

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

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Background: Intravenous thrombolysis with alteplase is the only approved treatment for acute ischemic stroke. In 1995, the National Institute of Neurological Disorders and Stroke reported that patients who receive alteplase within 3 hours of onset of stroke symptoms were 30% more likely to have minimal or no disability at 3 months than those who received placebo. A separate study failed to show benefit when the treatment window was extended to 6 hours. Therefore, the efficacy and safety of alteplase have only been established when given within 3 hours of symptom onset.

Purpose: To test the safety and efficacy of alteplase when administered between 3 and 4.5 hours after the onset of stroke.

Outcomes: The primary endpoint was disability at 90 days, characterized as either a favourable outcome (a score of 0 or 1 on the modified Rankin scale, which has a range of 0 to 6, with 0 indicating no symptoms at all and 6 indicating death) or an unfavorable outcome (a score of 2 to 6 on the modified Rankin scale). The secondary endpoint was a global outcome analysis of four neurologic and disability scores combined. Safety end points included death, symptomatic intracranial hemorrhage, and other serious adverse events.

Methods: The study was a double-blind, parallel-group trial that enrolled patients from multiple centers across Europe. Patients were eligible for inclusion in the study if they were 18 to 80 years of age, had received a clinical diagnosis of acute ischemic stroke, and were able to receive the study drug within 3 to 4 hours after the onset of symptoms. A head CT or MRI scan was required before randomization to exclude patients who had an intracranial hemorrhage or major ischemic infarction. The treatment window was extended to 4.5 hours for 2 reasons: pooled analysis showed that patients in this window may benefit from treatment and slow recruitment. All patients gave written informed consent. After enrolment, patients were randomised 1:1 to alteplase 0.9 mg/kg IV (max 90mg, 10% given as a bolus) or placebo.

Results: 418 patients were randomised to the alteplase group and 403 to the placebo group. More patients had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; $P=0.04$). In the global analysis, indicating the ability to return to an independent lifestyle, the outcome was also improved with alteplase as compared with placebo (odds ratio, 1.28; 95% CI, 1.00 to 1.65; $P<0.05$). The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 27.0% vs. 17.6%; $P=0.001$; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%; $P=0.008$). Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; $P=0.68$). There was no significant difference in the rate of other serious adverse events.

Bottom Line: Alteplase administered within 4.5 hours of stroke symptoms onset significantly improved clinical outcomes in patients with ischemic stroke at 90 days. However, there is an increase in symptomatic intracranial hemorrhage.