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November 2010

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## Recommended Citation

Khan, M., Kamal, A. (2010). Acute administration of rt-PA for acute stroke in Pakistani patients--what does the available evidence teach us?. *JPMA. The Journal of the Pakistan Medical Association*, 60(11), 967-969.

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## Evidence Based Medicine

### **Acute administration of rt-PA for acute stroke in Pakistani patients — what does the available evidence teach us?**

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**The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study-NINDS rt-PA, European Cooperative Acute Stroke Study ECASS III, AND Japanese Alteplase Clinical Trial J-ACT.**

#### **Why are these studies important and noteworthy?**

Strokes are an important public health problem; about two thirds of stroke mortality will now be borne by the developing world. Up until late 80's no treatment was available to improve the deficits once stroke had occurred. The NINDS Trial was the first randomized controlled trial undertaken to evaluate the efficacy of this agent.

After NINDS, European investigators undertook another trial to assess whether the benefit of alteplase could be extended beyond the 3 hour period as in the NINDS trial. Three such trials were undertaken, with different doses of alteplase and using different time windows. ECASS III finally showed benefit with the extended time window of up to 4.5 hours.

After NINDS, the Japanese also set out to evaluate the efficacy of alteplase (rt-PA) in their population. They showed that a dose of 0.6mg/kg was just as efficacious and safe as the original dose of 0.9 mg/kg used in the NINDS trial.

Although there is not a lot published about the administration of acute thrombolysis for stroke in Pakistan, studies show that despite the widespread absence of acute ambulance services and education, stroke is recognized early and about a quarter of the patients in urban areas present within the time window and are eligible for rt-PA. Additionally, the published studies show that our symptomatic ICH rates are unacceptably high—the reasons for which are yet to be elucidated. Keeping this in mind, the Japanese trial is particularly important as the risk of haemorrhage reported in our population with the conventional 0.9mg/kg dose is unacceptably high.

#### **Who were the participants?**

NINDS trial was carried out in two parts. Part 1 assessed whether alteplase had clinical activity and it assessed changes in neurologic deficits at 24 hours after

stroke. Part 2 used four outcome measures to assess different aspects of recovery and to judge whether there was a sustained clinical benefit. NINDS included patients, who had a clearly defined time of onset of stroke, were presenting within three hours of onset, and had a deficit measurable on the NIHSS and a CT head showing no evidence of intracranial haemorrhage. Patients with uncontrolled sugars, uncontrolled blood pressures, recent surgeries, low platelets and bleeding diatheses or deranged coagulations were excluded from the study. The average age of patients in the trial was around 68 years, 42% were females, and more than 60% were whites. What was of note was the NIHSS score which was an average of 14 or 15 in both parts, meaning that these were patients with moderately severe strokes. Uncontrolled sugars were not an issue, and the average blood glucose level was around 150 mg/dl in both parts.

ECASS III included patients from European countries between ages 18-80 years, presenting within 3-4.5 hours after stroke onset. The rest of the conditions were the same except that they also excluded patients with severe strokes (NIHSS >25) and those who had a combination of prior stroke and Diabetes. The primary efficacy end point was disability at day 90 as assessed by Modified Rankin Scale. 821 patients were randomized, 418 to the alteplase arm and 403 to the placebo arm. There were two significant differences in the active and placebo groups, first was the NIHSS which was lower in the alteplase group, and history of prior stroke which was also significantly lower in the alteplase group. The median NIHSS was lower in ECASS III overall compared with NINDS study.

Japanese Alteplase Clinical Trial was conducted at 22 centers in Japan, and enrolled 103 patients. The inclusion and exclusion criteria were similar to NINDS except they excluded patients with CT evidence of early ischaemic changes in a large territory, comatose state and an mRS of  $\geq 2$ . The baseline characteristics were also similar to the NINDS population, except that cardioembolic strokes were more frequent, and the mean time from onset to treatment was more in J-ACT than in the NINDS trial. There was no control arm, and results were compared to the NINDS placebo arm.

## What was the intervention?

From January 1991 to October 1994, 624 patients underwent randomization. For part 1, 144 patients were assigned to the rt-PA group and 147 to the placebo arm. For part 2, 168 patients were assigned to the rt-PA group and 165 to placebo. Alteplase was given at a dose of 0.9 mg/kg.

ECASS III also used alteplase at a dose of 0.9 mg/kg given within 3 to 4.5 hours of stroke onset.

J-ACT used alteplase at a dose of 0.6mg/kg given within three hours of stroke onset in 103 patients.

In all three trials use of anti thrombotics was prohibited in the first 24 hours of treatment.

## What was the outcome?

In part 1 of the NINDS trial no statistically significant differences were detected between groups in the primary outcome (improvement by 4 or more points in the NIHSS score or a complete resolution of the neurologic deficit). In part 2 however, the number of patients with favourable outcomes for each of the four primary outcome measures (mRS, Barthel Index, NIHSS and Glasgow outcome scale) three months after stroke was higher in the t-PA group than in the placebo group. As evaluated by the global test statistic, the odds ratio for a favourable outcome in the t-PA group was 1.7 (95 percent confidence interval, 1.2 to 2.6; P0.008). There was also an 11 percent absolute (55 percent relative) increase in the number of patients with an NIHSS score of 0 or 1 in the alteplase group.

In ECASS III, for the primary end point (disability at day 90), 219 of the 418 patients in the alteplase group (52.4%) had a favorable outcome (defined as a score of 0 or 1 on the modified Rankin scale) at three months, as compared with 182 of the 403 patients in the placebo group (45.2%). This represented an absolute improvement of 7.2 percentage points (odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; relative risk, 1.16; 95% CI, 1.01 to 1.34; P = 0.04). The global odds ratio for a favourable outcome was 1.28 (95% CI, 1.00 to 1.65; P<0.05), indicating that the odds for a favourable outcome (the ability to return to an independent lifestyle) after stroke were 28% higher with alteplase than with placebo.

In J-ACT, the proportion of favourable outcomes was 36.9%, well exceeding the predetermined threshold of 33.9%. Concerning the secondary efficacy end points, 50 patients (48.5%) had a BI of 95 to 100 at 3 months compared with 50% of the rt-PA arm and 38% of the placebo arm in the NINDS study (part 2). Fifty-one patients (49.5%) experienced improvement by 4 points or a decrease to 0 points on the NIHSS at 24 hours after stroke onset compared with 47% of the rt-PA arm and 39% of the placebo arm in the NINDS study (part 1).

## What was the risk of haemorrhage and death?

In the NINDS trial, there was a significantly larger proportion of patients with symptomatic intracranial haemorrhage (p=0.001). 11 deaths were attributable to intracerebral haemorrhage of which 9 occurred in the alteplase arm. Serious systemic bleeding also occurred in the alteplase group only and minor external bleeding was also more common with alteplase (23% vs 3%). However, mortality did not differ significantly between the two groups.

In ECASS III, the rate of symptomatic ICH was 2.4% in the alteplase group but this was significantly greater than the rate in the placebo arm (p=0.008). Also the rate of intracranial haemorrhage overall was significantly greater in the alteplase arm. However, there was no difference in mortality between the two groups.

In J-ACT, 5.8% patients had symptomatic ICH which was similar to the NINDS study. The overall mortality with 0.6mg/kg dose was 9.7% which was lower than the NINDS figure of 10-17%.

## What were the conclusions?

NINDS trial first established the efficacy of alteplase (0.9mg/kg) for acute ischaemic strokes within three hours of onset. ECASS III then demonstrated that the window for alteplase administration can be safely extended to 4.5 hours after onset, but only in patients without a combination of previous stroke and Diabetes. J-ACT concluded that similar benefits can be achieved at least in the Japanese population with a lower dose of alteplase (0.6mg/kg).

## How does this impact our clinical practice?

Alteplase is being used in Pakistan for the past 5-6 years. Previously a dose of 0.9mg/kg was the standard of care. However, a review from Pakistan was published in September 2009. The authors reported the experience with rtPA from two tertiary care hospitals. The complication rate that was reported was much greater than what has been reported from the NINDS study. The rate of fatal haemorrhage was 14%, non fatal haemorrhage was 10% and mortality was 19% which was much greater than the 13% reported in the NINDS stroke study. In view of this high complication rate, and the equally good results with the lower dose of alteplase in the Japanese trial, we must also evaluate the efficacy and safety of 0.6mg/kg dose in our population. Also we have to be extra careful when considering patients for this therapy, since DM is much more prevalent in our population and uncontrolled sugars are the single most important predictor of haemorrhagic transformation post rt-PA. At the very least, rt-PA should be offered in centers with experience with this therapy and the protocols in Pakistan need to develop a means of controlling glucose variations in

addition to Blood pressure fluctuations in these patients.

### **Recommended Reading**

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