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There have probably been enough reviews on tPA in stroke to keep anyone going for a while.

SYSTEMATIC REVIEW OF INTRAVENOUS THROMBOLYSIS IN ACUTE ISCHAEMIC STROKE

Most recently from ACEM, via their website. An independent review of the data was commissioned to inform ACEP Policy, which will now be updated based on these findings.

Background

Conflicting evidence prompted an independent review to inform ACEM Guidelines, which currently conclude that thrombolysis cannot be considered a standard of care in stroke.

Randomised control trials comparing Alteplase (rtPA) with control within 4.5 hours of onset of ischaemic stroke were reviewed, together with other evidence.

Main results

Six trials (2,221 participants; 1,105 given rtPA, 1,116 controls) were included. All were drug-company funded, with half concerning for potential conflict of interest.

Three (ECASS III, NINDS 1 & 2) had a treatment window within the 0-4.5 hour timeframe [NINDS was essentially 2 trials reported together, one assessing recovery at 24 hours showing no benefit and the other part assessing function at 90 days]. Another 3 (ATLANTIS A & B, ECASS II) provided data for this timeframe that could be extracted.

IST-3, the largest trial, was not included because it was open label, used different eligibility criteria, and had a treatment timeframe outside of 4.5 hours.

Key Findings

- rtPA within 4.5 hours increased the number of patients essentially back to baseline (mRS 0-1; i.e. none or minimal deficit) at 90 days (OR 1.58, 95% CI 1.26 to 1.99). NINDS data indicates that this benefit is sustained to 12 months (OR=1.7, 95% CI= 1.2 to 2.3).
- Treatment within 3 hours (OR=1.85, 95%CI=1.38 to 2.47) increases recovery to independence (mRS 0-1) compared to 3-4.5 hours (OR=1.27, 95%CI=1.01 to 1.60).
- NNT 10 for good functional outcome. (NNT of 7 within 3 hours; compared to NNT 18 at 3-4.5 hours, with wide confidence intervals).
- There was a trend to benefit that was not significant for recovery to independent function as measured by mRS 0-2 (OR=1.21, 95% CI=0.98 to 1.50). mRS 2 is for a patient with a disability but not requiring assistance.
- Alteplase increased symptomatic ICH during the first 10 days (OR=6.90, 95%CI=2.21 to 21.50) and early death from ICH (OR=7.39, 95% CI=1.93 to 28.29), though there was heterogeneity in the safety data.
- Numbers needed to harm (NNTH) 42 for symptomatic ICH (CI 13-119).
- Overall risk of death at 30 days is no different if given thrombolysis or not.
- No evidence that any of sex, age, ethnicity and comorbidities were predictive of patients who may respond better to rtPA.

Conclusion

rtPA increases the proportion of patients who were back to baseline (mRS 0-1) at 90 days after stroke, however, at a cost of increased intracranial symptomatic haemorrhage.

There is no difference from rt-PA in recovery to being functionally independent as measured by an mRS 0-2.
Poorer outcomes in non-specialist units are associated with clinician inexperience.

Practice variation exists, with inconsistency in level of risk or benefit portrayed to patients.

Table 2: Risk of bias within studies
All studies were drug company sponsored, and multiple sources of bias are detailed.

A reply from the Stroke Foundation:

Can’t say they’re not ambitious.


t-PA is currently recommended as a leading treatment for ischaemic stroke. The evidence that tPA reduces disability is unequivocal and also demonstrated in the ACEM review. We know this powerful treatment is proven to increase rates of recovery and independence in patients who suffer an ischaemic stroke [addit. the independent review did not conclude that].

It is crucial that t-PA is administered in stroke units, and emergency departments with appropriate expertise and infrastructure.

Current Stroke Foundation clinical guidelines recommend thrombolysis within 4.5 hours of symptom onset. Only 26% receive disability reducing (???) thrombolysis treatment within 60 minutes of hospital arrival, compared with 43% in America and 56% in the UK.

This is the latest of many reviews

www.bmj.com/content/350/bmj.h1075


The subsequent independent review concluded thrombolysis was effective.

**Alteplase is safe to use within existing treatment guidelines, says independent review**


The thrombotic drug alteplase is safe and effective for licensed use up to 4.5 hours after the onset of symptoms of acute ischaemic stroke in patients for whom it is licensed, an independent expert group set up by the UK Medicines and Healthcare Products Regulatory Agency has concluded.1


Of note are new recommendations from the FDA and AHA/ASA that contraindications and precautions outlined in existing Guidelines can be relaxed. The dogma that bad outcomes in non-stroke centre settings, notably in the Cleveland trial and subsequently, are due to protocol violations is now challenged by recommendations that thrombolysis can safely be given despite those protocol violations.

**AHA/ASA Scientific Statement**

Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

Stroke February 2016

The review concludes a “clear benefit” of alteplase in the elderly, severe stroke, diabetes and with minor early ischemic changes on CT, published online.

Clinical Policy: Use of Intravenous Tissue Plasminogen Activator for the Management of Acute Ischemic Stroke in the Emergency Department

Revised ACEP Guidelines highlight limitations in the evidence. For 0-3hr, ..."IV tPA should be offered and may be given"; for 3-4.5hr "... tPA may be offered and may be given...", with attention to risk and shared decision making.

Clear now?