To Exclude or Not to Exclude: Revisiting tPA Exclusion Criteria

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Disclosures

- No financial disclosures
- I will be discussing off label use of alteplase (rt-PA)

Objectives

- Review epidemiology of stroke
- Review exclusion criteria for tPA
- Review literature regarding exclusions in case based format.

Background

Stroke Statistics

- 795,000 people suffer a stroke each year.
  - 600,000 of these are first attacks
  - 185,000 are recurrent attack
- Stroke is the fourth leading cause of death in the United States.
- Over 143,579 people/year die from stroke.
- Stroke is the leading cause of serious, long-term disability in the United States.

NIHSS

7pts  Level of Consciousness (AO, commands)
2pts  Gaze
3pts  Visual Fields
3pts  Facial Palsy
16pts Motor (4 each limb)
2pts  Ataxia
NIHSS

3 pts Language
You know how.
Down to earth.
I got home from work.
Near the table in the dining room
They heard him speak on the radio last night.

NIHSS

2 pts Dysarthria
MAMA
TIP-TOP
FIFTY-FIFTY
THANKS
HUCKLEBERRY
BASEBALL PLAYER

NIHSS

2 pts Neglect
No symptoms at all
No significant disability despite symptoms; able to carry out all usual duties and activities
Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
Moderate disability; requiring some help, but able to walk without assistance
Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
Severe disability; bedridden, incontinent and requiring constant nursing care and attention
Dead

The New England Journal of Medicine

- Randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke.
- Eligible: ischemic stroke with defined time of onset, NIHSS, baseline CT with out hemorrhage.
- Exclusion by history and exam:
  - Recent stroke or head trauma in 3 months
  - Major surgery within 14 days
  - History of ICH, SBP > 185 mm Hg or DBP > 110 mm Hg
  - Rapidly improving or minor symptoms
  - Sx of SAH
  - GI or Urinary Bleed in 21 days
  - Arterial puncture at a non-compressible site in 7 days
  - Seizure at the onset of stroke.

- Part 1: assessed changes at 24h
  - No significant difference between two groups at 24h.
- Part 2: assessed outcome at 90 days/ 3 months
  - Patients treated with t-PA were at least 30% more likely to have minimal or no disability at three months.
  - ICH 6.4% in tPA group .6% in placebo
  - Mortality 17% in tPA group and 21% in placebo
Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Favorable Outcome: alteplase group 52.4% vs placebo 45.3%
ICH: alteplase 27.0% vs placebo 17.6%
Symptomatic ICH: alteplase 2.4% vs. 0.2%
Mortality alteplase 7.7% and placebo 8.4%.

Package says...

Contraindicated in the following:
• Evidence of intracranial hemorrhage on pretreatment evaluation
• Suspicion of subarachnoid hemorrhage on pretreatment evaluation
• Recent (within 3 months) intracranial or intraspinal surgery, serious head trauma, or previous stroke
• History of intracranial hemorrhage
• Uncontrolled hypertension at time of treatment (e.g. > 185 mm Hg systolic or > 110 mm Hg diastolic)
• Seizure at the onset of stroke

Package says...

Active internal bleeding
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Known bleeding diathesis including but not limited to:
• Current use of oral anticoagulants or an (INR) > 1.7 or a PT > 15 seconds
• Administration of heparin within 48 hours preceding the onset of stroke and have an elevated aPTT at presentation
• Platelet count < 100,000/mm³

Package also says...

Risks of Alteplase therapy should be weighed against the anticipated benefits:
• Patients with severe neurological deficit (e.g. NIHSS > 22) at presentation.
• Patients with major early infarct signs on CT scan.
• In patients with recent use of oral anticoagulants or heparin

Package also says...

Risks of Alteplase therapy should be weighed against the anticipated benefits:
• Alteplase treatment can be initiated prior to the availability of coagulation study results.
• However, infusion should be discontinued if either a pretreatment INR > 1.7 or PT > 15 seconds or an elevated aPTT.

Package also says...

Treatment should be limited to facilities that can provide appropriate evaluation and management of ICH.
Therefore, treatment of patients with acute ischemic stroke more than 3 hours after symptom onset is not recommended.
Special diligence is required in making this diagnosis in patients whose blood glucose values are
• < 50 mg/dL
• > 400 mg/dL
The safety and efficacy of treatment with Alteplase in patients with minor neurological deficit or with rapidly improving symptoms prior to the start of Alteplase administration has not been evaluated. Therefore, treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended.

Recent major surgery
Cerebrovascular disease
Recent GI or GU bleeding
Trauma
HTN: SBP >175mmHg and/or DBP >110
High likelihood of left heart thrombus

Acute pericarditis
SBE
Hemostatic defects (Hepatic or renal failure)
Pregnancy
Hemorrhagic ophthalmic conditions
Septic thrombophlebitis
Advanced age (>75)

So why use it?
Because it works.
**Outcomes**

<table>
<thead>
<tr>
<th>For Every 100 pts treated with IV Alteplase</th>
<th>0-1.5</th>
<th>1.5-3</th>
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<td>Additional patients with Excellent Outcome</td>
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Data combined from 7 trials: NINDS 1&2, ECAS I, II, & III, ATLANTIS A&B

**Remember...**

• rt-PA is the only FDA approved drug for acute ischemic stroke

• rt-PA is only FDA approved for up to 3 hours

• 3-4.5 hours is recommended by an AHA/ASA Science Advisory when following additional exclusion criteria.

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**Why are stroke patients excluded from TPA therapy?**

*An analysis of patient eligibility*

- All stroke patients over a 39 month period (1996-99)
- 1168 were diagnosed with ischemic stroke
  - 73.4% excluded because arrival > 3 hours
  - 18.2% excluded because of "clinical improvement"
  - 17.1% excluded because of "mild stroke"
  - 7.2% received t-PA

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**Case 1**

72M presents to VUMC ED via EMS:

- 1820 Had sudden onset of Right sided weakness and difficulty speaking. Wife called EMS. En route weakness improved.
- 1857 Noted by ED resident to have aphasia and R grip weakness.
- 1900 NIHSS 2 for aphasia

**Pertinent Facts:**

- Onset 1820 now 1910
- Head CT normal
- On aspirin and clopidogrel
- Labs normal

**t-PA: Yes? No?**
Randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke.

Eligible: ischemic stroke with defined time of onset, NIHSS, baseline CT with out hemorrhage.

Exclusion by history and exam:
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- Seizure at the onset of stroke.

1168 patients over a 39 month period (1996-99)
73.1% excluded because arrival > 3 hours
18.2% excluded because of "clinical improvement"
13.1% excluded because of "mild stroke"
7.2% received t-PA
13% of screened patients

876 patients over 6 year period with acute ischemic stroke
162 patients did not receive tPA because "mild or rapidly improving."
75% had "good" outcome at 3 months.
Case 1

72M received tPA.
Case 1

72M received tPA and discharged to home with NIHSS of 1. Has done well with no residual deficits. Now on therapeutic anticoagulation.

Case 2

36M with PMHx significant for migraines presents to VCH ED (VCH Employee) with Right side vision loss.

Time of onset was 0930.

Head CT normal at 1030

NIHSS: 2

Further information:
- Known history of migraines with visual aura.
- Known history of stroke 10 years prior, with PFO found. Declined closure at the time, maintained on aspirin.
- Was compliant with aspirin therapy until 4 months prior.
**Table r: Demographics of Patients rapidly improving or low NIHSS with Good or Poor Outcomes**

<table>
<thead>
<tr>
<th>Total</th>
<th>Good</th>
<th>Poor</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>60</td>
<td>55</td>
<td>11</td>
</tr>
<tr>
<td>Age (Y)</td>
<td>65 (43.3)</td>
<td>2 (32.4)</td>
<td>3 (37.3)</td>
</tr>
<tr>
<td>Male Gender</td>
<td>29 (48.3%)</td>
<td>2</td>
<td>3 (32.3%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>White</td>
<td>34 (56.7%)</td>
<td>30 (54.5%)</td>
</tr>
<tr>
<td>Non-White</td>
<td>27 (45.0%)</td>
<td>25 (45.5%)</td>
<td>7 (76.3%)</td>
</tr>
<tr>
<td>Time to Presentation (min)</td>
<td>93.4</td>
<td>94.4</td>
<td>70.4</td>
</tr>
<tr>
<td>NIHSS (median)</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Rapid Improvement</td>
<td>24 (38.4%)</td>
<td>20 (35.4%)</td>
<td>4 (44.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49 (78.3%)</td>
<td>40 (72.7%)</td>
<td>9 (81.8%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>20 (42.1%)</td>
<td>21 (45.5%)</td>
<td>3 (33.3%)</td>
</tr>
<tr>
<td>Diabetes Mellitus, Type 2</td>
<td>18 (22.3%)</td>
<td>11 (21.7%)</td>
<td>7 (72.7%)</td>
</tr>
<tr>
<td>Vascular</td>
<td>74 (11.4%)</td>
<td>44 (81.1%)</td>
<td>10 (10.0%)</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>17 (28.3%)</td>
<td>14 (27.5%)</td>
<td>3 (30.3%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>9 (13.8%)</td>
<td>7 (12.9%)</td>
<td>2 (21.2%)</td>
</tr>
<tr>
<td>CHF</td>
<td>11 (17.6%)</td>
<td>11 (20.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>20 (33.3%)</td>
<td>13 (24.5%)</td>
<td>7 (70.0%)</td>
</tr>
<tr>
<td>Length of Stay (days)</td>
<td>5.22</td>
<td>2.2</td>
<td>4.3</td>
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**Study Limitations**

- This is a retrospective chart review with a small sample size.
- Patients were not randomized.
- Treatment bias.
- Outcomes are based on hospital discharge not 3 month outcomes.
- Few conclusions can be drawn.
Observations

- Patients who did not receive t-PA because “too good to treat” had poor outcomes due to a neurologic cause presented with “right brain” symptoms or cerebellar symptoms.
- The NIHSS does not capture the right hemisphere or cerebellum well.
- Many of the patients with poor outcome and were “too good to treat” had rapidly improving symptoms. This could represent a separate disease process.

Future Questions

- Should “Get With the Guidelines” separate out low NIHSS and rapidly improving as separate t-PA exclusion criteria to allow for national performance tracking of the groups separately.
- Consider a randomized trial of low NIHSS to tPA and no tPA.
- Consider prospective database with 3 month outcomes of patients with low NIHSS and rapidly improving patients.

Does the National Institutes of Health Stroke Scale Favor Left Hemisphere Strokes?

- NINDS placebo arm
- Volume for right hemisphere stroke was statistically greater than for left hemisphere strokes
- NIHSS 16-20 median volume of infarct for L hemisphere strokes was .48mL compared with 133mL.

Is the Association of National Institutes of Health Stroke Scale Scores and Acute Magnetic Resonance Imaging Stroke Volume Equal for Patients With Right- and Left-Hemisphere Ischemic Stroke?

- NIHSS 0-5 mean volume of infarct for L hemisphere strokes was 3.2 cm³ compared with 8.8 cm³ for R hemisphere infarcts.

Intravenous Thrombolysis in Ischemic Stroke Patients With Isolated Homonymous Hemianopia

- 72pts with isolated HH given thrombolysis
- 56% improved at 7 days
- 71% with mRS at 90 days
- It is “safe” to give tPA

Case 2

36M was given tPA 1050 (1h and 20min after onset).
Discharged 48h later on aspirin with NIHSS 1
Follow up at about 50 days with NIHSS 0.
34F presenting to ED with gradual weakness and numbness of right side.

0545 woke up normal
0600 noticed gradual progression of tingling in R arm and leg
0700 noticed R arm weakness
0800 presented to local clinic after dropping kids off a school
0924 arrived via Life Flight at VUMC

CT scan was normal 0927

VITALS: P:80 BP: 119/69 Wt: 161
NIHSS 9: (1 LOC question; 1 facial droop; 3 RUE; 3 RLE; 1 sensory)

PMHx: migraines and hepatitis

It is now 1000 (4 hours). Delay was for INR and plts.

t-PA: Yes? No?
Case 3

1000 Examined by attending. Hoover negative. Concern for conversion disorder but exam was consistent also with stroke.

1012 tPA given for possible lacunar infarct.

Case 3

MRI was normal at 24h with continued symptoms that appeared functional.
+ Hoover (negative in ED)

Patient tearful and admitting multiple stressors

Psych consulted and agreed with conversion disorder 1012

Case 3

• tPA is a time sensitive decision.
• It is assumed 3-7% of IV tPA patients are stroke mimics.

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Case 4

39F at 37w gestation presented to ED with decreased responsiveness and inability to move left side.

PMHx: includes hypertension

LKN: 0930

NIHSS: 20 @ 1010

Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia

• 512 patients of which 106 (21%) did not have DWI changes post treatment
• 69 (14%) stroke mimics
• 37% presumed neuroimaging negative cerebral ischemia
• No systemic hemorrhage, intracerebral hemorrhage or angioedema.

Etiologies of Stroke Mimics

- Seizure
- Migraine
- Conversion disorder
- Aseptic meningitis
- Epidural spinal mass
- Heat stroke
- SyncopeVT

Source: 2005;36:e53-e55
Case 4
Head CT normal.
SBP 200/100
Only taking prenatal vitamin.

Pregnancy and Thrombolysis
• Stroke in pregnancy is “rare.”
• Three fold increase in incidence to the “non pregnant”
• Pregnancy is a hypercoagulable state.
• Patients who have thrombogenic states can not remain on coumadin.
• Higher risk of venous and arterial thrombus.
• Higher risk with patent foramen ovale or pulmonary AVM.

t-PA: Yes? No?

Literature says...
• Review of literature found 172 pregnant women treated with thrombolytic agents for “various” conditions and found maternal hemorrhagic complications in 8%.
• 8 stroke patients have been treated with iv rtPA in literature:
  3 in first trimester
  5 in second trimester
  2 patients with minor hemorrhage
  1 patient died from dissection of angioplasty

Pregnancy and Thrombolysis
• rtPA is a category C drug
• Pregnancy and exclusion for all studies
• Teratogenic effects were not observed in animal studies.
• rt-PA does not cross the placenta.
• 30 patients in the literature received rt-PA for MI, PE, prosthetic valve thrombosis, DVT and CVT with complication rates similar to non pregnant patients.
(Stroke. 2007;38:2612-2618)
Case 4

- Pt. was taken for IA rt-PA at 1430.
- 15mg of IA rt-PA was administered.
- Posterior communicating artery opened.
- Multiple attempt to cross M1 occlusion were made and unsuccessful.
- Procedure was terminated.

NIHSS post procedure was 7 (9 hours after onset of symptoms).
Pt. delivered by forceps-assisted vaginal delivery on day 3 post rt-PA.
Child was a healthy male infant w/o neurologic deficits.
At 2 month neurology follow-up patient had NIHSS 0 and child was normal.