

Evidence-Based Emergency Medicine

Clinical Synopsis

TAKE-HOME MESSAGE

When given for acute ischemic stroke within 3 hours of symptom onset, recombinant tissue plasminogen activator increases the likelihood of long-term improved functional capacity without an adverse effect on survival. However, there is an increased short-term risk of symptomatic and fatal intracranial hemorrhage.

METHODS

DATA SOURCES

The Cochrane Stroke Group's Trials Register, EMBASE, and MEDLINE for studies before October 2008. Hand search of non-English publications from 1979 to 2009. Pharmaceutical manufacturers and principal investigators for unidentified studies were also contacted. The authors assessed the content of the review, including non-English publications, as up to date as of February 15, 2009.

STUDY SELECTION

Nine randomized, controlled trials evaluating intravenous tissue plasminogen activator administered in acute ischemic stroke were included, contributing a total of 3,851 patients.

DATA EXTRACTION AND SYNTHESIS

Extracted data included all-cause mortality, symptomatic or fatal intracranial hemorrhage within the first 7 to 10 days, and the number of patients who were dependent on others or who died by the end of follow-up, defined by a modified Rankin score of 3 to 6 (3 being moderate disability requiring some assistance but able to walk without help, and 6 being death). Results were presented as odds ratios with 95% confidence intervals.

An installment of the Systematic Review Abstract series:

Update: Effect of Thrombolysis in Acute Ischemic Stroke

EBEM Commentators

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Results

Effect of thrombolysis with tissue plasminogen activator on symptomatic intracranial hemorrhage, dependency, and mortality when administered within 3 hours from onset of acute ischemic stroke compared with placebo.

Outcome	Odds Ratio	95% Confidence Interval	No. of Trials (No. of Subjects)
End of follow-up death or dependency (modified Rankin score 3–6)	0.64	0.5–0.83	5 (930)
End of follow-up all-cause mortality*	0.97	0.69–1.36	6 (957)
7- to 10-day symptomatic intracranial hemorrhage [†]	3.4	1.48–7.84	4 (306)

*Follow-up duration was 3 months.

[†]Risk of fatal intracranial hemorrhage may be higher than observed because not all patients received a posthumous computed tomographic scan.

When data from patients who received treatment within 3 hours from symptom onset were compared with that of patients who received treatment between 3 and 6 hours, there were similar outcomes with respect to death or dependency at end of follow-up, death during follow-up, and symptomatic intracranial hemorrhage.

Commentary

This Cochrane review provides strong evidence to support emergency department tissue plasminogen activator administration within 3 hours from symptom onset. Another meta-analysis¹ that pooled data from 4 trials²⁻⁶ demonstrated a favorable outcome in terms of functional capacity when tissue plasminogen activator was administered within 4.5 hours. There was no benefit beyond 4.5 hours when the hazard ratio for death increased. The recent European Cooperative Stroke

Study (ECASS III) trial,⁷ which was not included in either of these meta-analyses, reported improved functional outcome without a significant difference in mortality with the administration of tissue plasminogen activator between 3 and 4.5 hours. The increased risk of intracranial hemorrhage was not significantly different from that observed in previous randomized trials that administered tissue plasminogen activator within 3 hours.

The majority of patients enrolled in these trials were younger than 80 years and had few comorbidities, which limits generalizability. There remains a paucity of data identifying which patient subgroups are most likely to benefit from treatment; the International Stroke Study (IST-3) study,⁸ currently in progress, aims to address some of these issues.

Tissue plasminogen activator's narrow risk-benefit profile has raised concern about the safety of routine use in community settings; however, a number of registries provide evidence that routine clinical use is as safe and effective as that reported in randomized, controlled trials when administered within 3 hours of symptom onset.⁹⁻¹¹ Similar results were also reported in the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) observational study,¹² in which the duration of symptom onset to tissue plasminogen activator administration was extended to 4.5 hours. Although this suggests that the thrombolysis window may be extended to 4.5 hours, 72% of the pa-

tients in the SITS-ISTR study were treated between 3 and 3.5 hours. Additional research is required to further define patient subgroups with acute ischemic stroke that benefit from tissue plasminogen activator administered beyond 3 hours.

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This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area. The source for this systematic review abstract is: Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2009;(4):CD000213. DOI: 10.1002/14651858.CD000213.pub2. The *Annals'* EBEM editors assisted in the preparation of the abstract of this Cochrane systematic review.

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