: method of randomisation and degree of blinding; comparability of groups in control and intervention arms at baseline; the analysis of results on an intention to treat basis; completeness of follow-up; the blinding and objectivity of outcome assessment; the appropriateness and completeness of statistical analysis of results, including sensitivity analysis. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
Two reviewers independently performed data extraction and cross-checked for accuracy. Data were extracted on method of randomisation, setting, participants, interventions, baseline comparability, results, and withdrawals.
Methods of synthesis
How were the studies combined?
Aggregate outcomes were obtained by calculating a summary odds ratio (OR) and using a random effects meta-analysis. A narrative summary was also provided.

How were differences between studies investigated?
Heterogeneity was tested using the chi-squared test at a significance level of p<0.1.

Results of the review
Nine RCTs with a total of 1838 participants

Meta-analysis showed no significant differences between thrombolysis and surgery in terms of major amputation (relative risk (RR) 0.893, 95% confidence interval (CI): 0.576, 1.383) and mortality (RR 1.24 95% CI: 0.795, 1.9). However, there was an increased risk of haemorrhage with thrombolysis (RR 2.94 95% CI: 1.1, 7.9). Sub-group analysis suggests that short-duration occlusions (relative risk reduction (RRR) 72%, numbers needed to benefit (NNB)=3) and occluded grafts (RRR 58%, NNB=4) may benefit from thrombolysis. However, thrombolysis should be avoided in occlusions of greater than 14 days - particularly native vessel occlusions.

Cost information
The authors report that two US studies, using hospital data, evaluate the cost-effectiveness of thrombolytic therapy compared to surgery (actual data not reported).

Authors' conclusions
Despite the theoretical advantages of thrombolysis, there is still insufficient evidence to justify its widespread use except in graft occlusions and short-duration ischaemia.

CRD commentary
This is a well-written review with clear inclusion criteria and a reasonable search strategy. However, the search is limited to English language trials and no attempt is made to search for unpublished trials. Thus the possibility of publication bias cannot be ruled out. The methods of the review are not clearly stated, and although the quality of the included studies is assessed, it is not reported in the results of the review, or taken into account in the analysis. Given the above limitations, the authors' conclusions appear to follow on from the results of the review.

Implications of the review for practice and research
Practice: The authors state that these findings demonstrate that there may be situations in which thrombolysis is the appropriate form of treatment, but that used inappropriately it may result in sub-optimal results. Such findings support the need for a multidisciplinary-team approach to the management of acute limb ischaemia that will take into account the range of surgical and radiological options that are available for an individual patient. Such an approach may have a significant impact on the organisation of vascular services.

Research: The authors state that new trials of short duration occlusions of grafts with sufficient sample sizes are required.

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