Its About Time

- Lessons Learned from NINDS TPA Stroke Study
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25th Anniversary of Publication of the Results of the NINDS TPA Stroke Trials

No relevant financial relationship exists.
1988

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Table 4. Patient Status at First Neurologic Examination, Stroke Data Bank

<table>
<thead>
<tr>
<th>Category</th>
<th>Cerebral infarctions</th>
<th>Hemorrhages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infarct, unknown cause (n = 577)</td>
<td>Embolic (n = 246)</td>
</tr>
<tr>
<td>Median days onset to initial neurologic examination</td>
<td>2</td>
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Subjects and Methods
Between May 1984 and November 1985, 65 patients were admitted to a study of naloxone for the treatment of acute or progressing cerebral infarction. Patients were treated within 48 hours of the latest progression of symptoms at either the University of Cincinnati or University of Iowa Hospitals. Patients with cerebral infarction due to cardiogenic embolism, small vessel...
1981

Fig. 6. Ischemia thresholds. When local cerebral blood flow (ICBF) falls below about 23 cc/100 gm/min, reversible paralysis occurs. Even profound ischemia is reversible for a brief time. When ICBF falls below 10 cc/100 gm/min for 2 hours, or below 18 cc/100 gm/min during permanent occlusion, irreversible infarction occurs. MCA = middle cerebral artery.
Conceptual Model

• Reperfusion about 50%
• Any benefit decreased with time
• Hemorrhage increased with time
• It might take 30-60 minutes after infusion for the drug to work
• There was a point in time where risk would exceed benefit.
• The best chances of seeing an effect was before 2 hours from onset
• Needed to get the dose right—don’t jump ahead with cardiac dose
The Five NINDS Studies of TPA -- Time line

- February 1987 through September 1989, 74 patients at doses 22-81 mg, 4% hemorrhage rate 0-90 minutes.
- December 1988 through December 1989, 20 patients, 10% hemorrhage rate at higher doses 91-180 minutes.
- Randomized March 1990, through February 1991, 27 patients were placebo controlled randomized; 20 at less than 91 minutes and 7 greater than 90.
- NINDS Part 1 and Part 2, January 1991 through October 1994, 624 patients, 0.9mg/kg, any hemorrhage rate 6%.
Results of Part 1 and Part 2

- There was a statistically significant consistent and persuasive global odds ratio of no significant disability at 3 months 1.7:1 for Part 1 and 2.0:1 for Part 2 as measured on the modified Rankin Scale, the NIH Stroke Scale, the Barthel Index, and the Glasgow outcome scale.

- The part 1 and part 2 trials confirmed each other providing the evidence that led to the approval of TPA for stroke by FDA in 1996.

Attendance at ISC 1985-2005
The NINDS Stroke Study Was Not the Only Player

• There were studies of thrombolytics for stroke as early as 1958

• Other studies of intra-arterial and intravenous thrombolytics including TPA were ongoing during the 1970’s and 1980’s in Europe, Japan, and the United States.

• TPA grew up in a mutually supportive world community of investigators testing thrombolytics in a wide variety of stroke types, different doses, IV and IA administration. They used urokinase, streptokinase, and different forms of TPA.

• The placebo-controlled 620-patient European ECASS TPA trial results were published in October 1995 in JAMA two months before the publication of the NINDS results with results in December. The study enrolled patients with moderate and severe stroke up to 6 hours after stroke onset. This study did not show the effect seen in the 0-3-hour NINDS trial.

• International Symposia on Thrombolytic Therapy in Acute Ischemic Stroke started meeting in 1990 and are still meeting every two years.
Lessons Learned

• Publishing the trial was just a start—trials only tell you how good it could be
  • You can treat acute ischemic stroke
  • Change the medical care system
  • Follow up on remaining opportunities
  • Understand more about how the treatment works
  • Test and retest your assumptions.
• Produce good evidence
Lessons Learned

- Neither time or TPA or other acute stroke treatments work best alone.
- Most work gets done close to the perceived deadline.
- It takes a team, a community, a nation to build and improve effective treatment for acute stroke.
Conclusion

• Many thought they would fail, but with a lot of help and support across the world, the NINDS TPA Stroke Study Group succeeded by their determination to show it could be done, their commitment to reducing stroke disability, and their insistence on maintaining scientific integrity to rigorously test their ideas. The trial results have powered a transformation in acute stroke care and driven efforts to find new treatments and more effective medical care delivery for stroke.
Clinical centers:


Writing Team For NEJM 1995 Report Aerlie House, VA