Thrombolytic Therapy Should be The First Line Treatment in The Management of Acute Ischemic Stroke

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Temporal profiles of neurologic deficits that point to the underlying pathologic cause.

- Mayo Clinic
Ischemic Stroke

• **Sudden onset of a non-convulsive, FND due to CVD**

• *Embolic strokes*
  – Deficit reaches its peak almost at once
  – Reverses itself within a **few hours or days**

• *Thrombotic strokes*
  – Evolve more slowly over a period of several min/hrs and occasionally days
  – Improve gradually over **weeks or months**

• *Cerebral Hemorrhage*
  – There is severe deficit of rapid but not necessarily instantaneous onset
Thrombotic

- 1/3 of ischemic strokes, occlude large cerebral arteries (ICA, MCA, basilar), small penetrating arteries (lacunar strokes), cerebral veins, and venous sinuses.
- Symptoms evolve over minutes to hrs.
- Often preceded by TIA in same territory causing similar deficits.
Ischemic Stroke: Embolic

• Proximal origin of clot
• Occurs at any time
• Frequently during periods of vigorous activity
• History of AF, valvular vegetations, thromboembolism from MI, ulcerated plaques in carotid system
• Seizures in 20% of cases
Embolic

• 2/3 of ischemic strokes, from thrombus in heart, aortic arch, large cerebral artery or medium sized branches of brain a.

• In anterior circulation usually effect MCA, in posterior circulation usually effect branch point of basilar or PCA.

• Produce maximal neurological deficit at onset.

• When TIAs precede, symptoms vary because emboli lodges in different places.
<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>Frequency, %</th>
<th>CT Findings</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar stroke</td>
<td>20-25</td>
<td>Hypodensity usually &lt;1 cm³</td>
<td>Lipohyalinosis of small vessels</td>
</tr>
<tr>
<td>Large vessel</td>
<td>1-5</td>
<td>Varies</td>
<td>Atherosclerosis of intracranial arteries</td>
</tr>
<tr>
<td>Embolic</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>20</td>
<td>Wedge-shaped cortical/subcortical hypodensity</td>
<td>See Table 361-2</td>
</tr>
<tr>
<td>Artery-artery</td>
<td>15</td>
<td>Wedge-shaped cortical/subcortical hypodensity</td>
<td>Aortic, carotid or intracranial atherosclerosis</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>30</td>
<td>Wedge-shaped cortical/subcortical hypodensity</td>
<td>Extensive workup reveals no cause</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>Varies</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraparenchymal</td>
<td>10</td>
<td>Hyperdensity within brain substance</td>
<td>Hypertension, AVM, amyloid angiopathy</td>
</tr>
<tr>
<td>Subdural</td>
<td>&lt;1</td>
<td>Hyperdensity within subdural space</td>
<td>Trauma</td>
</tr>
<tr>
<td>Epidural</td>
<td>&lt;1</td>
<td>Hyperdensity within</td>
<td>Trauma</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>1-2</td>
<td>Hyperdensity within subarachnoid space</td>
<td>Ruptured aneurysm, trauma</td>
</tr>
</tbody>
</table>

**NOTE:** AVM, arteriovenous malformation; CT, computed tomography.
Acute Ischemic Strokes
Objectives

• Acute Management
  – Thrombolytic Therapy (resolution)
  – Antithrombotic Therapy (reduce progression and recurrence, and prevent VTE)

• Secondary Prevention
  – Antiplatelet therapy
PROACT II Trial

• First phase III trial of I.A.T.
• Pro-UK + heparin vs IV heparin within 6h.
• 180 patients, M1 or M2 MCA occlusion.
• Average NIHSS 17.
• Median time to I.A.T 5.7 hours.
PROACT II Trial

• mRS < 2 : 40% VS 25% (+- SIG)
• Recanalisation at 2h: 66% vs 18%
• Hemorrhage at 36h:
  – all: 46% vs 16%
  – symptomatic: 10% vs 2%
• No difference in mortality
I.A.T. Rate of Recanalisation

- PROACT II: 66% overall
- Urbach et al 2002:
  - Thrombus 53%: 23% carotid T,
    - 74% distal M1
    - 60% M2
NINDS results

• No significant differences in Mortality at 3 mos or 1 year (24% vs 28%)

• Complete or near complete recovery at 3 months was 38% with tPA and 21% with placebo (ARR-17%, NNT~6)
<table>
<thead>
<tr>
<th>Outcomes at 90 days</th>
<th>Alteplase</th>
<th>Placebo</th>
<th>Relative change</th>
<th>NNT/H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin 0 to 1</td>
<td>52%</td>
<td>45%</td>
<td>19%</td>
<td>12</td>
</tr>
<tr>
<td>Barthel Index &gt;95%</td>
<td>63%</td>
<td>59%</td>
<td>8.4%</td>
<td>NS</td>
</tr>
<tr>
<td>NIHSS 0 to 1</td>
<td>50%</td>
<td>43%</td>
<td>16%</td>
<td>15</td>
</tr>
<tr>
<td>Glasgow Outcome Scale of 1</td>
<td>51%</td>
<td>45%</td>
<td>12%</td>
<td>NS</td>
</tr>
<tr>
<td>ICH</td>
<td>27%</td>
<td>18%</td>
<td>53%</td>
<td>11</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>2.4%</td>
<td>0.2%</td>
<td>864%</td>
<td>47</td>
</tr>
</tbody>
</table>
Do we thrombolyse or is this just a TIA?

- 312 pts randomized to placebo group in the NINDS trial
- Medial time to treatment was 90 minutes
- Only 2% were symptom free at 24 hours
- “unlikely that patients with a persistent neurologic deficit of longer than 90 minutes will resolve spontaneously”

Hx and Physical

“in general, the diagnosis of stroke is straightforward”

• Emergency physicians correctly identified 152 or 176 consecutive stroke patients (sens 86.4%) and 1818 of 1835 patients without stroke (spec 99.1%)
  
Anticoagulants?

• Several studies with heparin, LMW heparins, heparinoid

• Conclusion:
  – parenterally administered anticoagulants are associated with an increased risk of serious bleeding complications (level I)
  – early administration of the rapidly acting anticoagulants does not lower the risk of early recurrent stroke, including among patients with cardioembolic stroke (level I)
Anticoagulants

• Recommendations:
• Urgent routine anticoagulation with the goal of improving neurological outcomes or preventing early recurrent stroke is not recommended for the treatment of patients with acute ischemic stroke (grade A)

Antiplatelets

• 2 large trials with aspirin:
  – Chinese Acute Stroke Trial
  – International Stroke Trial
Chinese Acute Stroke Trial (CAST)

• Prospective, randomized, placebo controlled trial of >21000 pts, where ASA 160mg/day or placebo was given within 48h of stroke onset

• Aspirin reduced early mortality
  – 3.3 vs 3.9%

• No effect on the proportion of patients who were dead or dependent at hospital discharge
  – 30.5 vs 31.6%; p=0.08
International Stroke Trial (IST)

- Prospective, randomized, open-label trial of ASA and unfractionated heparin in >19000 pts
- half received ASA and half were instructed to avoid ASA, then half of pts in each group received unfractionated heparin
- Significant reduction in recurrent events but acute mortality was not reduced (level I)
- Small significant (0.1% absolute) significant increase in the incidence of intracranial hemorrhage (level I)
  - IST: a randomized trial of aspirin, subcutaneous heparin, both or neither among 19435 patients with acute ischemic stroke. Lancet 1997;349:1569-1581
NINDS

• multicentre, randomized, placebo-controlled trial
• 624 patients with ischemic stroke were treated with intravenous t-PA (0.9 mg/kg) within 3 hours of the onset of stroke symptoms.
• Part 1: primary endpoint was neurological improvement at 24h (complete neuro recovery or improvement of 4 points or more on NIHSS)
• Part 2: primary end point was global odds ratio for favorable outcome (defined as complete or nearly complete neurological recovery at 3 months after stroke)
Part 1: t-PA recipients did not suddenly improve, and there were no significant outcome differences at 24 hours.

Part 2: patients treated with t-PA were more likely to have a favorable neurological outcome at 90 days (odds ratio 1.7; 95% CI, 1.2-2.6; p=0.008).

Compared to controls, t-PA recipients had a 12% absolute (32% relative) increase in the proportion with minimal or no disability.
ECASS

- compared rtPA (1.1 mg/kg) to placebo in patients with <6 hours of symptoms
- early intracranial hemorrhage, fatal cerebral edema and early mortality were more common in treated patients than in controls
- surviving t-PA recipients were more likely to have minimal or no disability at 3 months
- authors concluded: while some patients benefit, the rate of negative outcomes was prohibitively high
- Intravenous rtPA was not more effective than placebo in improving neurological outcomes at 3 months after stroke (level I)
ECASS vs NINDS

• ECASS: higher dose, longer window of treatment
• Post hoc analysis concluded that pts treated within 3 hours appeared to benefit from rtPA
ECASS-II

- applied the same eligibility criteria and used the same 0.9 mg/kg rtPA dose, but enrolled patients within 6 hours of symptom onset
- More than 1/3 of pts in each group made an excellent recovery and no significant benefit was noted from treatment
- rtPA did not significantly increase the rate of favorable 90-day outcomes (40.3% vs. 36.6%, p=0.277), and was associated with a higher incidence of parenchymal hemorrhage (11.8% vs. 3.1%), symptomatic intracranial hemorrhage (8.8% vs. 3.4%), and early death due to intracranial hemorrhage (11 vs. 2 cases)
ECASS-II

- no significant differences in 30- or 90-day mortality
- subgroup analysis showed a trend towards improved neurological outcomes in patients with <3 hours of symptoms, but the numbers were small and statistically insignificant
- ECASS-II therefore failed to reproduce the positive results of NINDS
ECASS-II

• Recruitment bias?
• Avoided recruitment of pts with Multilobar infarctions
• Thus severity of strokes was less than in other trials
• Generally more favorable prognosis may have reduced the likelihood of detecting a therapeutic effect
Cochrane Stroke Group Trials Register

- Up to January 2003
- Objective: assess safety and efficacy of thrombolytic agents in patients with acute ischemic stroke
- Selection criteria: randomized trials of any thrombolytic agent compared with control in patients with definite ischemic stroke
- 18 trials, 5727 patients
- Urokinase, streptokinase, recombinant tissue plasminogen activator, recombinant pro-urokinase
- 2 trials: intra arterial administration
- 16 trials: intra venous administration
- 50% of data from tPA
- Little data over age 80
Thrombolytic therapy:

• For patients treated within three hours of stroke, thrombolytic therapy 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)
Cochrane conclusions:

• Overall, thrombolytic therapy appears to result in a significant net reduction in the proportion of patients dead or dependent in activities of daily living.

• The data from trials using rtPA suggest that it may be associated with less hazard and more benefit
Table 1. Trials of Intravenous Thrombolytic Therapy After Visualization of the Clot by a Cerebral Angiogram

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Patients</th>
<th>Partial or Total Recanalization, %</th>
<th>Recanalization of MCA Only, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Hemorrhagic Infarctions, %</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mori et al,&lt;sup&gt;3&lt;/sup&gt; 1992</td>
<td></td>
<td></td>
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<tr>
<td>Recombinant tissue plasminogen activator, mg/kg</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1.17</td>
<td>10</td>
<td>50</td>
<td>71</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>0.73</td>
<td>9</td>
<td>44</td>
<td>67</td>
<td>56</td>
<td>22</td>
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<tr>
<td>Placebo</td>
<td>12</td>
<td>17</td>
<td>13</td>
<td>33</td>
<td>17</td>
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<tr>
<td>Yamaguchi et al,&lt;sup&gt;4&lt;/sup&gt; 1993</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Recombinant tissue plasminogen activator, 0.73 mg/kg</td>
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<tr>
<td>Placebo</td>
<td>47</td>
<td>57</td>
<td>NA</td>
<td>47</td>
<td>9</td>
</tr>
<tr>
<td>Placebo</td>
<td>46</td>
<td>24</td>
<td>NA</td>
<td>47</td>
<td>13</td>
</tr>
</tbody>
</table>

<sup>a</sup> The time to treatment was 6 hours for all trials. MCA indicates middle cerebral artery; NA, data not available.

Figure Legend:

Trials of Intravenous Thrombolytic Therapy After Visualization of the Clot by a Cerebral Angiogram
Come to Light