

Clinical Use of tPA in Acute Ischemic Stroke

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Objectives

- Present a clinical case history
- Review the NINDS clinical trials
- Examine phase IV tPA clinical data
- Discuss tPA use in ischemic stroke in light of the phase IV clinical data

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Clinical History

A 62 year old female acutely developed aphasia and right sided weakness while in the grocery store. The store clerk immediately called 911, with the arrival of CFD paramedics within 9 minutes, at 6:43 pm. She arrived at the ED at 7:05 pm, completed her head CT at 7:25 pm, and obtained a neuro consult at 7:35 pm, approximately one hour after the onset of her symptoms. What are the next Rx steps?

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ED Presentation

On exam, BP 116/63, P 90, RR 16, T 98, and pulse oximetry showed 99% saturation. The patient appeared alert, and was able to slowly respond to simple commands. The patient had a patent airway, no carotid bruits, clear lungs, and a regular cardiac rate and rhythm. The pupils were pinpoint, and there was neglect of the R visual field. There was facial weakness of the R mouth, and R upper and lower extremity motor paralysis. DTRs were 2/2 on the left and 0/2 on the right. Planter reflex was upgoing on the right and downgoing on the left. The patient's estimated weight was 50 kg.

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Clinical Use of tPA Questions

- What did the NINDS clinical trials show?
- What are the important design issues of the NINDS clinical trials?
- What documentation is necessary when using tPA in the clinical setting?
- What is the difference between clinical efficacy and effective tPA use?

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Clinical Use of tPA Questions

- What did the phase IV studies show?
- What specific findings from these phase IV studies are most notable?
- What clinical considerations can be derived from these phase IV studies?
- What can be concluded from the NINDS clinical trials and these phase IV studies?
- What issues are relevant when considering the phase IV reports of tPA use?

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NINDS Clinical Trials: Main Results

- tPA within 180 minutes: 30% better outcome at 90 days
- ICH rate at 36 hours 3x greater (10.9 vs. 3.5%)
- Symptomatic ICH rate 10x greater (6.4 vs. 0.6%)
- Mortality at 90 days comparable (17 vs. 21%)

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NINDS Clinical trials: Design Issues

- BP above 185/110 excluded
- “Aggressive Rx” of BP patients excluded
- All anti-coagulated pts (48 hrs) excluded

- No anti-coag or anti-platelet Rx for 24 hrs
- BP kept “within pre-specified values”

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Clinical tPA Use: E.D. Documentation

- With tPA use, there is a 30% greater chance of a good outcome at three months
- With tPA use, there is 10 fold greater chance of a symptomatic ICH
- Mortality rates at three months are comparable, even though ICH is more common with tPA use
- The rationale for using or not using tPA, given the potential for benefit and the risks of Rx

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Clinical Efficacy vs. Effective Clinical Use

- Efficacy: power or capacity to produce a desired effect
- Effective clinical use: can a drug be used with efficacy outside of the rigors of a clinical trial?
- Can Emergency Physicians on the front line replicate the outcomes seen in the clinical trial?
- Why might outcomes differ in clinical practice?

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Clinical Use: Outcome Differences

- Differences in:
 - Patient selection
 - Intervention administration
 - Concomitant therapy administration
 - Outcome measurement
 - Expertise of the practitioners in providing this care
- Which of these are the cause (if any) of the differences seen in the phase IV reports?

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Clinically Relevant tPA Issues: Stroke Severity

- NINDS NIHSS Severity: median score = 14
- NIHSS: 42 point scale, 11 categories
- Mild facial paralysis: NIHSS = 1
- Complete r hemiplegia with aphasia, gaze deviation, visual field deficit, dysarthria, sensory loss: NIHSS = 25

- NIHSS severity is critical to pt selection

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**Clinically Relevant tPA Issues:
Clinical Considerations**

- Age
- Size of stroke, based on NIHSS and CT
- % of eligible patients who receive Rx
- Timing of the tPA administration within the 180 minutes (NINDS trials Rx: 48% within 90 minutes)
- How is BP managed?

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**Clinically Relevant tPA Issues:
Clinical Considerations**

- Patient selection is painfully difficult
- Histories are unreliable
- Timing issues hard to press for stroke
- Every CT has a hypodense area
- Tendency not to intervene
- First do no harm
- What we did vs. what was destined to be

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**NINDS Clinical trials of tPA:
Clinical Upshot**

- tPA must be considered
- Patient selection is very difficult
- Must maximize risk/benefit ratio
- Must avoid hemorrhage, if possible
- Need adequate severity, but not too severe
- Less than 2% of patients will meet criteria

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**Phase IV Reports of tPA Use:
An Overview**

- 13 publications: Jan 1998 to Sep 2002
- US 8, Germany 3, Canada 2
- One to 57 hospitals
- Mix of community and academic centers, 56% community
- 37 to 389 patients (312 in NINDS trials)
- Rx of 1.8 to 22% of eligible patients

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**Phase IV Reports of tPA Use:
Patient Selection, Time to Rx**

- Age: 63-71 years old (NINDS = 68 years)
- Median NIHSS: 10-15 (NINDS = 14)
- Median time to Rx: 126 to 165 minutes

- Age and NIHSS comparable
- Time to Rx higher than in NINDS trials

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**Phase IV Reports of tPA Use:
Favorable Outcome, Mortality, ICH**

- Good outcome: 30-95% (NINDS = 31-54%)
- Mortality: 5.3-25% (14%) (NINDS = 17%)
- ICH rate: 9-31% (9.6%) (NINDS = 11%)
- Sx ICH: 3.3-15.7% (5.2%) (NINDS = 6.4%)

- Two reports: sx ICH rates of 10.8, 15.7%
- Mortality comparable in these two reports
- Comparable rates overall

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Phase IV Reports of tPA Use: Protocol Deviations

- Deviations occurred in 1.3-67% of patients
- Rx beyond 180 min: 0-22%
- Anti-coagulant use: 2.2-37%
- BP not controlled: 3-7%
- Baseline coagulopathy: 1.5-10%
- CT shows large stroke: 2-15%
- CT edema/mass effect: 2-10% (NINDS 3-5%)

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Phase IV Reports of tPA Use: Notable Specific Findings

- Chiu: *Stroke* 1998
 - NIHSS 5 points higher, dec good outcome by 69%
 - (NIHSS 24 vs. 14, 90% less likely good outcome)
- Grond: *Stroke* 1998
 - Germany, 22% of eligible pts treated
 - Two patients awoke with stroke sx, still Rx'd

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Phase IV Reports of tPA Use: Notable Specific Findings

- Smith: *Acad Emer Med* 1999
 - 70% Rx'd in last 30 minutes
 - 19% Outside of 180 minute window
 - 11% Sx ICH rate, but mortality comparable
- Tanne: *Neurology* 1999
 - Organized stroke triage system and tPA experience
 - 30% protocol violation rate, comparable outcome

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Phase IV Reports of tPA Use: Notable Specific Findings

- Wang: *Stroke* 2000
 - Regional stroke network
 - 6.3% of eligible pts Rx'd, highest in US
 - Median time to Rx: 150 minutes
- Buchan: *Neurology* 2000
 - Canada, 16% protocol deviation rate
 - 10/11 (90%) of protocol deviation pts
 - Sx ICH, mortality, or severe disability

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Phase IV Reports of tPA Use: Notable Specific Findings

- Albers (STARS study): *JAMA* 2000
 - Largest series to date (389 patients), prospective
 - Median Rx time: 165 minutes
 - 33% protocol violation rate
 - Results similar to NINDS results
- Katzan: *JAMA* 2000
 - Cleveland: 3,948 pts screened, 1.8% Rx'd
 - 50% protocol violation rate, less over time
 - 37% use of anticoagulants, 13% outside of window
 - Low measurement of NIHSS, BP control a problem

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Phase IV Reports of tPA Use: Notable Specific Findings

- Koennecke: *Stroke* 2000
 - Germany, 75 pts over 2 years, at 144 minutes
 - 17% treated after three hours, 3% ICH, 15% mortality
 - Over 2 yrs, median door-needle 96 to 73 min (14%)
 - Patients per month increased 100% (2 to 4 pts)
- Chapman: *Stroke* 2000
 - Canada, single university hospital
 - 1.8% of 2,556 pts Rx'd
 - Median time to Rx: 165 minutes
 - 17.4% violations, 2.2% sx ICH

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Phase IV Reports of tPA Use: Notable Specific Findings

- **Schmulling: *Stroke* 2000**
 - 150 German pts over 2+ years, academic center
 - Protocol deviations in only 1.3% of patients
 - Lowest mortality rate: 4% at three months
- **Grotta: *Arch Neurol* 2001**
 - Houston, 269 patients, 16% of eligible patients
 - In protocol deviation pts, 15% sx ICH rate
 - Sx ICH rate declined over the four year period
 - Median NIHSS declined 79% (14 to 3)

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Phase IV Reports of tPA Use: Notable Specific Findings

- **Bravata: *Arch Internal Med* 2002**
 - 2.5 year retrospective look from 10 CT hospitals
 - Only one hospital had 24/7 neurology, radiology
 - 63 pts, 42 (67%) with a protocol violation
 - Time > 180 minutes (22%), edema on CT, baseline coagulopathy, and anticoagulants given (all 10%)
 - Comparable (6%) sx ICH rate
 - Highest in-house mortality rate: 25%

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Phase IV Reports of tPA Use: Overall Findings

- Time to Rx near 180 minute window
- Many reports of protocol violations
- Most common protocol deviation: giving tPA at > 180 minutes
- NINDS population and results can be duplicated

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Clinical Use of tPA : The Issue of Age and Outcome

- Only one study specifically addresses age
- NINDS clinical trial: 69 ± 12 years
 - 66% of patients in age range 57-81 years
 - 95% of patients in age range 45-93 years
- Maximum ages in studies: 87,90,91, 100 yrs
- Many deaths result from AMI
- Albers, STARS study examined age, outcome

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Clinical Use of tPA : Albers' STARS Study

- Age > 85 years causes greater risk
 - 40-50% less likely to have a good outcome
 - Neurologic independence or recovery
- Age < 65 not associated with better outcome
 - Improved odds, but not statistically significant

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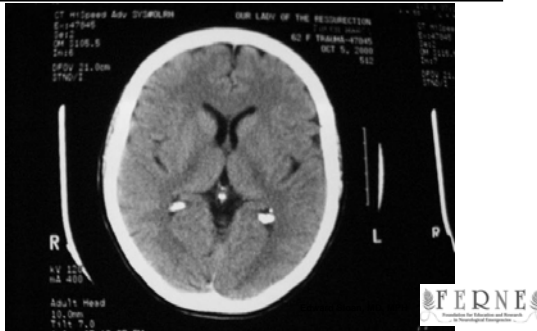
Clinical Use of tPA : Conclusions About Age

- Greater age, greater risk
 - Complication risk greater
 - Outcome risk less
- Is severity greater in older patients?
- Do ICH occur more often after tPA?
- Is data as good as with tPA use in AMI?
- More information must be provided

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Clinical Use of tPA: CT Result in the Clinical Case



Clinical Use of tPA: ED Management of the Clinical Case

- CT: no low density areas or bleed
- No clear contra-indications to tPA
- NIH stroke scale: approximately 20
- Neurologist said OK to treat
- No family to defer tPA use
- tPA administered without comp

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Clinical Use of tPA: tPA Use & Repeat Exam

- tPA dosing:
 - 8:21 pm, approx 1'45" after CVA sx onset
 - Initial bolus: 5 mg slow IVP over 2 minutes
 - Follow-up infusion: 40 mg infusion over 1 hour
- Repeat exam at 90 minutes:
 - Repeat Px Exam: Increased speech & use of R arm, decreased mouth droop & visual neglect
 - Repeat NIH stroke scale: approximately 14-16

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Clinical Use of tPA: Hospital Course & Disposition

- Hospital Course: No hemorrhage, improved neurologic function
- Disposition: Rehab hospital
- Deficit: Near complete use of RUE, speech & vision improved, some residual gait deficit

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Clinical Use of tPA : Overall Considerations

- NINDS clinical trials: Improved outcome
- Narrow therapeutic window important
- Phase IV reports: Effective tPA use possible
- Need to follow NINDS protocol in clinical use
- Need to determine time of sx onset exactly
- Need to know guidelines, know CT findings
- Lewandowski: Eight needed to treat in order to return one pt to full recovery

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Clinical Use of tPA : Overall Conclusions

- tPA is effective, but complications do occur
- Narrow therapeutic window for tPA
- In practice, relatively few pts receive tPA Rx
- Outcomes as in NINDS trials can be achieved
- Knowing the NIHSS is important in pt selection
- A checklist of exclusion criteria is critical
- BP Rx to achieve 185/110 is critical
- Protocol violations occur, know the protocol!

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Questions??

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