Tissue plasminogen activator for the treatment of deep venous thrombosis of the lower extremity: a systematic review

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Authors' objectives
To provide a summary of the evidence of the efficacy (short-term venographic patency), safety (major and minor haemorrhage, pulmonary embolism), optimal dose, and route of administration of recombinant tissue plasminogen activator (rt-PA) in the treatment of lower-extremity deep vein thrombosis (DVT).

Searching
MEDLINE was searched from 1966 to September 1999, and Current Contents from 1997 to week 33, 1999. The search terms were listed in the paper. The authors of the included trials were contacted and the bibliographies of the identified papers were searched. Pharmaceutical companies who manufacture rt-PA were contacted for unpublished information.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials only were included.

Specific interventions included in the review
rt-PA. Studies were included if they compared the following: rt-PA plus unfractionated heparin with unfractionated heparin alone; local versus systemic administration of rt-PA; and high-dose (0.5 mg/kg per day) versus low-dose (0.25 mg/kg per day) rt-PA administration.

Participants included in the review
Only studies evaluating patients with lower leg DVTs were included.

The patients were included if they had a DVT diagnosed within the 14 days prior to treatment. No information on the age or gender of the included patients, or of any risk factors or co-morbidities, was given.

Outcomes assessed in the review
For inclusion, the study had to describe efficacy in terms of the percentage of thrombus lysed and describe the complications in detail. The outcomes assessed were:

the percentage of lysis of the clot as evidenced from a venogram (greater than, or less than or equal to 50%);

all complications, including those which required discontinuation of therapy;

major haemorrhage, which was defined as a drop in haemoglobin of greater than 2 g/dL, a haemorrhage requiring blood transfusion, or a clinically overt intracerebral, intra-articular, retroperitoneal intra-ocular, or gastrointestinal haemorrhage; and

minor bleed, pulmonary embolism, and other complications.

How were decisions on the relevance of primary studies made?
There was no information on who made the decisions regarding the relevance of the primary studies.

Assessment of study quality
The quality of the trials was assessed using the scale of Jadad et al. (see Other Publications of Related Interest). Those scoring less than 3 (i.e., considered to be of a low quality) were to be excluded from the review, although no such studies were identified. Both authors reviewed the studies for the quality assessment. It was not stated whether this was
performed independently, or whether the reviewers were blind to the source.

**Data extraction**

Both authors reviewed the included studies, although it was not stated whether this was conducted independently. Data were abstracted using standardised forms. The following data were tabulated from each study: the number of patients; inclusion criteria (diagnosis within 'n' days of symptoms); intervention (dosage and route of administration of therapy); outcome (efficacy and complications), and quality score.

**Methods of synthesis**

- **How were the studies combined?**
  The studies were combined according to the outcome measures, so not all of the studies were included in each set of combined results. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method.

- **How were differences between studies investigated?**
  Differences between the studies, in terms of the inclusion criteria, method of administration and outcome assessment, were described in the text. The heterogeneity was not formally investigated.

**Results of the review**

Six trials reported in 5 papers were included in the review. It was unclear whether the total number of participants was 352 or 322, since the number of participants in one paper was reported differently in the text and in the table. Four trials assessed rt-PA plus heparin versus heparin alone (n=169 or 139); one assessed local versus systemic administration of rt-PA (n=151); and one assessed high- versus low-dose rt-PA (n=32).

Patients treated with rt-PA in addition to heparin were more likely to have greater than 50% lysis of the thrombus, compared with those treated with heparin alone (OR 11.7, 95% CI: 2.61, 52.5). However, that treatment regime was also significantly associated with a higher risk of adverse events (OR 9.95, 95% CI: 2.21, 44.72). The odds of a major haemorrhage and intracranial haemorrhage were raised in the groups receiving rt-PA, although the results did not reach conventional levels of statistical significance; the ORs were 2.52 (95% CI: 0.48, 13.29) and 1.55 (95% CI: 0.03, 989.8), respectively. This final result was based on one instance of an intracranial haemorrhage. The number-needed-to-treat to achieve one clot lysis was 3.83, and each 4.10 treated patients would result in one harmed patient (all complications).

No differences in outcome were noted when comparing high- and low-dose administration of rt-PA (OR 0.88, 95% CI: 0.02, 36.01). In addition, no statistically-significant differences in complication rate were noted (OR 5.04, 95% CI: 0.89, 31.43). These are the results of one study.

No differences in outcome were noted when comparing local and systemic administration of rt-PA (OR 0.82, 95% CI: 0.38, 1.77). In addition, no statistically-significant differences in complication rate were noted (OR 1.71, 95% CI: 0.78, 3.79). These are the results of one study.

**Authors' conclusions**

The evidence did not support the routine use of rt-PA in patients with lower extremity DVT. Although such treatment does increase the venographic patency, the increased risk of complications among patients given rt-PA does not justify a change in practice. The authors also stated that higher doses of rt-PA do not appear to be more efficacious and are possibly more dangerous than lower doses. Locally-administered rt-PA may have more complications and is no more effective than systemic administration.

The authors suggested that rt-PA may be of use among subgroups of patients, such as those with limb-threatening thrombosis, if the risk of bleeding was not excessive. However, this would be need to be examined in a randomised multicentre trial.
CRD commentary
This systematic review was carried out relatively well, although only a small number of studies could be included. The review question was pertinent, and the inclusion criteria were relevant to the question. The search strategy was inadequate, as EMBASE was not searched and the search terms used may have been limiting. One of the pharmaceutical companies contacted searched EMBASE, and identified two studies missed by the reviewers. Despite this, the reviewers made no attempt to repeat their search using other databases. Since review articles were excluded, studies referenced in their bibliographies may also have been missed. These observations suggest that the search process was not sufficiently thorough.

The validity of the studies was assessed by one person. Details of the studies excluded on the basis of validity were listed, and the reasons for their exclusion appear to have been valid. The quality of the included trials was judged on a frequently used scale. However, insufficient data were presented to allow assessment of this in the review, and some of the presented data suggest that the included trials may not have been of a high methodological rigour. For example, one study had 53 patients in the active group and 12 in the control group; no explanation for this discrepancy was provided.

Few details of the primary data, such as the age, gender or other risk factors of the included patients, were given. The numbers of participants in two trials (one paper) differed between the text and the table.

The data pooling was adequate, but no investigation of statistical heterogeneity was reported. In addition, there was no information on the modifying effects of patient attributes, although it is unclear whether this is because these data were unavailable from the primary data sources.

The following limitations of the study were acknowledged by the authors: the clinical importance of the outcomes used in the review (50% clot lysis; all complications, including minor haemorrhage) was unknown;

the review suffered from a lack of power to detect an increased risk in major complications;

the inclusion of patients with older and recent symptoms may have decreased the ability to detect an influence of treatment (older clots are less responsive);

two studies included patients who had clots post-operatively. The authors state that thrombolytic agents should not be used in this case.

The conclusions made by the authors regarding efficacy of rt-PA, i.e. that the weight of evidence does not support the routine use of rt-PA, are not qualified given the limitations of the inadequate search strategy and possible methodological problems of the included studies. Furthermore, recommendations on dose comparisons and route of administration were made on the basis of one study of each. This ought to have been emphasised more strongly in the conclusions.

Implications of the review for practice and research
Practice: The authors conclude that the evidence does not support the routine use of rt-PA in patients with lower extremity DVT. This implies that no changes to current practice, i.e. use of heparin only, is warranted.

Research: The authors state that a randomised multicentre trial is needed to assess the efficacy of rt-PA for certain patient subgroups who may benefit from this treatment.

Reviewer's comment: It is the opinion of this abstract reviewer that further work in the area of dose comparisons and route of administration is needed, before the results from one study are accepted as definitive.

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