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Tenecteplase for stroke salvage therapy--extending the therapeutic window via CT based

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Tenecteplase for stroke salvage therapy — extending the therapeutic window via CT based selection

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Why is this study important?

Alteplase, tissue type plasminogen activator,t-PA has been the gold standard for fibrinolytic therapy in acute ischaemic stroke, approved for use by FDA within 3 hours of symptom onset. Tenecteplase, a genetically engineered mutant tissue plasminogen activator, with prolonged plasma half life and higher fibrin selectivity, has emerged as a promising alternative intravenous alteplase. This article reviews the efficacy and safety of 2 doses of tenecteplase with alteplase as revealed by the phase 2B trial and attempts to compare their relative merits.

Who were the study participants?

Out of the 2678 patients between 2008 and 2011 with clinical features of stroke, 75 patients, age $\geq$ 18 years, were recruitedin this randomized and blinded trial after screening within 6 hours. Inclusion criteria were set at NIHSS score $\geq$ 4 and modified Rankin scale of $\leq$ 2. Other baseline characteristics of patients were as follows: mean age 70 ± 8.2 years, 51 % males, 61 % hypertensive, 25 % diabetics and 25 % of the patients were currently smokers. Those with contraindication to alteplase were excluded. Prior to being enrolled in the trials patients underwent CT imaging employing multi detector scanners (16 or 64 slice) and only those with intracranial occlusion in the anterior cerebral, middle cerebral or posterior cerebral artery were included in the study. CT criteria for selection were: a perfusion lesion 20 % greater than the infarct core and evidence of associated vessel occlusion on CT angiography.

What was the intervention?

Patients were divided randomly into three subgroups to receive standard dose of alteplase (0.9 mg per kilogram, the first 10% administered as an initial bolus and the remainder over a 1-hour period, with a maximum dose of 90 mg) or to tenecteplase (0.1 mg per kilogram, administered as a single bolus, with a maximum dose of 10 mg; or 0.25 mg per kilogram, administered as a single bolus, with a maximum dose of 25 mg). Central block randomization was done in blocks of 15 which allowed blind review after every 15 patients.

What were the results?

Perfusion-weighted magnetic resonance imaging was done to assess difference in re perfusion 24 hours after treatment. NIHSS scale was employed to establish change in clinical presentation and symptoms before and after treatment. Other useful indicators of therapy benefit like vessel recanalisation post 24 hours and variation in infarct size were duly noted. Modified Rankin scale was employed to assess recovery and was hence calculated at the start of the study and repeated 90 days post treatment.

Primary imaging efficacy outcome as assessed by percentage reperfusion at 24 hours was higher for Tenecteplase, 79.3±28.8 compared to Alteplase, 55.4±38.7 ($p < 0.004$). Improvement in NIHSS score was used to evaluate clinical efficacy and was higher for Tenecteplase group 8.0±5.5 than Alteplase group 3.0±6.3 ($p < 0.001$). Infarct growth when analyzed, attested to better clinical picture with Tenecteplase with size going from 3 to 2 ml when seen 24 hours after therapy and then 90 days later and from 14 to 12 ml for the same time interval in Alteplase group ($p < 0.01$). Secondary clinical efficacy showed a greater change in modified Rankin scale for tenecteplase than Alteplase, the improvement being from 32(24 hour) to 27(90 day) and 9 (24 hour) to 10 (90 day) respectively for the two groups. Results broadly showed that higher dose of Tenecteplase yielded better results than lower dose tenecteplase and Alteplase for all measures of clinical outcomes

What were the conclusions?

Tenecteplaseuse was associated with better thrombolytic performance in imaging-selected stroke patients compared to Alteplase. Greater reperfusion as exhibited by tenecteplase also

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reflected onto a better clinical picture after treatment.

What does this mean for our patients?

Although expensive, it is far more easier to "drip and ship" tenecteplase patients than alteplase treated patients. In addition, although not widely recommended at this time, the idea of using a tissue based selection therapy for stroke is useful in that it will eventually avoid unnecessary toxic treatment. The development of stroke centers in Pakistan, which will generally be free for service will benefit from more stringent selection criteria to avoid both toxicity and cost. Additionally, alteplase is neurotoxic and promotes apoptosis in tissue cultures , tenecteplase has not been reported to do the same.

Acknowledgements and Disclosures:

There are no relevant conflicts of interest to declare with regards to this review.

Recommended Reading:

1. Gonzalez RG. Tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med 2012; 367: 275-6, author reply 276.