New York State Stroke Conference
Maximizing Stroke Quality of Care: Key Ingredients
May 31, 2012 / 3:10 - 3:30 pm

Treating Mild Strokes

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Presenter Disclosure Information

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Treating Mild Strokes

FINANCIAL DISCLOSURES:
• Grants/Research Support: NIH, PCORI
• Received travel reimbursement to a scientific meeting by Genentech, Inc.
• Received consulting fees from Genentech, Inc. given to stroke research

UNLABELED/UNAPPROVED USES DISCLOSURE: none
The NINDS rt-PA Stroke Trial that showed efficacy of IV t-PA within 3 hours excluded all minor stroke patients.

1. True
2. False ✔
3. Uncertain
Background

The NINDS rt-PA Stroke Trial Manual of Procedures

January 24, 1991

Chapter 3 – Eligibility Assessment

Page 22: Form 3 (revised 1/22/91):

Exclusion Criteria

1. Patient has:

   (a) only minor stroke symptoms... 1[ ] Yes  2[ ] No

   (b) major symptoms that are rapidly improving by the time of randomization........ 1[ ] Yes  2[ ] No
Enrollment in the NINDS rt-PA Stroke Trial

- Almost 4 years of recruitment
- 16,700 patients were recorded as screened but not enrolled
- Primary reason “symptoms too minor” in 1,748 (10%) patients
Supplemental Figure A2.

TPA for Cerebral Ischemia within 3 Hours of Onset- Changes in Final Outcome Due to Treatment

Changes in final outcome as a result of treatment:
- Normal or nearly normal
- Better
- No major change
- Worse
- Severely disabled or dead

Package Insert for Activase® (recombinant Alteplase)

• “Safety and efficacy in patients with minor neurological deficit has not been evaluated”

This statement depends on the definition of minor stroke – and must be interpreted within the context of the entire Study where patients with minor neurological deficits were studied and presumed stroke subtype was not a predictor of treatment response.
“Thrombolytic therapy cannot be recommended for persons who had one of the following reasons for exclusion from the NINDS study, including … isolated mild neurological deficits, such as ataxia alone, dysarthria alone, or minimal weakness.”

Minimal weakness was not a pre-specified exclusion criteria
Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility
Barber et al Neurology. 2001;57:1739-40

Major reasons for delay included:
• Uncertain time of onset (24%), patients waited to see if symptoms would improve (29%)
• Delay caused by transfer from an outlying hospital (9%)
• Inaccessibility of treating hospital (6%)

27% of patients with ischemic stroke (314/1168) were admitted within 3 hours of symptom onset & of these 84 (27%) patients received IV TPA.

The major reasons for exclusion in this group of patients (<3 hours) were:
• Mild stroke (13%)
• Clinical improvement (18%)
• Perceived protocol exclusions (14%)
• ED referral delay (9%)
• Significant co-morbidity (8%)

Of those patients who were considered too mild or were documented to have had significant improvement, 32% either remained dependent at hospital discharge or died during hospital admission. In prospective series mRS 2-6 in 29-32% of mild strokes.
Mild Stroke as rt-PA Exclusion Criterion

- Consistently evidence of “mild” stroke as a major reason for not treating those who arrive early to EDs
  - 31% mild/improving in GWTG (only exclusion)
  - 43% mild in Cincinnati (only exclusion)
  - 47% mild in Coverdell (MA, GA, NC, IL)

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YET substantial disability of 27-39% with baseline NIHSS 1-5

Literature rates of SxICH for minor stroke = 0 - 2.6%

Kleindorfer, Personal Communication, 2010; George, MMWR, 2009; Smith, Stroke, 2011, Fisher 2010
In NY State & Nationally, Get With the Guidelines data show that stroke that is too mild is the number 2 reason for not giving IV t-PA.

1. True  
2. False  
3. Uncertain
From: *Get With The Guidelines-Stroke* (with permission from the AHA), courtesy of Zainab Magdon-Ismail, Founders Affiliate

**Data from 2011**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Too Mild</th>
<th>RISS</th>
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</thead>
<tbody>
<tr>
<td>National</td>
<td>13,098 (31%)</td>
<td>16,611 (40%)</td>
</tr>
<tr>
<td>NY State</td>
<td>1,199 (31%)</td>
<td>1,552 (41%)</td>
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</tbody>
</table>

*Reasons for no IV rt-PA (Contra/Warning)*

<table>
<thead>
<tr>
<th>Time Period</th>
<th>National Too Mild</th>
<th>National RISS</th>
<th>NY State Too Mild</th>
<th>NY State RISS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>31-60 days</td>
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<td>61-120 days</td>
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<tr>
<td>121-180 days</td>
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<tr>
<td>181-240 days</td>
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<tr>
<td>241-365 days</td>
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<tr>
<td>365+ days</td>
<td></td>
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</tr>
</tbody>
</table>

*Legend*

- Red: All Hospitals - 01/01/2011 - 12/31/2011
- Blue: All NY Hospitals - 01/01/2011 - 12/31/2011
Thresholds to Activate Acute Stroke Team for Minor Strokes

- A good number of hospitals have a protocol for only considering t-PA for NIHSS ≥ 4 or ≥ 5
  - NO SCIENTIFIC BASIS
  - Some of these are still disabling strokes

- Teams may only rely on NIHSS and not a more complete neurological examination, including gait
Limited Data on IV rt-PA for Mild Strokes

• NINDS rt-PA Study
  – Few with NIHSS ≤5 enrolled
    • 9% (58/624); ~30-40% in recent observational studies
    • 2,971 excluded for primarily “rapidly improving” or “minor”
  – Some syndromes explicitly excluded (per MOP)
    • None with isolated ataxia, dysarthria, facial weakness, sensory symptoms, or NIHSS = 0
  – Others largely excluded
    • ≤3 patients with any isolated deficit
    • i.e., no hemimotor, 2 aphasia, 3 homonymous hemianopsia

What percentage of patients excluded from IV t-PA because their stroke was NIHSS $\leq 5$ are disabled (mRS > 1) 3 months later?

1. 5-10%
2. 10-20%
3. ~ 30%
4. Over 50%

The correct answer is 3. ~ 30%.
Disability Rate by NIHSS in Bern, Switzerland

Proportion with Disability (mRS 2-6) at Three Months

Baseline NIHSS Score

- 1 (n=48): 29.2%
- 2 (n=59): 35.6%
- 3 (n=49): 38.8%
- 4 (n=44): 37.1%
- 5 (n=49): 57.1%
- 6 (n=35): 55.6%
- 7 (n=35): 81.2%
- 8 (n=18): 71.4%
- 9 (n=16): 75.0%
- 10 (n=14):
- 11 (n=12):
- 12 (n=11): 81.8%

Courtesy of Fischer & Mattle, 2010
Substantial Disability Rates Among Mild Strokes (NIHSS ≤5)

• Numerous series of poor discharge outcomes
  – GWTG 28%, Calgary 33%, Boston 27%, CA 34%....

• Prospective cohorts with 90-day outcomes
  – 32% mRS 2-6 in Bern, Switzerland (n = 249)
  – 29% mRS 2-6 ASAP: Charlottesville, VA (n = 136)

Khatri et al. Stroke 2011
Fischer, Personal Communication. 2010
“Minor” stroke, however, can have a significant impact on a patient's health status

- Diminished quality of life & limitations in higher levels of physical functioning are often underestimated in stroke & are not fully captured by measures such as the Barthel Index & the Rankin Outcome Scale.
- Duncan et al used additional measures to assess the health status of 304 persons with mild stroke & to compare these individuals with 184 persons with TIA & 654 persons without history of stroke/TIA but at elevated risk for stroke (asymptomatic group).
- The consequences of even mild stroke affected all dimensions of health except pain.
- Standardized assessment of persons with stroke must evaluate across the entire continuum of health-related functions.

• Patients with minor or improving symptoms can also benefit.
• About 1/3 of acute stroke patients with rapid improvement of neurological deficit on arrival at the hospital develop severe subsequent deterioration.
• In 19 patients with rapidly improving symptoms, treatment with IV rt-PA was associated with good outcome.
• These preliminary data suggest that withholding IV rt-PA because of mild or improving symptoms may not always be justified.
NIHSS = 3

• Moderate-severe language impairment = disabling stroke
• Mild facial weakness or asymmetry + mild dysarthria + mild upper extremity drift = likely non-disabling stroke
Data from NINDS rt-PA Trial

• Benefit of IV t-PA in eligible patients
• Eligibility was a measurable neurological deficit on NIHSS (i.e. a minimal NIHSS = 1)
• The Study specified several highly specific Exclusion Criteria based on the type of neurological deficits:
  - Pure sensory stroke
  - Isolated: dysarthria, facial weakness, or ataxia
Background

• The Study enrolled a broad clinical spectrum of AIS patients, including some whose neurological deficits were minor

• Given potential risk of ICH from t-PA, its value in patients with less severe clinical deficits has been questioned - therefore worthy of a more detailed evaluation

• Need to clarify what a “minor stroke” is for sharper conceptualization & standardization
Objectives

• To define what constitutes a “minor stroke”
• To study the effect of t-PA on minor stroke
• To address the question: “Should patients with a minor stroke receive t-PA?”
Methods

• Multivariate analyses from the NINDS rt-PA Stroke Study: RCT of 624 pts. treated ≤ 3 hours of symptom onset
• Explore the relationship among stroke severity, t-PA tx, & stroke outcome
• “Minor stroke” defined 5 different ways based on data available at the time of tx decision: NIHSSS, NIHSS individual items scores, & stroke subtype
Minor Stroke Definitions

• “Working” definitions of minor stroke developed prior to analyzing the data
• Consensus reached by the NINDS rt-PA Stroke Study Steering Committee
• Each of these definitions was considered reasonable to operationally define a minor stroke syndrome
Conclusions

Recognizing the limitations of post hoc analyses:

• t-PA remained beneficial, regardless of whether or not the patient had a minor stroke.

• There is no evidence of an increased risk for symptomatic ICH in the group with minor stroke as compared to the NINDS trial overall.

• Our data suggest that the risk-benefit ratio for using t-PA in specified minor stroke patients favors treatment in eligible patients.
Relative Exclusion Characteristics for Patients With Ischemic Stroke Who Could Be Treated With tPA Within 3 Hours From Symptom Onset

- Recent experience suggests that under some circumstances—with careful consideration & weighing of risk to benefit—patients may receive fibrinolytic therapy despite ≥1 relative contraindications. Consider the risk to benefit of rt-PA administration carefully if any of these relative contraindications is present:
  - Only minor or rapidly improving stroke symptoms (clearing spontaneously)
  - Seizure at onset with postictal residual neurologic impairments & documentation of an appropriate intracranial occlusion on CT or MR angiography
  - Major surgery or serious trauma within previous 14 d
  - Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
  - Recent acute MI (within previous 3 mo)

Perspective on Who to Treat & Who to Study

• IV rt-PA is indicated if:
  – Clearly disabling deficit regardless of NIHSS score

• Potential study population:
  – Mild or improving ischemic stroke subjects with pre-treatment NIHSS score ≤5 and judged to be not clearly disabling by treating physician

• Clearly disabling deficits will consist of those that, if persistent, would prevent the ability to work or continue activities of daily living without difficulty
I will change practice on using t-PA for minor stroke

1. No – will continue to exclude “minor stroke”
2. No – will continue to treat minor strokes that are potentially disabling
3. Yes – will treat more minor stroke
4. Yes – will treat less minor stroke
5. No change
TREAT Task Force Consensus: Definition of Rapidly Improved Stroke Symptoms (RISS) as an Exclusion Criterion for IV rt-PA

- Improvement to a mild stroke with NIHSS ≤5 with remaining deficits appearing non-disabling. The following should be considered disabling deficits:
  - Complete hemianopsia (≥ 2 on the NIHSS Q3), or
  - Severe aphasia (≥ 2 on NIHSS Q), or
  - Visual or sensory neglect (≥ 1 on NIHSS Q), or
  - Any weakness limiting sustained effort against gravity (≥ 2 on NIHSS Q6 or Q7), or
  - Any remaining deficit considered disabling in the view of the patient and the treating practitioner.
"...and instead of a brain, the wizard gave the scarecrow a smartphone."