tPA In Acute Ischemic Stroke: Con

For Neurological Emergencies / RVH Day
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The use of tPA in acute ischemic stroke is controversial

CAEP: "Further evidence is necessary to support the widespread application of stroke thrombolysis outside research settings."

ACEP: "Further studies are needed to define more clearly those patients most likely to benefit from fibrinolytic therapy in acute ischemic stroke."

SAEM: "It is not yet clear whether the treatment risk is outweighed by the likely therapeutic benefit. "Currently insufficient data exist to mandate thrombolytic therapy as the standard of care for acute ischemic stroke for all patients across all medical treatment settings."

AAEM: "Objective evidence regarding the efficacy, safety, and applicability of tPA for acute ischemic stroke is insufficient to warrant its classification as standard of care."
Intro

Thrombolysis for stroke versus thrombolysis for MI
Randomized Data

It is impossible to prove a therapy doesn’t work

Predicted arrangement of multiple trials:
  a bell-shaped curve

6:1
Randomized Data

ECASS-I 1995

MAST-I 1995

ASK 1996

MAST-E 1996

ECASS-II 1998

ATLANTIS 1999

Hacke, JAMA 2005

MAST-I Study Group, Lancet 1995

Donnan, JAMA 1996

MAST-E Study Group, NEJM 1996

Hacke, Lancet 1998

Clark, JAMA 1999
Randomized Data

Explanations for discrepant results in NINDS
tPA vs. streptokinase
Lower tPA does in NINDS vs. ECASS
The 3 hour cutoff
Chance
STROKE

KNOw STROKE
KNOw THE SIGNS. ACT IN TIME.

STROKE

TROUBLE WALKING
TROUBLE SEEING
WEAKNESS ON ONE SIDE
TROUBLE SPEAKING

Stroke is A Brain Attack
Are You At Risk?

The Warning Signs Are:
• Sudden Weakness
• Sudden Numbness
• Sudden Severe Headache
• Sudden Change In Vision
• Sudden Confusion

Call 911 if you experience any of these Warning Signs.

Stroke (Brain Attack) Risk Factors
• Previous stroke or mini-stroke: 10x higher risk
• High Blood Pressure: 7x higher risk
• Diabetes: 4x higher risk
• atrial fibrillation: 6x higher risk
• Heart Disease: 5x higher risk
• Carotid Artery Disease: 4x higher risk

Important Questions To Ask Your Doctor
• Do I have atrial fibrillation (irregular heartbeat)?
• Is my blood pressure below 140/90?
• Is my blood sugar below 120?
• Is my cholesterol below 160?
• Do I have heart disease?
• Are my carotid arteries (arteries in the neck) narrowed?

NATIONAL STROKE COUNCIL

UNIVERSITY OF MARYLAND MEDICINE
The Maryland Brain Attack Center

The patient stroke information line call 1-800-492-5538
For physician stroke recommendations, call 1-800-377-4377
and ask for the Maryland Brain Attack Team.
www.umm.edu/stroke
NINDS

“2 Trials”

3 month mRS 0-1: tPA 39%, placebo 26%

Symptomatic ICH: tPA 6.4%, placebo .6%

NINDS Investigators, NEJM 1995
49% in the very early group

Failure of randomization in the 91-180 minute group

Marler, Neurology 2000
Failure of randomization in the 91-180 minute group

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Treatment Group</th>
<th>0–5 (Q₁)</th>
<th>6–10 (Q₂)</th>
<th>11–15 (Q₃)</th>
<th>16–20 (Q₄)</th>
<th>&gt;20 (Q₅)</th>
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<tr>
<td>All patients</td>
<td>Placebo</td>
<td>16 (28%)</td>
<td>83 (55%)</td>
<td>66 (50%)</td>
<td>70 (49%)</td>
<td>77 (55%)</td>
<td>312 (50.2%)</td>
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<td>t-PA</td>
<td>42 (72%)</td>
<td>67 (45%)</td>
<td>65 (50%)</td>
<td>73 (51%)</td>
<td>63 (45%)</td>
<td>310 (49.8%)</td>
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<tr>
<td></td>
<td>Total</td>
<td>58</td>
<td>150</td>
<td>131</td>
<td>143</td>
<td>140</td>
<td>622</td>
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<tr>
<td>OTT† 0–90 minutes</td>
<td>Placebo</td>
<td>9 (41%)</td>
<td>37 (55%)</td>
<td>31 (44%)</td>
<td>37 (48%)</td>
<td>31 (47%)</td>
<td>145 (48.0%)</td>
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<td>t-PA</td>
<td>13 (59%)</td>
<td>30 (45%)</td>
<td>39 (56%)</td>
<td>40 (52%)</td>
<td>35 (53%)</td>
<td>157 (52.0%)</td>
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<tr>
<td></td>
<td>Total</td>
<td>22</td>
<td>67</td>
<td>70</td>
<td>77</td>
<td>66</td>
<td>302</td>
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<tr>
<td>OTT 91–180 minutes</td>
<td>Placebo</td>
<td>7 (19%)</td>
<td>46 (55%)</td>
<td>35 (57%)</td>
<td>33 (50%)</td>
<td>46 (62%)</td>
<td>167 (52.2%)</td>
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<td>t-PA</td>
<td>29 (81%)</td>
<td>37 (45%)</td>
<td>26 (43%)</td>
<td>33 (50%)</td>
<td>28 (38%)</td>
<td>153 (47.8%)</td>
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<tr>
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<td>Total</td>
<td>36</td>
<td>83</td>
<td>61</td>
<td>66</td>
<td>74</td>
<td>320</td>
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</tbody>
</table>
NINDS

The two part trial

No difference at 24h:
A face validity question
Misdiagnosis

Magnitude of benefit

Libman, Arch Neurol. 1995  
Kahn, J Emerg Med 2005  
Bateman, Stroke 2006
Reanalyses

Cochrane Review 2003

Pooled Analysis of NINDS, ECASS, and ATLANTIS

Wardlaw, Cochrane Database 2003
Wardlaw, West J Med 2002
Hacke, Lancet 2004
Lenzer, Healthy Skepticism 2005
Usage Studies

Tanne, Neurology 1999, Henry Ford Review: 13/16 hospitals identified as high-volume specialty centers from select cities, most of which used a stroke team. 136 patients, 6% symptomatic ICH, but 11% where there were protocol violations, which occurred 30% of the time in these specialty centers.

Albers, JAMA 2000, STARS cohort. Selective review of 57 expert-based american centers that participated in the ATLANTIS study. 389 patients, 3.3% symptomatic hemorrhage rate with a high proportion of positive outcomes.

Katzan, JAMA 2000, The Cleveland Cohort. Inclusive review of all patients with stroke in the city except for the VA over a one year period. Treatment rate was 1.8%. 15.7% symptomatic ICH, 50% protocol violations. In-hospital mortality 15.7% vs. 5.1%.

Bravata, Arch Int Med 2002, The Connecticut Cohort. An inclusive review of all patients in the state over 2.5 years. Treatment rate was .6%. In-hospital mortality was 25% (vs. NINDS 13%).

Szoeke, MJA 2003, Royal Melbourne Hospital, all diagnosed ischemic stroke patients over 3 years. Treatment rate 3.2%, protocol violation rate with dedicated stroke unit with stroke neurologist, stroke fellow, and stroke RN was 23%.

Heuschmann, JAMA 2004, German Stroke Registry 57,000 strokes from 2000-2003. tPA treatment rate 3%. Inhospital mortality 10% tPA vs. 4.6% no tPA.

Saposnik, JAMA 2004: Prospective UWO registry 1999-2003. Rate of cerebral hemorrhage at 36 hours was 10.4%.

Hill, CMAJ 2005: Selective CASES registry 1999-2001: Excellent clinical outcome of treated patients 31.8%, closer to NINDS placebo, though reported as 37%, which is closer to NINDS treatment arm.

Bateman, Stroke 2006: In this inclusive database the thrombolysis cohort had a higher in-hospital mortality rate compared with the nonthrombolysis patients (11.4% versus 6.8%).
How it happened

Big Pharma & the media frenzy

Expert effect

Bandwagon bias

Desire to do something

Trotter, West J Med 2002

Woods 2006
Conclusions

There is one randomized trial that demonstrates a modest benefit for IV tPA in acute ischemic stroke. This trial is at odds with almost all of the other randomized data on the subject, and suffers from a number of internal and external validity problems that can explain its discrepant results.
Conclusions

If thrombolysis is considered in the most conceivably generous light, it benefits an absurdly small number of stroke patients, and the present expenditure of resources on this agent that could be diverted to therapies of unquestionably greater value—such as stroke units—is irresponsible.

Donnan, Med J Aust 2003
Conclusions

The logical conclusion to draw from the available data is that tPA does not work; the optimistic view is that tPA might work for a yet-unidentified subset of patients. It is clear that if the trial results pattern were switched (such that NINDS were the only trial that didn't show a benefit), NINDS would have been ignored, and it is also clear that the focus on tPA as a therapy for stroke is driven by forces other than the data.
Conclusions

A therapy as dangerous as tPA must *conclusively* demonstrate benefit before it can be considered for routine use. That tPA has been adopted in some settings as standard of care, and that it is being touted as a cure for stroke to a public unversed in its limitations and consequences, and that an entire "brain attack" industry and regional stroke system is being implemented before more convincing data is available is at best uninformed and at worst shameful. At this time, the use of any intravenous thrombolytic should be confined to rigorously controlled settings where it can be administered as part of a research effort to determine in which patients, if any, the benefit outweighs the risk.
References


References


References


References


31 Trotter G. Why were the benefits of tPA exaggerated? West J Med. 2002 May;176(3):194-7.

