The safety, efficacy, and pharmacoeconomics of low-dose alteplase compared with urokinase for catheter-directed thrombolysis of arterial and venous occlusions


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Two catheter-directed therapies for the treatment of acute peripheral arterial occlusive disease (PAO) and deep vein thrombosis (DVT) were examined. The therapies were a low-dose (<=2 mg/hour) of alteplase (a tissue plasminogen activator, t-PA) versus urokinase (URK). Recommended dosages were used.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with PAO and DVT. The inclusion criteria were acute (less than 14 days) limb ischaemia (International Society for Cardiovascular Surgery/Society for Vascular Surgery classification I-3 or II), or acute (<=30 days) symptomatic DVT of the limb in patients who underwent catheter-directed therapy with URK or t-PA.

Setting
The setting was a hospital. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness and resource use data were gathered from October 1997 to February 1999 for URK patients, and from December 1998 to June 2000 for t-PA patients. The prices were estimated in 1998 and 1999.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was conducted retrospectively on the same sample of patients as that included in the effectiveness study.

Study sample
Power calculations were not reported. Details of the methods used to select the sample were not provided. A sample of 89 patients with 93 treated extremities was considered. There were 45 cases in the t-PA group and 48 cases in the URK group. The t-PA group had a mean age of 52.2 (+/- 19.6) years and comprised 51.1% women. There were 24 cases with DVT and 21 with PAO. The URK group had a mean age of 53.6 (+/- 19.) years and comprised 54.2% women. There
were 30 cases with DVT and 18 with PAO. It was not stated whether some patients were excluded for any reason from the initial study sample.

**Study design**
This was a retrospective cohort study that was conducted at a single centre (details not provided). The length of follow-up was not reported. The duration of therapy depended on the results of the follow-up angiograms. No patients appear to have been lost to the follow-up assessment. No details of the outcome evaluation were provided.

**Analysis of effectiveness**
It appears that all the patients included in the initial study sample have been accounted for in the analysis of effectiveness. The health outcomes used were:

- thrombolytic success, defined as complete or partial lysis with PAO (improvement of the International Society for Cardiovascular Surgery/Society for Vascular Surgery scale by one or more classifications) or DVT (resolution of the acute pain and oedema of the extremity after intervention); and
- rate of major or minor complications.

Major complications were defined as death, intracranial haemorrhage, or bleeding requiring transfusion or surgery, or an increase in length of hospital stay. Minor complications were defined as adverse events requiring only conservative therapy, such as small access site haematomas.

Infusion-related outcomes, such as the hourly-infused dose, total drug dose, and infusion time, were also assessed. A multivariate regression analysis was conducted to identify potential predictors of thrombolytic complications. The study groups were comparable at baseline in terms of their demographics and disease characteristics.

**Effectiveness results**
The complete and partial thrombolytic success rate for the whole sample was 88.9% with t-PA (87.5% for DVT and 90.5% for PAO) and 85.4% with URK (83.4% for DVT and 88.9% for PAO). These differences did not reach statistical significance.

Similarly, no statistically significant differences were observed in terms of major and minor complications. In particular, both groups had one major complication (1 patient receiving t-PA had spontaneous lower gastrointestinal bleeding and 1 patient receiving URK had a large access site haematoma).

There were no deaths, intracranial haemorrhages, need for intensive care unit monitoring, or surgical interventions in either group.

Four patients (8.9%) treated with t-PA and 5 (10.4%) with URK had minor bleeding events.

The infusion time was 24.6 (+/- 11) hours for t-PA and 33.3 (+/- 13.3) hours for URK, (p=0.0009), for the whole sample.

Similar results were obtained in the sub-groups of DVT and PAO patients.

The hourly-infused dose was 0.86 (+/- 0.50) mg/hour with t-PA and 13.5 (+/- 5.6) 4 U/hour with URK.

The total drug dose was 21.1 (+/- 15.1) mg with t-PA and 4.485 (+/- 2.394) million U with URK.

The multivariate regression analysis showed that none of the baseline factors was significantly associated with the rate of complications.
Clinical conclusions
The effectiveness analysis showed that the two groups were comparable in terms of efficacy and safety. However, the infusion times with t-PA were shorter.

Measure of benefits used in the economic analysis
No summary benefits measure was used in the economic analysis since the two interventions were considered equally effective. In effect, a cost-minimisation analysis was conducted.

Direct costs
Discounting was not relevant since the costs were incurred during a short timeframe. The unit costs were not presented separately from the quantities of resources used. The health services included in the economic evaluation were the study drugs only. The cost/resource boundary of the study was not reported. Resource use was estimated using actual patient-level data derived from the sample of patients that was involved in the effectiveness analysis. The drug costs were obtained from list prices in 1998 and 1999.

Statistical analysis of costs
Student's t-test was used to test the statistical significance of differences in the estimated costs.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were not carried out.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
Overall, the estimated drug costs were $466 (+/- 331) with t-PA and $6,871 (+/- 3,667) with URK. For DVT, the drug costs were $511 (+/- 331) with t-PA versus $7,408 (+/- 4,078) with URK, while for PAO they were $418 (+/- 334) versus $6,032 (+/- 2,833), respectively. The difference was statistically significant for each comparison, (p<0.0001).

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant since a cost-minimisation analysis was conducted.

Authors' conclusions
Tissue plasminogen activator (t-PA) was as effective and safe as urokinase (URK), but its costs were far lower and the infusion times in t-PA patients were faster.

CRD COMMENTARY - Selection of comparators
The authors justified the choice of the comparators in their analysis. URK was considered as the standard approach for
a long time, while t-PA was used as an alternative treatment because of the possible risks associated with URK. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on a retrospective review of patients' charts. Since the outcomes were estimated in two different timeframes, some factors other than the study interventions could have affected the study results, despite the baseline comparability of the two groups of patients. Some time-related bias could also have been introduced. The authors controlled the impact of potential confounding factors on some outcome measures and, subsequently, it was found that none of them was a predictor of complications.

No justification for the sample size was given. In addition, it was unclear whether the study sample was appropriate for the study question, although the study groups appear to have been comparable in terms of demographics and disease characteristics. Limited information on the follow-up was provided. Further, the evidence came from a single centre. The method of selecting the patients was not described, thus it could not be assessed whether the study sample was representative of the patient population. These issues tend to limit the internal validity of the analysis.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-minimisation analysis was conducted.

Validity of estimate of costs
The perspective of the study was not explicitly reported, but only the drug costs were considered. The impact of the interventions on other health care resources was not investigated. This was mainly due to the equal efficacy of the two treatments. Therefore, it was implicitly assumed that services pertaining to, for example, the treatment of adverse events, were comparable. The source of the data was reported, as were the dates when resource use was collected. The unit costs were not presented. The cost estimates were specific to the study setting and no sensitivity analyses were conducted. Statistical tests were performed when the costs were compared. The years during which the costs were estimated were reported.

Other issues
The authors stated that their main findings, showing the equal efficacy of the two treatments, were consistent with those from published studies. The issue of the generalisability of the study results to other settings was not addressed and all the estimates were specific to the study setting. This affected the external validity of the analysis. The authors noted that the validity of their conclusions was limited by the study design.

Implications of the study
The authors stressed that the results of their analysis should be corroborated in a large, prospective, randomised, multi-centre, clinical trial.

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Other publications of related interest


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