The Early Treatment of Ischemic Stroke

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Epidemiology

• 700,000 acute ischemic strokes a year
• Estimated 22 million silent strokes a year
• Stroke is the third leading cause of death in the USA.
• Leading cause of disability in the elderly
• Stroke incidence is increasing with the aging of the population

Stroke Epidemiology WHO

• Accounts for 4.6 million deaths annually
  – One-third of strokes occur in the developed nations
• The sixth leading cause of disability-adjusted life years (DALY)
  – one DALY is one year of healthy life lost
• 2.4% of DALYs worldwide
  – Respiratory and diarrhea illness represent 9.1% & 8.1%

Theory Behind Acute Stroke Therapy

• Ischemic penumbra:
  – The zone of ischemic tissue that is stunned or in the early stages of apoptosis/necrosis
  – 8gm/deciliter O2 brain tissue dies
  – 13gm/deciliter O2 ion pumps fail
  – 20gm/deciliter O2 electrical activity fails

Strategies

• Neuroprotectants:
  – Lazeroids
  – NMDA antagonists (Dextromethorphan)
  – Citicholine
  – Alphabet soup (glutamate antagonists)
  – Nimodipine in SAH
• Anti-inflammatory:
  – Indomethacin
  – Aspirin
• Ischemia reperfusion:
  – anti-MAC antibodies

History of Thrombolitics

• Reperfusion of the ischemic penumbra
• Early recanalization of arteries
• Streptokinase in the sixties (disaster)
• Thrombolysis abandoned until 1980s and the successful treatment of myocardial infarction
Streptokinase: Not Effective in the Setting of Acute Stroke

- Multicentre Acute Stroke Trial-Europe (MAST-E)
  - Death from intracranial hemorrhage
- Australian Streptokinase, 3-4 hours after stroke,
  - Death from intracranial hemorrhage
- Multicentre Acute Stroke Trial-Italy (MAST-I)
  - Death from intracranial hemorrhage
  - 1.6 million units of streptokinase
  - 300mg ASA for ten days after event
  - Slight reduction of death and disability in tx groups

Tissue Plasminogen Activator for Acute Ischemic Stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group

- Objective: randomized placebo double blinded study of rt-PA given within three hours of onset
- Two parts
  - Part one:
    - 291 patients
    - Goal: to determine if rt-PA had clinical activity within 24 hours
    - Endpoint: 4 point improvement in the NIHSS or resolution of the neurological deficit
  - Part two:
    - 333 patients
    - Global assessment statistic to assess outcome at three months

Tissue Plasminogen Activator for Acute Ischemic Stroke: The NINDS and Stroke rt-PA Stroke Study Group

- Conclusions
  - At three months thirty to fifty percent greater likelihood of minimal or no disability
  - Symptomatic ICH within 36 hours:
    - 6.4% with TPA
    - 0.6 in the placebo (P<0.001)
  - Mortality at three months
    - 17% in the rt-PA and
    - 21 % in the placebo (P=0.30)
**Tissue Plasminogen Activator for Acute Ischemic Stroke. The NINDS rt-PA Stroke Study Group Recommendation**

- Based on these results, rt-PA has been recommended as an acute stroke therapy if time of onset is less than 3 hours (1995)
- FDA approved therapy (1996)

**Intravenous Thrombolysis With Recombinant Tissue Plasminogen for Acute Hemispheric Stroke. The European Cooperative Acute Stroke Study (ECASS)**

Objective: to evaluate safety and efficacy of IV rt-PA in patients with acute stroke
- 620 patients
- 1.1mg/kg vs. 0.9 mg/kg NINDS of rt-PA
- 6 hours of onset vs. 3 hours onset

**Randomized Double-blind Placebo-controlled Trial of Thrombolytic Therapy With Intravenous Alteplase in Acute Ischemic Stroke (ECASS II)**

- Objective: to test efficacy of rt-PA at 0.9 mg/kg within six hours of onset
- 800 patients with good CT criterion
- Two groups: 0-3 hours and 3-6 hours
- Rankin dichotomized (0-1) favorable and (2-6) unfavorable outcome
Randomized Double-blind Placebo-controlled Trial of Thrombolytic Therapy With Intravenous Alteplase in Acute Ischemic Stroke (ECASS II)

- No difference between placebo and treatment groups in the 0-3 and 3-6 hour groups primary endpoint
- NIHSS (secondary outcome) was significant in tx Group at 90 days (P=0.035)
- Pot-hoc analysis of Rankin scales (death or dependency) showed absolute difference between rt-PA and placebo = 8.3% (P=0.024)

Recombinant Tissue-type Plasminogen Activator (Alteplase) for Ischemic Stroke 3-5 Hours After Symptom Onset. The ATLANTIS Study: A Randomized Controlled Trial

- Objective: to test the efficacy of rt-PA administered between 3 and 5 hours
- Phase 3, placebo controlled, double blinded randomized study of 0.9 mg/kg of rt-PA vs. placebo
- Intent to treat population of 613 acute ischemic strokes, 547 treated in 3-5 hr time frame
- Outcomes: Primary outcome was neurologic recovery at 90 days NIHSS<1
- Secondary outcome was Barthel index, Rankin, and Glasgow outcome scale at 30 and 90 days as well as serious adverse events

Results: 32% of the placebo and 34% of the treatment had an excellent recovery at 90 days (P=0.65)

- There was no difference in the secondary outcomes
- ICH was higher in the control than placebo
- Mortality at 90 days was 6.9% with placebo and 11.0% with rt-PA (P=0.03)

ATLANTIS: Safety Data

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>Placebo (n = 306)</th>
<th>rt-PA (n = 307)</th>
<th>P Value</th>
<th>Placebo (n = 279)</th>
<th>rt-PA (n = 279)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic ICH</td>
<td>4.2</td>
<td>11.3</td>
<td>.001</td>
<td>4.7</td>
<td>11.4</td>
<td>.004</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>1.3</td>
<td>6.7</td>
<td>&lt;.001</td>
<td>1.1</td>
<td>7.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fatal ICH</td>
<td>0.0</td>
<td>2.6</td>
<td>&lt;.001</td>
<td>0.0</td>
<td>3.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death within 30 d</td>
<td>6.9</td>
<td>10.9</td>
<td>.08</td>
<td>5.0</td>
<td>11.0</td>
<td>.93</td>
</tr>
<tr>
<td>Death within 30 d</td>
<td>4.2</td>
<td>7.6</td>
<td>.08</td>
<td>4.4</td>
<td>7.0</td>
<td>.18</td>
</tr>
</tbody>
</table>

*rt-PA indicates recombinant tissue-type plasminogen activator; ICH, intracerebral hemorrhage. Data are presented as percentages unless otherwise indicated. The target population received treatment as assigned between 3 and 5 hours after symptom onset.
ATLANTIS: Disability at 90 days Placebo vs. rt-PA

| NIHSS Day 90 |  |
|---|---|---|---|---|---|
| 0-1 | 2-5 | >5 | Death |
| Placebo | 25 | 45 | 23 | 7 |
| rt-PA | 35 | 28 | 14 | 23 |

Percentage of Patients

| Barthel Index Day 90 |  |
|---|---|---|---|---|---|
| 95-100 | 55-90 | 0-50 | Death |
| Placebo | 49 | 21 | 23 | 7 |
| rt-PA | 45 | 19 | 13 | 23 |

Percentage of Patients

Recombinant Tissue-type Plasminogen Activator (Alteplase) for Ischemic Stroke 1-3 Hours After Symptom Onset: The ATLANTIS Study: A Randomized Controlled Trial

- No favorable benefit for the use of I.V. rt-PA 0.9 mg/kg in the 3-5 hour time range

Intravenous Ancrod for Treatment of Acute Ischemic Stroke: the STAT Study: a Randomized Controlled Trial

- Ancrod is a purified fraction of venom from the Malaysian pit viper (Calloselasma rhodostoma)
- It causes rapid defibrinogenation resulting in anticoagulation
- Products of defibrinogenation may affect thrombolysis
- Used in Europe and Canada for DVTs and retinal vein occlusions

Intravenous Ancrod for Treatment of Acute Ischemic Stroke: the STAT Study: a Randomized Controlled Trial

- Objective to evaluate the safety and efficacy of Ancrod in acute ischemic stroke (1993-1998)
- 500 patients
- Randomized within three hours of onset of symptoms
- Goal to decrease fibrinogen levels to 1.18-2.03 micromole/liter
- 90 day outcome Barthel, ICH, and death

Results: Ancrod (n=248) and placebo (n=252)
- Better functional outcome at 90 days 42.2% vs. 34.4% (P=0.04)
- Mortality was the same in both groups (25%)
- More observed ICH in the treatment group

Mortality and Outcome 90 Days Ancrod Study
Intra-arterial Pro-urokinase for Acute Ischemic Stroke: the PROACT II Study: a Randomized Controlled Clinical Trial

- Objective: to determine the efficacy and safety of pro-urokinase (rpro-UK) in patients with acute stroke at less than 6 hours from onset
- 180 patients with angiographically proven occlusion of the MCA without hemorrhage or signs of early infarction on CT
- 9MG of IA rpro-UK plus heparin (n=121) or heparin only (n=59)
- Primary endpoints: neurologic disability (Rankin) at 90 days
- Secondary outcomes: recanalization, ICH, death, neurologic deterioration

PROACT: ICH vs. Heparin Dose

Table 3. Intracranial Hemorrhage

<table>
<thead>
<tr>
<th>Heparin Dose  Treatment Group</th>
<th>n</th>
<th>HI and/or PH Within 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>9</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>14</td>
<td>1 (7.1%)</td>
</tr>
<tr>
<td>Heparin</td>
<td>35</td>
<td>11 (31.4%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>26</td>
<td>11 (42.3%)</td>
</tr>
<tr>
<td>Heparin</td>
<td>26</td>
<td>12 (46.2%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>59</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Heparin</td>
<td>59</td>
<td>14 (23.7%)</td>
</tr>
</tbody>
</table>

Heparin Dose  Treatment Group

- 105 patients had angiogram
- 59 excluded from randomization
- 46 randomized
- 40 treated, 26 rpro-UK, 14 placebo

Recanalization was increased with heparin
- 81% for high heparin
- 40% for the low heparin

Hemorrhagic transformation
- 15.4% rpro-UK
- 7.1% of placebo (P=0.64)

Conclusion: treatment of ischemic stroke within 8 hours improves clinical outcome at 90 days
- 40% rpro-UK vs. 25% of the controls had Rankin <2 at 90 days (P=0.04)
- Mortality was the same for both groups
- Recanalization was 65% for the rpro-UK and 18% for the control (P=0.01)
- Intracranial hemorrhage and neurologic deterioration occurred in 10% of rpro-UK and 2% of the controls (P=0.06)
**PROACT II: Reperfusion after Pro-Urokinase 1hr vs. 2hr**

![Graph showing reperfusion rates after 1hr and 2hr of Pro-Urokinase treatment compared to control.](Image)

- r-ProUK, 1 hr (n=102)
- r-ProUK, 2 hr (n=108)
- Control (n=50)

**PROACT II: ICH, Placebo VS. Pro-Urokinase**

![Graph showing bleeding incidence at different time points after treatment.](Image)

- Patients, %
- Elapsed Time from Start of Therapy

**PROACT II Disability at 90 Days**

Placebo vs. Pro-Urokinase

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Pro-Urokinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>n=59</td>
<td>n=121</td>
</tr>
<tr>
<td>mRS = 0</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

**Modified Rankin Scale Score**

- P = .04

**Intra-arterial Thrombolysis**

- Intra-arterial thrombolysis opens occluded arteries
- Recanalization is less effective in internal carotid and basilar arteries
- Heparin may increase the efficacy of intra-arterial recanalization
- Intra-arterial thrombolysis may be safer than IV thrombolytics

**Thrombolytics in Acute Stroke**

<table>
<thead>
<tr>
<th></th>
<th>Benefit</th>
<th>Questionable</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECASS N=628</td>
<td>0-6</td>
<td>Questionable</td>
<td>none</td>
</tr>
<tr>
<td>ECAS II N=806</td>
<td>0-3.9</td>
<td>Questionable</td>
<td>none</td>
</tr>
<tr>
<td>ATLANTIS N=347</td>
<td>3.5</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>STAT N=248</td>
<td>0-2</td>
<td>Benefit</td>
<td>none</td>
</tr>
<tr>
<td>NIH I N=298</td>
<td>0-3</td>
<td>None at 30 days</td>
<td>none</td>
</tr>
<tr>
<td>NIH II N=333</td>
<td>0-3</td>
<td>Benefit</td>
<td>none</td>
</tr>
<tr>
<td>PROACT N=105</td>
<td>0-6</td>
<td>None/Safety</td>
<td>none</td>
</tr>
<tr>
<td>PROACT II N=188</td>
<td>0-6</td>
<td>Benefit</td>
<td>none</td>
</tr>
</tbody>
</table>

**Intra-arterial Thrombolysis**

- Intra-arterial thrombolysis opens occluded arteries
- Recanalization is less effective in internal carotid and basilar arteries
- Heparin may increase the efficacy of intra-arterial recanalization
- Intra-arterial thrombolysis may be safer than IV thrombolytics
Effect of ICH on Outcome
NINDS TPA trial

- Post-hoc analysis: factors associated with ICH
  - Severity NIHSS (OR, 1.8 CI, 1.2-2.9)
  - Brain Edema (OR 7.8 CI, 2.2-27.1)
  - Patients with severe neurologic deficit who received rt-PA had a better outcome at three months
  - Mortality was 4% less in the Placebo Vs rt-PA groups

Effect of ICH on Outcome

- Although there is an increase in ICH and ICH mortality in the treated groups
- The overall mortality in the rt-PA groups is less or equal to placebo when given within the three hours

ICH: Placebo vs. Thrombolytics Each Study

<table>
<thead>
<tr>
<th>Study</th>
<th>n (n)</th>
<th>Mortality</th>
<th>Symptomatic ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECASS</td>
<td>N=620</td>
<td>Placebo 13% Treatment 18%</td>
<td>Placebo 6.9% Treatment 19%</td>
</tr>
<tr>
<td>ECASS II</td>
<td>N=600</td>
<td>Placebo 3% Treatment 8%</td>
<td>Placebo 3.4% Treatment 5.3%</td>
</tr>
<tr>
<td>ATLANTIS</td>
<td>N=247</td>
<td>Placebo 7% Treatment 11%</td>
<td>Placebo 6% Treatment 21%</td>
</tr>
<tr>
<td>STAT</td>
<td>N=248</td>
<td>Placebo 21% Treatment 26%</td>
<td>Placebo 21% Treatment 9%</td>
</tr>
<tr>
<td>NIH 1</td>
<td>N=280</td>
<td>Placebo 23% Treatment 27%</td>
<td>Placebo 4% Treatment 5%</td>
</tr>
<tr>
<td>NIH 2</td>
<td>N=333</td>
<td>Placebo 23% Treatment 17%</td>
<td>Placebo 4% Treatment 9%</td>
</tr>
<tr>
<td>PROACT</td>
<td>N=165</td>
<td>Placebo 43% Treatment 36%</td>
<td>Placebo 3% Treatment 40%</td>
</tr>
<tr>
<td>PROACT II</td>
<td>N=180</td>
<td>Placebo 27% Treatment 26%</td>
<td>Placebo 4% Treatment 19%</td>
</tr>
</tbody>
</table>

Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2.

- 17,187 patients
  - i) streptokinase
  - ii) 1 month ECASA
  - iii) both
  - iv) neither.
- 5 week vascular mortality

Comparison NINDS vs ISIS-2

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Odds Ratio Disability or Death</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>624</td>
<td>0.49</td>
<td>(0.35-0.69)</td>
</tr>
<tr>
<td>ISIS-2</td>
<td>17,187</td>
<td>0.78</td>
<td>(0.71-0.85)</td>
</tr>
</tbody>
</table>

The Impact of Thrombolytics in the Setting of Acute Stroke

- Philosophical: Therapeutic nihilism is no longer acceptable, acute stroke is treatable
- The development of statistical techniques that can measure differences in neurologic outcomes within a diverse population
The Impact of Thrombolytics in the Setting of Acute Stroke

- Best treatment rates for acute stroke with IV rt-PA is 10%
- 10% of 700,000 is 70,000
- 30-50% of 70,000 is 21,000-35,000 improved outcomes per year
- Fairfax hospital that equals 40-80 strokes a year