



**FERNE / MEMC IV Brain Illness and Injury Course:
tPA in Ischemic Stroke
Joseph Lex, MD, FAAEM**



**tPA in Stroke:
What's All the
Fuss?**



***FERNE Brain Illness
and Injury Course***




**4th Mediterranean
Emergency Medicine
Congress
Sorrento, Italy
17 September 2007**

Joseph Lex, MD 


**Joseph R. Lex Jr.
MD, FAAEM**

Assistant Professor

Department of Emergency Medicine
Temple University School of Medicine
Philadelphia, PA US


Joseph Lex, MD 

**Advisory Board, FERNE
Editorial Board,
www.EMedHome.com
Editorial Board,
Medscape Emergency
Medicine**

Joseph Lex, MD 

Disclosures

None

Joseph Lex, MD 

Objectives

- Review the results of the NINDS clinical trials
- Discuss Phase Four clinical data on clinical use of tPA for stroke
- Describe an appropriate informed consent for use of tPA in stroke

Joseph Lex, MD



In the Beginning...

Joseph Lex, MD



Joseph Lex, MD



NINDS Trial Results

| | tPA | Placebo |
|-----------------------------|-----------|----------|
| Number of patients | 157 | 145 |
| •Modified Rankin Scale | 40% (63) | 28% (41) |
| •Glasgow Outcome Scale | 43% (68) | 32% (46) |
| •NIH Stroke Score | 34% (53) | 20% (29) |
| Symptomatic ICH in 36 hours | 6.4% (10) | 0.6% (1) |
| Death by 90 days | 17% (27) | 21% (30) |

Joseph Lex, MD



IV Thrombolysis: Up Side

- Rankin: 12% absolute benefit
- Glasgow: 11% absolute benefit
- NIHSS: 14% absolute benefit
- Conclusion: treat 7 – 8 patients with t-PA to have one additional patient with better outcome

Joseph Lex, MD



NINDS Trial Results

| | tPA | Placebo |
|-----------------------------|-----------|----------|
| Number of patients | 157 | 145 |
| •Modified Rankin Scale | 40% (63) | 28% (41) |
| •Glasgow Outcome Scale | 43% (68) | 32% (46) |
| •NIH Stroke Score | 34% (53) | 20% (29) |
| Symptomatic ICH in 36 hours | 6.4% (10) | 0.6% (1) |
| Death by 90 days | 17% (27) | 21% (30) |

Joseph Lex, MD



IV Thrombolysis: Down Side

- 6% absolute increase in number of symptomatic intracranial hemorrhages
- Conclusion: treat 16 patients with tPA to have one additional symptomatic intracranial hemorrhage

Joseph Lex, MD 

IV Thrombolysis: Summary

**So if you treat 1000 patients who meet t-PA criteria...
...120 will have an absolute benefit, but...
...60 will have symptomatic intracranial haemorrhage**

Joseph Lex, MD 

IV Thrombolysis: Summary

Two patients will have minimal or no deficit for every one patient with symptomatic intracranial hemorrhage

Joseph Lex, MD 

NINDS: Design Issues

Patients were excluded if...
...blood pressure > 185/110 mm Hg
...required “aggressive treatment” of blood pressure
...anti-coagulated within 48 hours
...anti-platelet treatment within 24 hours

Joseph Lex, MD 

And then...

...Jeff Mann and
...Jerome Hoffman and
...Jeanne Lenzer and
...several others looked more closely at the data.

Joseph Lex, MD 

| Baseline NIHSS | % tPA (n=153) | % placebo (n=167) |
|----------------|---------------|-------------------|
| 0 – 5 | 19.0% (29) | 4.2% (7) |
| 6 – 10 | 24.2% (37) | 27.5% (46) |
| 11 – 15 | 17.0% (26) | 21.0% (35) |
| 16 – 20 | 21.6% (33) | 19.8% (33) |
| >20 | 18.3% (28) | 27.5% (46) |

**FERNE / MEMC IV Brain Illness and Injury Course:
tPA in Ischemic Stroke
Joseph Lex, MD, FAAEM**


| Baseline NIHSS | % tPA (n=153) | % placebo (n=167) |
|----------------|---------------|-------------------|
| 0 – 5 | 19.0% (29) | 4.2% (7) |
| 6 – 10 | 24.2% (37) | 27.5% (46) |
| 11 – 15 | 17.0% (26) | 21.0% (35) |
| 16 – 20 | 21.6% (33) | 19.8% (33) |
| >20 | 18.3% (28) | 27.5% (46) |

NINDS Baseline Imbalance

| Corrected | 0 – 90 minutes | 91 – 180 minutes | 0 – 180 minutes |
|-----------|----------------|------------------|-----------------|
| tPA | 32% | 39% | 36% |
| Placebo | 33% | 32% | 32% |

Simple random assignment accounted for 4% of the absolute reduction


Wardlaw JM, Lindley RI, Lewis S. Thrombolysis for acute ischemic stroke: still a treatment for the few by the few. West J Med. 2002 May;176(3):198-9. Joseph Lex, MD



IV Thrombolysis: Summary

So if you treat 1000 patients who meet t-PA criteria...
...80 will have an absolute benefit, but...
...60 will have symptomatic intracranial haemorrhage


Joseph Lex, MD



NINDS in Clinical Practice


- Must consider tPA, but patient selection very difficult
- Must maximize risk/benefit ratio
- Must avoid haemorrhage, if possible
- Need adequate severity, but not too severe
- <2% of stroke patients meet criteria

Joseph Lex, MD



Phase IV
Post-Marketing Studies


Joseph Lex, MD



Phase IV tPA Use

- Many later publications
- Mix of community and academic centers
- 37 to 389 patients (312 in NINDS trials) at one to 57 hospitals
- Treatment given to 1.8% - 22% of eligible patients

Joseph Lex, MD



Phase IV t-PA trials

| Author | Patients receiving tPA(%) | Mean time to Rx | Favorable outcome | % ICH | % Symptomatic ICH | % Protocol deviation |
|---------|---------------------------|-----------------|-------------------|-------|-------------------|----------------------|
| NINDS | 312 | | 31-54% | 10.9% | 6.4% | |
| Chiu | 30(2.9%) | 2'37" | 63% | 10% | 6.6% | |
| Tanne | 189 | >2' | | 9% | 5.8% | 30% |
| Wang | 57(6.3%) | 2'28" | 44-54% | 9% | 5% | 9% |
| Buchan | 68(4.4%) | | 95% | 31% | 9% | 16% |
| Albers | 389 | 2'44" | 35-43% | 11.5% | 3.3% | 33% |
| Katzan | 70(1.8%) | | | 22% | 15.7% | 50% |
| Chapman | 46(1.8%) | 2'45" | 30-48% | 9% | 2.2% | 17% |
| Grotta | 269(16%) | 2'17" | 33% | | 4.5% | 13% |
| Bravata | 63 | | | 17% | 6% | 67% |
| Total | 928(5.8%) | 2'25" | 33-95% | 9.6% | 5.2% | 13-67% |

Joseph Lex, MD 

Phase IV vs NINDS

Age: 63 – 71 years old

NINDS = 68 years

Median NIHSS: 10 – 15

NINDS = 14

Median time to treatment: 126 – 165 minutes

NINDS = 89 minutes

Joseph Lex, MD 

Phase IV vs NINDS

Good outcome: 30 – 95%

NINDS = 31 – 54%

Mortality: 5.3 – 25% (Mean: 14%)

NINDS = 17%

**Symptomatic ICH: 3.3 – 15.7%
(Mean: 5.2%)**

NINDS = 6.4%

Joseph Lex, MD 

Phase IV: Deviations

In 1.3 – 67% of patients

Treatment beyond 180 min: 0 – 22%

Anti-coagulant use: 2.2 – 37%

BP not controlled: 3 – 7%

Baseline coagulopathy: 1.5 – 10%

CT showed large stroke: 2 – 15%

**CT edema or mass effect: 2 – 10%
(NINDS 3-5%)**

Joseph Lex, MD 

Phase IV tPA: Overall

- Time to treatment near 180 minute window
- Many protocol violations
- Most common protocol violation: giving tPA >180 minutes after symptom onset
- NINDS population and results can be duplicated

Joseph Lex, MD 

Cochrane Database

- Randomised trials of any thrombolytic agent compared with control in patients with definite ischaemic stroke
- 18 trials including 5727 patients
 - Not all trials looked at each outcome
 - Sixteen trials were double-blind

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E.
Thrombolysis for acute ischaemic stroke.
Cochrane Database Syst Rev. 2003;(3):CD000213.

Joseph Lex, MD 

Cochrane Database

Lytic administered up to 6 hours after ischaemic stroke **significantly reduced** proportion of patients who were dead or dependent (modified Rankin 3 to 6) at 3 to 6 month follow-up (OR 0.84, 95% CI 0.75 to 0.95)

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2003;(3):CD000213.

Joseph Lex, MD



Cochrane Database

In lytic groups there was significant increase in...

...odds of death within first 10 days (OR 1.81, 95% CI 1.46 to 2.24), the main cause of which was fatal intracranial haemorrhage (OR 4.34, 95% CI 3.14 to 5.99)

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke.

Cochrane Database Syst Rev. 2003;(3):CD000213.

Joseph Lex, MD



Cochrane Database

In lytic groups there was significant increase in...

...symptomatic intracranial haemorrhage (OR 3.37, 95% CI 2.68 to 4.22)

...death at end of 3 to 6 month follow-up (OR 1.33, 95% CI 1.15 to 1.53)

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2003;(3):CD000213.

Joseph Lex, MD



Cochrane Database

- If treated within 3 hours of stroke, lytics appeared more effective in reducing death or dependency (OR 0.66, 95% CI 0.53 to 0.83) with no statistically significant adverse effect on death (OR 1.13, 95% CI 0.86 to 1.48)

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke.

Cochrane Database Syst Rev. 2003;(3):CD000213.

Joseph Lex, MD



Cochrane Database

Conclusion

- Net benefit despite real hazards
- Heterogeneity and wide CI make results unreliable
- Additional trial data required

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2003;(3):CD000213.

Joseph Lex, MD



Informed Consent

Joseph Lex, MD



What Do We Tell the Patient?

- “If we do nothing, there is a 40% chance you’ll have good recovery.”
- “If we give you tPA, there is a 52% chance you will have good recovery after 3 months.”
- “That means there is a one in eight chance that the drug will help.”

Joseph Lex, MD 

Explain to Patient / Family

- “There is no evidence that tPA will make any difference before 3 months, so we won’t know right away if it’s working.”
- “If we use tPA, there is a one in sixteen chance that you will develop bleeding in your brain.”

Joseph Lex, MD 

Explain to Patient / Family

- “Despite this increase in brain bleeding, your risk of being dead at 3 months is about the same with or without tPA.”

Joseph Lex, MD 

Conclusions

Joseph Lex, MD 

Clinical Considerations

- Patient selection difficult
- Histories unreliable: must have exact time of onset
- Hypodense area on CT: may be old stroke, older than 180 minutes
- Old habits: tendency not to intervene
- First do no harm

Joseph Lex, MD 

Overall Conclusions

- Data supports use of IV t-PA when NINDS protocol strictly followed
- Outcomes similar to NINDS can be achieved
- Sooner may be better
- Narrow therapeutic window

Joseph Lex, MD 

Overall Conclusions

- In practice, relatively few patients receive tPA treatment
- Document decision-making well on all patients, t-PA or not

Joseph Lex, MD



Questions?

Joseph.Lex@TUHS.Temple.edu

Joe@JoeLex.net

+01 215 707-5036

www.ferne.org

ferne_memc_2007_braincourse_lex_tpa_091707_finalcd
9/17/2007 5:29 AM

Joseph Lex, MD

