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Extending the window for thrombolysis in acute stroke.

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Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials

Why is this study of clinical importance?

Stroke outcomes improve with early administration of intravenous recombinant tissue plasminogen activator (rt-PA). Analysis of combined data from individual patients from different studies has suggested potential benefit beyond 3 hours from stroke onset.

This study is an updated pooled analysis that aimed to assess the effect of time to treatment with the intravenous rt-PA alteplase on therapeutic benefit and clinical risk. The hypothesis of this updated pool is that the benefit of rt-PA would be smaller and the risk greater in patients who were treated at later time points within the 6-h our window after stroke onset. As intravenous rt-PA alteplase is the main treatment in acute stroke, it is important to know the clinical benefits and harms associated with the extension of time window for alteplase.

What are the trials included in this study?

Eight trials are analyzed in this study which represents the major randomized placebo controlled trials of r-PA (alteplase) for acute stroke. These trials are the two NINDS trials (parts 1 and 2), the first two ECASS trials, two Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischaemic Stroke (ATLANTIS) trials and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET).

The time allowed from stroke onset to start of treatment (OTT) varied among trials. In the NINDS studies, the protocols dictated that treatment start within 3 hours of onset of symptoms, and within 90 min for half the patients. In ECASS and ECASS II, patients were enrolled 0-360 min from symptom onset. ECASS III included patients between 180 min and 270 min from stroke onset. Patients in ATLANTIS A were enrolled from 0 min to 360 min. ATLANTIS B initially recruited patients timeframe was restricted to 180-300 min from symptom onset. EPITHET included patients from 180-360 min only.

What was the intervention?

In NINDS, ATLANTIS, ECASS II, ECASS III, and EPITHET, patients in the alteplase group were assigned to receive a total intravenous dose of 0·9 mg/kg bodyweight (90 mg maximum) whereas in ECASS I the total dose was 1·1 mg/kg (100 mg maximum).All studies gave 10% of the dose as a bolus during the first minute. The remainder was infused over 1 hour. Patients allocated to control groups received matching infusions of placebo. All trials allowed inclusion of patients who had taken antiplatelet agents before their stroke, but precluded the use of oral or intravenous anticoagulants or antiplatelet agents for the first 24 hours after treatment.

What was the outcome?

Investigators in all studies measured NIHSS score, modified Rankin Scale, and Barthel Index up to 3 months after stroke onset, calculated mortality, carefully determined the occurrence of haemorrhage with CT, and relied on clinical scales for their primary outcome measures.

This pooled analysis focused on the 3-month favourable outcome defined in two ways: by modified Rankin Scale (0-1) alone; and by a composite measure consisting of three neurological function scores of modified Rankin Scale (0-1), Barthel Index (95-100), and NIHSS (0-1). For all three measures the dichotomies were chosen to represent minimal or no post stroke deficit (favourable, not favourable). Of particular interest was the extent to which the odds of a favourable outcome altered as OTT increased.

Treatment was started within 360 min of stroke onset in 3670 patients randomly allocated to alteplase (n=1850) or to placebo (n=1820). Odds of a favorable 3-month outcome increased as OTT decreased (p=0·0269) and no benefit t of alteplase treatment was seen after around 270 min.

Around one in three patients treated with alteplase within 3 hours of symptom onset, and one in six treated within 4.5 hours, achieves significant benefit. This analysis identified that approximately five patients need to be treated 0-90 min, nine patients 91-180 min, or 15 patients 181-270 min after symptom onset for one of them to have an

excellent outcome attributable to treatment.

What were the conclusions?

This updated pooled analysis shows that treatment with thrombolysis until 4.5 hours from stroke onset enhances the chance of favourable outcome. Serious haemorrhage rates are independent of OTT, but mortality increases with OTT longer than 4.5 hours. However, across the time window studied, this analysis showed that the greatest benefit t comes from earlier treatment, since net benefit is diminishing with time and beyond 4.5 hours, risk might outweigh benefit

How does this impact us?

This pooled analysis reemphasises on the importance of time window in the clinical management of acute ischaemic stroke with alteplase. Although clinical benefit of alteplase is seen up to 4.5 hours in carefully selected patients, to increase benefit to a maximum, every effort should be taken to shorten delay in initiation of treatment. Given the great expense and disability of stroke, we need to upgrade the infrastructure that can support such treatment in more centers throughout Pakistan. In addition, perhaps looking into cheaper thrombolytic agents, drug delivery within transit, telestroke are other viable options for stroke patients in far flung areas in Pakistan.

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Recommended Reading

1. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010; 375: 1695-703.