Early thrombolysis for acute myocardial infarction

Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation

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Executive summary

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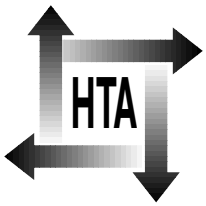

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Executive summary

Background

Coronary heart disease (CHD) is a major cause of morbidity and mortality in the UK accounting for around 125,000 deaths a year. Acute myocardial infarction (AMI) affects an estimated 274,000 people each year. Of these, approximately 50% (137,000) die within 30 days of AMI and over half these deaths occur prior to reaching hospital or other medical assistance.

The development and introduction of new pharmacological agents has made it necessary to review the clinical and cost-effectiveness of older and newer agents used for early thrombolysis. Those reviewed in this document include streptokinase, alteplase, reteplase and tenecteplase.

Objectives

To examine the clinical and cost-effectiveness of available drugs for early thrombolysis in the treatment of AMI in hospital and pre-hospital settings.

Methods

The search incorporated a number of strategies for clinical effectiveness and economic evaluation. The search strategy covered the period from 1980 to 2001 and included the following electronic databases: MEDLINE, EMBASE, Science Citation Index/Web of Science, Cochrane Trials Register, NHS Centre for Reviews and Dissemination Health Technology Assessment (NHS CRD HTA), Database of Abstracts of Reviews of Effectiveness (DARE) and NHS Economic Evaluation Database (NHS EED). Search terms included were **myocardial infarction/heart infarction** combined with specific drug terms including **alteplase**, **reteplase**, **streptokinase**, **tenecteplase**, **anistreplase** and **urokinase**. Reference lists of included studies and pharmaceutical company submissions to the National Institute for Clinical Excellence (NICE) were searched to identify other relevant studies.

In addition, a number of medical journals were handsearched to identify any newly published papers that might not yet have been indexed in electronic databases.

Study selection

Randomised controlled trials (RCTs) that included comparison of the specified drugs (alteplase, reteplase, streptokinase and tenecteplase) in the early stages of AMI delivered in the pre-hospital or hospital setting were included in the review. Studies that examined the use of anistreplase or urokinase were identified but not included in the analysis. Data on the following outcome measures were included in the review: mortality, bleeding, stroke, reinfarction, allergy and anaphylaxis.

Economic evaluation included studies reporting efficacy data primarily based on drug versus drug randomised controlled clinical evidence, explicit synthesis of costs and outcomes in a cost-effectiveness ratio, full economic evaluation.

Quality assessment

The methodological quality of studies for clinical effectiveness was assessed using the criteria based on the NHS CRD Report No. 4 (University of York, 1996).

The quality of cost-effectiveness was assessed using a checklist updated from that produced by Drummond and colleagues.*

Results

Clinical effectiveness

Hospital

A total of 162 references were identified to which the inclusion criteria were applied. Of these, 20 studies reported in 50 articles fulfilled the inclusion criteria. These included 14 comparative studies involving a total study population of 142,907 patients. Data from two studies were combined in the study reports and this combination of data is maintained in the review.

* Drummond M, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford Medical Publications; 1987.

Definitive conclusions on efficacy (30–35-day mortality) are that streptokinase is as effective as non-accelerated alteplase, that tenecteplase is as effective as accelerated alteplase, and that reteplase is at least as effective as streptokinase.

Some conclusions require interpretation of data, i.e. whether streptokinase is as effective as, or inferior to accelerated alteplase; and whether reteplase is as effective as accelerated alteplase or not.

Depending on these, two further conclusions on indirect comparisons arise, whether tenecteplase is superior to streptokinase or not, and whether reteplase is as effective as tenecteplase or not.

That these questions remain to be resolved illustrates that any differences in mortality between drugs is small.

There seem to be significant differences between drugs in incidence of stroke, with streptokinase having the lowest rate.

Streptokinase causes more allergic reactions than other drugs.

Pre-hospital

The search failed to identify any studies conducted in the pre-hospital setting that compared the effectiveness of different drugs. There is no reason to believe that the effectiveness of a drug will be altered by administration in the pre-hospital setting.

Nine RCTs that examined the efficacy and safety of pre-hospital thrombolysis were identified and are discussed. The required use of heparin with either of the bolus products does not seem to provide any practical barrier to their widespread use.

Cost-effectiveness and modelling

A detailed review of the economic literature was undertaken. Of the 107 articles assessed, only eight met the quality criteria that led them to be evaluated in detail. The general quality of economic analyses undertaken in this area was disappointing and largely focused on evaluating cost-effectiveness in healthcare environments outside the NHS.

A critique and re-analysis were also undertaken of the two detailed economic models contained in the industry submissions to NICE. Both models were rerun using the assumptions contained in the competitor model. In addition, they were re-analysed using a preferred set of coefficients that reflected, as far as possible, the weight of the available evidence.

Variations in quality-adjusted life-years (QALYs) gained between the individual drugs were small. Supposed advantages presented in the industry submissions to NICE largely related to comparatively minor variations in efficacy or minor improvements in aspects of the side-effect profile associated with each individual drug. Streptokinase was clearly the most cost-effective drug and other drugs were compared to it. Costs per QALY for newer drugs compared to streptokinase ranged up to £17,000. Given the similarity in outcome, cost-effectiveness becomes largely determined by the acquisition costs of the drug. This conclusion was robust to a range of variations in assumptions. In contrast to this robust conclusion, differences between alteplase, tenecteplase and reteplase were small and their relative ranking in cost-effectiveness changed according to the assumptions used.

Implementation

There are substantial opportunities for refining hospital thrombolysis procedures to meet National Service Framework (NSF) targets. Changing drugs is a very minor element in achieving improved door-to-needle time.

Pre-hospital thrombolysis will be necessary in some areas to allow NSF targets to be met. The choice of drug for pre-hospital thrombolysis is determined by acquisition cost and by convenience. Our experts did not wish to consider the use of infusion products (e.g. alteplase or streptokinase) but preferred bolus administration (reteplase and tenecteplase).

The cost-impact of switching to the more expensive bolus drugs could be as much as £50 million per year, over and above existing costs of approximately £30–40 million for the NHS in England and Wales.

Conclusions

Clinical effectiveness

The decision regarding which agent to use is therefore a balance of the risks and benefits related to mortality and stroke. No clear conclusion, based on statistical comparison, can be drawn. ▶

Economic evaluation

Given the similarity in outcome, cost-effectiveness becomes largely determined by the acquisition costs of the drug. This conclusion was robust to a range of variations in assumptions. Streptokinase was therefore the most cost-effective drug.

Publication

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NHS R&D HTA Programme

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