OBJECTIVES:
1. Describe the areas of controversy surrounding the use of fibrinolytics for acute ischemic stroke.
2. Explain the controversy surrounding the NINDS t-PA trial.
3. Discuss the need to have a system of care in place for acute ischemic stroke management.

INTRODUCTION

The concept of using t-PA for the treatment of acute ischemic stroke became a reality in the mid-1980s when research began via the National Institute of Neurological Disorders and Stroke (NINDS) Pilot Studies Program. Indeed, the first patient with acute ischemic stroke treated with t-PA in a clinical trial setting was performed by members of the Greater Cincinnati/Northern Kentucky Stroke team in 1987. Subsequent to that, dose ranging trials of t-PA for acute ischemic stroke were performed in the late 1980s and into the early 1990s. In 1990, the NINDS announced plans for the first of two randomized trials of t-PA and acute ischemic stroke. Subsequent work ultimately led to the publication of the NINDS t-PA results in December of 1995 in The New England Journal of Medicine. The NINDS t-PA Stroke Trials and subsequent FDA approval of t-PA treatment for acute ischemic stroke have since lead to considerable controversy, particularly within the field of Emergency Medicine. This manuscript will discuss the controversy surrounding the use of t-PA for stroke centering on the research itself as well as with widespread implementation of the treatment.

One major criticism of the FDA approval of t-PA within the three hour window of acute ischemic stroke results from the fact multiple other fibrinolytic trials of acute ischemic stroke have had negative results. As noted from the two figures, there were 3 negative trials of streptokinase and 3 negative t-PA trials in acute ischemic stroke. Critics suggest of the 7 published trials, the NINDS study was the only trial with a positive outcome. This has fostered criticism of fibrinolytic therapy for acute ischemic stroke. In addition, a subsequent Cochrane Review similarly questioned the validity of fibrinolysis in general for acute ischemic stroke. Supporters of the use of t-PA in acute ischemic stroke note t-PA is a very different agent than streptokinase, leading to potentially different results especially with regard to the rate of symptomatic intracranial hemorrhage. Supporters of fibrinolytic therapy for stroke also suggest the other three t-PA trials in stroke had prolonged time windows for treatment of up to five or six hours. They note that time to treatment after symptom onset is considered such a significant predictor of patient outcome that the trials can not be directly compared.
In addition to the controversy of comparable trials of fibrinolysis, a number of elements of the NINDS trial itself came under significant scrutiny. The first and most significant trial-related controversy was the finding there was a significant imbalance in the baseline stroke severity between the treatment and placebo patients. The ultimate outcome of interest in the trial was good neurological outcome. The fact there were more patients with relatively mild strokes in the t-PA treated patients led to a call for a second analysis of the NINDS data to ensure this baseline imbalance did not invalidate the effectiveness of t-PA. In response to this and other criticisms of the trial, the NINDS commissioned a re-analysis of the original data from the t-PA Stroke Trial. The official charge communicated to an independent review team was: “to address whether there is concern that eligible stroke patients may not benefit from t-PA given according to the protocol used in the trials and whether the subgroup imbalance (in baseline stroke severity) invalidates the entire trial as claimed by some of the critics.” The ultimate results of this second analysis were published in the journal *Stroke* in 2004.\(^\text{11}\) The independent group found a clinically important and statistically significant benefit of t-PA therapy despite subgroup imbalances in baseline stroke severity and despite the increase in symptomatic intracranial hemorrhage in t-PA treated patients. Exploratory analyses were also performed but could find no statistical evidence that the t-PA treatment effect differed among patient subgroups. They concluded t-PA treatment of acute ischemic stroke patients within 3 hours of onset using the NINDS t-PA stroke trial protocol was effectively supported by this NINDS trial.

Additional controversy generated from the NINDS publication was the sample size; only 624 total patients were randomized. Critics were concerned about such a significant alteration in patient care being based on so few patients. Comparisons can be drawn to the publication of two recent stroke related trials, both of which invalidated previously promising trial outcomes. In both cases, trials of a similar magnitude to the NINDS trial had positive results but definitive larger trials subsequently had a negative finding. The first example comes from the treatment of intracerebral hemorrhage with recombinant Factor VII. A randomized trial of 399 patients with intra-cranial hemorrhage (ICH) randomized to treatment with varying doses of recombinant Factor VII within 3 hours of symptom onset demonstrated a significant mortality benefit at 90 days (Figure 3).\(^\text{12}\) Treated patients had a mortality rate of 18% while placebo patients had a mortality rate of 29%. This was found to be statistically significant with a p value of 0.02. A subsequent trial with substantially more patients, however, found no benefit to therapy, invalidating the previous trial’s ultimate conclusion.\(^\text{13}\)

In a similar fashion, a promising neuroprotective agent was studied in acute ischemic stroke patients within 6 hours of symptom onset. The study agent, NXY-059, was evaluated in 1699 patients.

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**Figure 1. Three trials evaluating streptokinase for acute ischemic stroke**

<table>
<thead>
<tr>
<th>Study</th>
<th>Time to Treatment</th>
<th>No. of Patients</th>
<th>Treatment Group</th>
<th>Mortality</th>
<th>Intracerebral Hematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASK</td>
<td>≤ 4 hours</td>
<td>340</td>
<td>SK + ASA versus ASA</td>
<td>36.2%</td>
<td>13.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ASA</td>
<td>20.5%</td>
<td>3.0%</td>
</tr>
<tr>
<td>MAST-E</td>
<td>≤ 6 hours</td>
<td>310</td>
<td>SK versus Placebo</td>
<td>34%</td>
<td>21.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18%</td>
<td>2.6%</td>
</tr>
<tr>
<td>MAST-I</td>
<td>≤ 6 hours</td>
<td>622</td>
<td>SK+ASA versus ASA</td>
<td>34%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SK versus</td>
<td>19%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Standard therapy</td>
<td>13%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

**Figure 2. Three trials evaluating t-PA for acute ischemic stroke with negative results.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Time to Treatment</th>
<th>No. of Patients</th>
<th>Treatment Group</th>
<th>Mortality</th>
<th>Intracerebral Hematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlantis</td>
<td>3-5 hours</td>
<td>579</td>
<td>0.9 mg/kg t-PA versus placebo</td>
<td>11.0%</td>
<td>7.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.5%</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>ECASS-I</td>
<td>≤ 6 hours</td>
<td>620</td>
<td>1.1 mg/kg t-PA versus placebo</td>
<td>17.9%</td>
<td>19.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12.7%</td>
<td>6.8%</td>
<td></td>
</tr>
<tr>
<td>ECASS-II</td>
<td>≤ 6 hours</td>
<td>800</td>
<td>0.9 mg/kg t-PA versus placebo</td>
<td>10.5%</td>
<td>8.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10.7%</td>
<td>3.4%</td>
<td></td>
</tr>
</tbody>
</table>
and published in 2006. The investigators concluded the administration of NXY-059 within 6 hours after onset of acute ischemic stroke significantly improved the primary outcome, the reduction in disability at 90 days, but did not significantly improve other outcomes including neurological function as measured by the National Institute of Health Stroke Scale. This initial finding was statistically significant with a p value equal to 0.038. This was heralded as the first positive clinical trial for the primary outcome of a neuroprotective agent.

A subsequent trial of 3306 patients, however, found no benefit to this drug as a neuroprotective agent in acute ischemic stroke patients treated within 6 hours of symptom onset. Again, a relatively large scale clinical trial primary outcome was found to be invalid when the protocol was expanded to a larger patient population.

In this analysis, 2775 patients from over 300 hospitals and 18 countries randomized to t-PA or placebo for acute ischemic stroke within 6 hours of symptom onset were analyzed (Figure 4). Ultimately, this pooled analysis demonstrated patients treated within 4.5 hours of acute ischemic stroke onset with t-PA have an improved outcome. Clearly, such arguments have statistical merit, however some clinicians remain unconvinced.

It must be noted the generalized efficacy of t-PA is supported by a well done pooled analysis of all patients treated with t-PA for acute ischemic stroke. In this Lancet publication in 2004, all patients treated with t-PA for acute ischemic stroke within 6 hours of symptom onset in 5 large clinical trials were pooled and subsequently analyzed. This methodology is different than a meta-analysis in which papers are reviewed and data compared. In the methodology of a pooled analysis, individualized patient data from multiple trials are pooled together and subsequently analyzed. In this analysis, 2775 patients from over 300 hospitals and 18 countries randomized to t-PA or placebo for acute ischemic stroke within 6 hours of symptom onset were analyzed (Figure 4). Ultimately, this pooled analysis demonstrated patients treated within 4.5 hours of acute ischemic stroke onset with t-PA have an improved outcome. This is true for each individual 90 minute increment from 0-90 minutes, 91-180 minutes, and 181-270 minutes after symptom onset. Beyond 4.5 hours, patients treated with t-PA for acute ischemic stroke were found to actually do worse than placebo patients. There is clearly an inflection point based on time at approximately 4.5 hours after symptom onset when t-PA therapy becomes potentially harmful.

Most recently, the publication of the Safe Implementation of Thrombolysis in Stroke – Monitoring Study (SITS-MOST) was initiated over concern regarding the generalizability of this therapy. In this registry of 6,483 patients from 285 centers and 14 countries, patients treated...
with t-PA for acute ischemic stroke had outcomes similar to the pooled analysis results with regard to both ICH and mortality. The investigators concluded intravenous alteplase was safe and effective in routine clinical use when administered within 3 hours after stroke onset, even by centers with little previous experience using fibrinolytic therapy for acute ischemic stroke.\(^{19}\)

Among the greatest controversies of acute ischemic stroke treatment, specifically with fibrinolysis, is the generalizability of this therapy. Skeptics appropriately point out the NINDS trials were conducted by highly motivated, highly skilled investigators. The concern is that physicians who do not specialize in stroke management using such a potentially dangerous therapy may not have similar outcomes. A JAMA publication in 2000 highlighting “the Cleveland area experience” fueled this controversy further.\(^{16}\) This publication outlined an extremely well done study evaluating the rate of intravenous t-PA use for acute ischemic stroke, the incidence of symptomatic intracerebral hemorrhage, and the inpatient outcomes in a large urban community. This report provided a unique opportunity to evaluate standardized data collected on every stroke patient admitted to 29 Cleveland area hospitals by the Cleveland Health Quality Choice Project. Using these data, a research team was able to definitively document patterns of t-PA use and subsequent inpatient outcomes. This study demonstrated over a one year period extending between 1997 and 1998, that 70 patients (1.8%) out of a total of 3,948 stroke patients in the Cleveland area were treated with intravenous t-PA. The symptomatic intracerebral hemorrhage rate was found to be 15.7%, and patients treated with t-PA were found to have protocol violations in 50% of the cases. The authors noted the in-hospital mortality was significantly higher for patients treated with t-PA (15.7%) compared to patients not receiving t-PA (5.1%), and compared to a predictive model finding of 7.9%. This publication questioned the generalizability of this therapy across hospital centers.

There is no doubt employing t-PA therapy for acute ischemic stroke requires a well organized system and physicians who are both interested in, and properly trained to provide, such management. The investigative team from Cleveland ultimately led a stroke quality improvement program initiated at over 9 hospitals in the Cleveland area. A subsequent analysis of patients treated with t-PA after the clinical improvement program was implemented demonstrated a dramatic decrease in protocol violations and ultimately improved patient outcomes which matched the original NINDS t-PA trial results.\(^{17}\) Based on this study, it

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**Figure 4. Pooled analysis of five large trials of t-PA administered for ischemic stroke within six hours of symptom onset**

Adjusted odds ratio with 95% confidence interval by stroke onset to treatment time (N=2776)

![Graph showing adjusted odds ratio over time](image)

**What remains clear, however, is that successful implementation of this therapy requires appropriate infrastructure and system support for the treating physicians.**
seems clear this therapy is not generalizable without the implementation of specific system improvements for generalized stroke care. It indicates such improvements can lead to outcomes replicating the NINDS t-PA experience. Emergency physicians who are asked by colleagues to be involved in the challenging care of critical stroke patients must therefore demand a support system which will ensure appropriate treatment of patients.

In summary, there has been significant controversy regarding the treatment of stroke over the past decade. At present, the majority of the physicians and scientists in the stroke community support the use of t-PA therapy for acute ischemic stroke within 3 hours after symptom onset utilizing the NINDS study protocol. Guidelines for such therapy are well published and widely available. What remains clear, however, is that successful implementation of this therapy requires appropriate infrastructure and system support for the treating physicians. Emergency physicians tasked with the care of acute ischemic stroke patients should expect support from their institution relative to consultation by neurology specialists expert in stroke care and appropriately trained radiologists for image interpretation.

REFERENCES


4. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. Multicentre acute stroke trial--Italy (MAST-I) group. Lancet. 1995;346:1509-1514


