
**Stroke Patient Management
Using IV tPA:
When and How Should It Be
Utilized in ED Patients?**

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**Emergency Medicine
Associates**

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Disclosures

- All past advisory board or speakers' bureau activities have expired within the past year

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Sessions Objectives

- Discuss the NINDS study results
- Discuss the Follow-up studies to NINDS
- Discuss the NINDS reanalysis

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Case Presentation...

- 55 yo M presents to ED
- Weakness on his left side
- “Couldn’t grasp cup of coffee or key”
- Symptoms began 30 minutes
- Hx NIDDM, smoker
- No recent illness

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Give TPA?

- Code Grey
- Radiology resident read of CT
- Stat Neurology consult?
- Standard of care?
- Medicolegal risk?

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TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE t-PA STROKE STUDY GROUP*

Abstract Background. Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke after recent pilot studies suggested that t-PA was beneficial when treatment was begun within three hours of the onset of stroke.

Methods. The trial had two parts. Part 1 (in which 291 patients were enrolled) tested whether t-PA had clinical activity, as indicated by an improvement of 4 points over base-line values in the score of the National Institutes of Health stroke scale (NIHSS) or the resolution of the neurologic deficit within 24 hours of the onset of stroke. Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at three months, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS.

Results. In part 1, there was no significant difference between the group given t-PA and that given placebo in

the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed (global odds ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA but only 0.6 percent of patients given placebo ($P < 0.001$). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group ($P = 0.30$).

Conclusions. Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. (N Engl J Med 1995;333:1581-7.)

The NINDS Study

- TPA works for acute stroke!!
- TPA causes IC bleed
- 3 hour window: TIA or stroke mimic
- NINDS: only (+) study
only enrolled 624 patients
sicker pts in placebo group

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Thrombolytic Clinical Trials

- Initial IV streptokinase studies failed: MAST-E (Europe), MAST-1 (Italy), ASK (Australia):
 - (-) benefit; [6 hr window]
- Initial IV TPA trial: ECASS (Europe):
 - (-) benefit. However, selected subgroups may benefit; [6 hr window]
- Next IV TPA trial: NINDS (US):
 - (+) benefit; [dose finding & 3 hr window]

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The NINDS Study

- 3 hr treatment window
- TPA dose: 0.9 mg/kg (max 90 mg)
 - 10%: bolus
 - 90%: IV infusion over 1 hr
- TPA patients with 30% greater chance for minimal or no disability (at 3 mo)
- Increased IC bleed risk (0.6 vs 6.4%)

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NINDS Follow-up Studies

- NINDS (+) at 1 yr follow-up
- Other follow-ups studies:
 - STARS study: JAMA 2000
 - Cleveland experience: JAMA 2000
 - Trouillas et al: Stroke 1998
 - Buchan et al: Neurology 2000
 - Grond et al: Stroke 1998
 - Chiu et al: Stroke 1998
 - TPA stroke survey group: Neurology 1999
 - Oregon Experience: J Stroke Cerebrovasc Dis 1999
 - Wirkowski et al: J Stroke Cerebrovasc Dis 1999

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Pooled Analysis

- Hacke et al: Lancet 2004
- Graham GD: Stroke 2003
- IC bleed is the main risk
- Risk at ~ 5.2%

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Special Report

Findings From the Reanalysis of the NINDS Tissue Plasminogen Activator for Acute Ischemic Stroke Treatment Trial

Timothy John Ingall MB, BS, PhD; William Michael O'Fallon, PhD;
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Background and Purpose—Following publication of concerns about the results of the National Institute of Neurological Disorders and Stroke (NINDS) intravenous tissue plasminogen activator (t-PA) in acute stroke treatment trial, NINDS commissioned an independent committee “to address whether there is concern that eligible stroke patients may not benefit from t-PA given according to the protocol used in the trials and, whether the subgroup imbalance (in baseline stroke severity) invalidates the entire trial.”

Methods—The original NINDS trial data were reanalyzed to assess the t-PA treatment effect, the effect of the baseline imbalance in stroke severity between the treatment groups on the t-PA treatment effect, and whether subgroups of patients did not benefit from receiving t-PA.

Results—A clinically important and statistically significant benefit of t-PA therapy was identified despite subgroup imbalances in baseline stroke severity and an increased incidence of symptomatic intracerebral hemorrhage in t-PA treated patients. The adjusted t-PA to placebo odds ratio (OR) of a favorable outcome was 2.1 (95% CI 1.5 to 2.9). Although these exploratory analyses found no statistical evidence that the t-PA treatment effect differed among patient subgroups, the study was not powered to detect subgroup treatment differences.

Conclusions—These findings support the use of t-PA to treat patients with acute ischemic stroke within 3 hours of onset under the NINDS t-PA trial protocol. Health professionals should work collaboratively to develop guidelines to ensure appropriate use of t-PA in acute ischemic stroke patients. (*Stroke*. 2004;35:2418-2424.)

NINDS Reanalysis

- Subgroup patient assignment
- 91-180 minute treatment arm (worse Px)
- Placebo group had sicker patients in this arm (NIHSS < 5: 19 vs 4%)
- Study results reaffirmed

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Conclusions

- TPA for CVA data support its use in selected patients
- NINDS study data has been debated thoroughly

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Questions?

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