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Title 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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Aim

1. To assess the effectiveness of thrombolytic drugs.
2. To assess the effectiveness of neuroprotective drugs.
3. 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 ways to overcome the barriers.
4. To model the economic impact of thrombolytic therapy.

Conclusions and results

For the efficacy of thrombolysis, 17 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 hemorrhage (OR = 4.15) and increased the odds of death at the end of followup (OR = 1.31). Despite the increase in deaths, thrombolytic therapy within 6 hours significantly reduced the proportion of patients who were dead or dependent at the end of followup (OR = 0.83). Heterogeneity between trials may be due to: the thrombolytic drug used, variation in concomitant use of aspirin and heparin, stroke severity, and time to treatment. The most widely tested agent, rt-PA, shows slightly less hazard and more benefit than other agents.

Key barriers to acute stroke treatment: patient/family inability to recognize stroke symptoms or failure to seek urgent help; patient/family calls general practitioner instead of ambulance; inefficient process of emergency stroke care in hospital; delay in neuroimaging.

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 susceptible to assumptions used in the model.

Recommendations

The evidence on thrombolysis does not support widespread unselective use of thrombolytic therapy for acute ischemic stroke in routine clinical practice in the NHS. Data on thrombolytic drugs are limited and estimates of effectiveness and cost effectiveness are imprecise. The data were insufficient to estimate the cost of modifying NHS services to enable safe and effective delivery of rt-PA. A neuroprotective drug with even modest benefit is likely to be cost effective, but none is available. The cost of overcoming known barriers to acute stroke treatment is likely to vary by center and depend on the baseline level of stroke services.

Methods

Many sources were searched to identify: all unconfounded randomized trials comparing either a thrombolytic or a neuroprotective agent with placebo (or open control) in acute stroke patients; all published reports of studies identifying barriers to effective acute stroke care. A panel developed an economic model of acute stroke care. The data on thrombolysis were checked, where possible, with the original trialists. Completed systematic reviews on

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neuroprotection were sought. To review barriers to acute care and interventions to overcome them, two reviewers independently selected studies meeting the inclusion criteria and extracted data. Differences were resolved by discussion. Standard Cochrane quantitative systematic review methods were used; a fixed-effect model was used and results were expressed as odds ratios (ORs). A Markov model was created to estimate the number of life-years and quality-adjusted life-years (QALYs) gained with thrombolytic therapy.

Further research/reviews required

1) Determine the effects of rt-PA on short- and long-term survival and identify patients most likely to benefit (large-scale randomized trials comparing thrombolytic therapy with control).
2) Determine the nature and costs of changes in NHS services needed to deliver rt-PA therapy safely and effectively to acute stroke patients (including admitting suspected acute ischemic stroke patients to hospital much more quickly).

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