Thrombolytic and neuroprotective therapy for acute ischaemic stroke

A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS

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Executive summary

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Executive summary

Background

There is strong evidence that, for patients with acute stroke, admission to a stroke unit providing organised stroke care and rehabilitation saves lives and reduces disability. Medical treatments such as thrombolysis or neuroprotective agents, given within the first few hours of onset of ischaemic stroke, offer the prospect of at least moderate additional benefit. Most of the evidence of benefit of thrombolysis came from trials performed in healthcare systems that are rather different to the NHS. This review therefore aims to assess whether, when used in the NHS, these new agents are likely to be effective and cost-effective.

Objectives

The objectives of the current report are:

- to assess the effectiveness of thrombolytic drugs
- to assess the effectiveness of neuroprotective drugs
- to map current pathways of acute stroke care, identify barriers to implementation of emergency drug treatments for acute stroke in the NHS, and to suggest solutions to overcome these barriers
- to model the health economic impact of thrombolytic therapy.

Methods

Data sources and study selection

Multiple bibliographic sources were searched to identify: all unconfounded randomised trials comparing either a thrombolytic or a neuroprotective agent with placebo (or open control) in patients with acute stroke; and all published reports of studies identifying barriers to effective acute stroke care. A panel developed an economic model of acute stroke care from the Lothian Stroke Register, and by consensus discussion between the research team members supplemented by data on outcome after stroke derived from relevant publications where necessary.

Data extraction

For the review of thrombolysis, the data included in the analyses were checked where possible with the original trialists. For the review of neuroprotection completed systematic reviews were sought. For the review of barriers to acute care and interventions to overcome them, two reviewers independently selected studies meeting the inclusion criteria and extracted the data; differences were resolved by discussion.

Data synthesis

Standard Cochrane quantitative systematic review methods were used (Cochrane Revman 4.1 software); a fixed-effect model was used and results were expressed as odds ratios (ORs). For the economic analyses, a Markov model was created to estimate the number of life-years and quality-adjusted life-years (QALYs) gained with thrombolytic therapy. Sensitivity analyses were used to test the robustness of the estimates.

Results

Efficacy of thrombolysis

Seventeen trials (5216 patients) of urokinase, streptokinase, recombinant tissue plasminogen activator (rt-PA) or recombinant pro-urokinase were included. About 50% of the data came from trials testing intravenous rt-PA, mostly given within 6 hours of stroke onset. Thrombolytic therapy significantly increased the odds of fatal intracranial haemorrhage (OR = 4.15; 95% confidence interval (CI), 2.96 to 5.84). Thrombolytic therapy also increased the odds of death at the end of follow-up (OR = 1.31; 95% CI, 1.13 to 1.52). However, despite the increase in deaths, (because it markedly reduced the degree of disability in survivors), thrombolytic therapy within 6 hours significantly reduced the proportion of patients who were dead or dependent at the end of follow-up (OR = 0.83; 95% CI, 0.73 to 0.94). There was heterogeneity between the trials that could have been due to: the thrombolytic drug used, variation in the concomitant use of aspirin and heparin, severity of the stroke, and time to treatment. The most widely tested agent, rt-PA, may be associated with slightly less hazard and more benefit than other agents.

Efficacy of neuroprotective drugs

No agent has yet been proven to be sufficiently effective in man to be granted a product licence. Useful economic analyses were therefore not possible.

Barriers to acute stroke treatments

The key barriers identified were:

- the patient's or family's inability to recognise stroke symptoms or failure to seek urgent help
- patient or family calls general practitioner instead of an ambulance
- inefficient process of emergency stroke care in hospital, and
- delay in neuroimaging.

Some interventions to overcome specific barriers had been evaluated:

- education programme for the public and healthcare workers
- training programme for paramedical staff to improve the accuracy of diagnosis, and
- reorganisation of in-hospital systems to streamline acute stroke care.

None of the evaluation studies provided reliable estimates of effect.

Cost-effectiveness of thrombolysis with rt-PA

The model suggested that if eligible patients were treated with rt-PA there was a 78% probability of a gain in quality-adjusted survival during the first year, at a cost of £13,581 per QALY gained. Over a lifetime, rt-PA was associated with a cost-saving of £96,565 per QALY. However, the estimates were imprecise and highly susceptible to the assumptions employed in the economic model; under several plausible assumptions, rt-PA was much less cost-effective than standard care and under others, a great deal more cost-effective.

Conclusions

Implications for healthcare

Thrombolytic drugs

The data available are limited and the estimates of effectiveness and cost-effectiveness are imprecise. The data were judged to be insufficient to provide reliable estimates of the cost of modifying NHS services for patients with acute stroke to enable rt-PA to be delivered safely and effectively within the NHS. In the authors' opinion, the data do not, therefore, support the widespread use of thrombolytic therapy in routine clinical practice in the NHS.

Neuroprotective drugs

An agent associated with even modest benefit is likely to be cost-effective, but none is available yet.

Barriers

The cost of overcoming the known barriers to acute stroke treatment is likely to vary from centre to centre and will depend chiefly on the baseline level of stroke service provision.

Recommendations for research

There is a case for further research to:

- determine reliably the effects of rt-PA on short- and long-term survival and to identify which patients are most likely to benefit (and which to be harmed); this would require new large-scale randomised trials comparing thrombolytic therapy with control
- determine the nature (and costs of) the changes in NHS services that would be needed to deliver rt-PA therapy safely and effectively to patients with acute stroke (if rt-PA is licensed in the UK); this would include the costs of service changes that would be necessary to ensure that patients with suspected acute ischaemic stroke are admitted to hospital much more quickly than is currently the norm.

Publication

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NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme continues to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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