Endovascular Treatment of Acute Ischemic Stroke

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The Trial That Started It All!

624 patients with ischemic stroke within 3 hours

Intravenous alteplase (0.9 mg/kg)  Placebo

Improvement at 24 hrs
47%  39%

Favorable outcome at 3 m
43%  27%

Intracerebral hemorrhage
6.4%  0.6%
### Results of Intravenous Alteplase for Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Death or dependency</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>312</td>
<td>57%</td>
</tr>
<tr>
<td>ECASS II</td>
<td>81</td>
<td>58%</td>
</tr>
<tr>
<td>STARS</td>
<td>389</td>
<td>57%</td>
</tr>
</tbody>
</table>

The search for new treatments must continue!

Is Intra-arterial Approach Superior?

- High concentration of thrombolytics can be delivered at the site of occlusion
- Exposure to a lower systemic dose
- Avoid unnecessary and potentially hazardous use of thrombolytics in patients who do not have a occlusion
- Potential for mechanical disruption of clot

Endovascular Thrombolysis Strategies

- Pharmacological Thrombolysis
- Mechanical Thrombolysis
- Pharmacological and Mechanical Thrombolysis
Endovascular Thrombolysis Strategies

Pharmacological Thrombolysis

Mechanical Thrombolysis

Pharmacological and Mechanical Thrombolysis
Structure of Pro-urokinase

Pro-urokinase
411-amino acids
[glycosylated]

Urokinase

Fibrin bound plasmin
Prolyse in Acute Cerebral Thromboembolism (PROACT) II

180 patients with occlusion of middle cerebral artery within 6 hours of onset

Intraarterial Prourokinase (9mg) vs Placebo

Follow-up at 3 months

Recanalization
- Prourokinase: 66%
- Placebo: 18%

Symptomatic ICH
- Prourokinase: 10%
- Placebo: 2%

Favorable outcome
- Prourokinase: 40%
- Placebo: 25%

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Endovascular Thrombolysis Strategies

- Pharmacological Thrombolysis
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- Pharmacological and Mechanical Thrombolysis
Combined Mechanical and Pharmacological Thrombolysis: Intra-arterial Reteplase, Mechanical Disruption, and Stent Placement

Qureshi AI: Neurosurgery 2002;51:1319-1329
Mechanical Thrombolysis

Mechanical Disruption using the Snare
Disruption of Thrombus-vessel Wall Bond

Platelet adhesions with endothelium and subendothelium, Essential component of thrombus stability

Platelet-vessel wall adhesions disrupted, Reduced stability of thrombus

Not all Occlusions Are Alike

Normal vessel and embolus

Atherosclerotic vessel and superimposed thrombus
Mechanical Thrombolysis

Mechanical devices

Mechanical disruption
- Clot busters
- Balloon catheters
- Snares
- EKOS
- Angiojet

Mechanical retrieval
- Clot removal

Algorithm for Patients with Ischemic Stroke

Qureshi AI: Neurosurgery 2001;49:41-50

- Acute onset neurological deficits
  - CT scan head
    - No Intracranial Hemorrhage AND Early Infarction <1/3 of Vessel Distribution
      - Onset < 3 hours
        - NIH stroke scale $\geq 16$
          - Recent surgery
          - IV Alteplase (0.9 mg/kg)
      - Onset 3-6 hours
        - IA Reteplase (2-4 U)
        - Mechanical thrombus Disruption
          - Angioplasty/Microsnare
Angioplasty Balloon Catheter
Basilar Artery Occlusion Resistant to Thrombolysis
Angioplasty at Site of Thrombus
Post-angioplasty Response
Microvena Snare
Middle Cerebral Artery Occlusion
Microcatheter Crossing the Thrombus
Snare Maneuver
Post Snare Angiogram
Intravascular Stents
Occlusion of Middle Cerebral Artery Resistant to Thrombolysis
Stent Deployment
Immediate Recanalization
Angiographic Response to Incremental Doses of Reteplase

Modified TIMI Perfusion Grade

Reteplase Dose (units)
Conclusions

• In our study, aggressive mechanical thrombolysis resulted as adjunct to low dose Reteplase resulted in a high rate of recanalization. (Synergistic effect)

• Reduced doses of thrombolytics may be associated with a lower intracranial hemorrhage rate. (Safer?)

• This strategy offers potential in those patients considered poor candidates for intravenous thrombolysis.
Endovascular Thrombolysis Strategies

Pharmacological Thrombolysis

Pharmacological and Mechanical Thrombolysis

Mechanical Thrombolysis
Clot Retrieval Devices

Concentric Retriever System
Concentric Retriever System

Thrombus Retriever X5
Concentric Thrombus Retriever – *In vivo*
Patient 04-002
Pre/Post Angiogram

Pre Treatment

Post Treatment
Patient 03-002 – Clot
Results from Phases I and II trial of Concentric Retriever System


114 patients with ischemic stroke
0-3 hours (not candidates for IV rTPA)
OR
3-8 hours

Recanalization: 46%
Symptomatic intracranial hemorrhages: 8%

90 day results
Favorable outcome (Modified Rankin 0-2): 34%
Mortality: 39%
111 patients with ischemic stroke
0-3 hours received IV rTPA (27%)  
OR
3-8 hours

Recanalization: 69%  
Symptomatic intracranial hemorrhages: 9%

Symptomatic intracranial hemorrhages:  
7% with IV rt-PA  
10% without IV rt-PA
Thrombolysis Strategies: Everything works but what works best!
Comparison of Recanalization Rates Between Different Strategies

- Pharmacological
- Mechanical
- Combined

N=40
N=121
N=80
N=114
N=46
Comparison of Symptomatic Intracranial Hemorrhages Between Different Strategies

- Pharmacological: N=40
- Mechanical: N=121
- Combined: N=80
- N=114
- N=46
Conclusions

• Combination of mechanical and pharmacological thrombolysis result in high rates of recanalization without an increased rate of intracranial hemorrhage.

Comparison of Recanalization Rates Between Different Strategies

- **IA rt-PA**
- **EKOS ultrasound**
- **Retriever+ IA rt-PA**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Recanalization Rate</th>
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<tbody>
<tr>
<td>IMS</td>
<td>60</td>
</tr>
<tr>
<td>IMS-II</td>
<td>80</td>
</tr>
<tr>
<td>MERCI</td>
<td>60</td>
</tr>
<tr>
<td>Multi-MERCI</td>
<td>80</td>
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Comparison of Recanalization Rates Between Different Strategies

Part II of both studies demonstrate superiority of the combined approach
Putting it all together in 2009

A management algorithm

Protocol for acute ischemic stroke treatment at University of Minnesota Medical Center-Fairview and Hennepin County Medical Center

Ischemic stroke

0-3 hrs

IV thrombolysis

NIHSS score <10

NIHSS score ≥10

3-6 hrs

Endovascular treatment (mechanical/pharmacological approach)

>6 hrs

MRI diffusion-clinical mismatch
Protocol for acute ischemic stroke treatment at University of Minnesota Medical Center-Fairview and Hennepin County Medical Center

Ischemic stroke

- 0-4.5hrs
  - IV thrombolysis
  - NIHSS score <10
  - NIHSS score ≥10

- 3-6 hrs
  - Endovascular treatment (mechanical/pharmacological approach)

- >6 hrs
  - CT Perfusion-Volume mismatch
Protocol for acute ischemic stroke treatment at University of Minnesota Medical Center-Fairview and Hennepin County Medical Center

Ischemic stroke

- 0-3 hrs
  - IV thrombolysis
  - NIHSS score <10

- 3-6 hrs
  - MRI diffusion-clinical mismatch

- >6 hrs
  - NIHSS score ≥10
  - MRI diffusion-clinical mismatch
  - Endovascular treatment (mechanical/pharmacological approach)
  - IV Platelet GP IIb/IIIa Inhibitors
  - Reocclusion
  - Angioplasty/stent
  - Residual thrombus
Lessons that Impact the Future

- A high rate of recanalization can be achieved using third generation thrombolytics, glycoprotein IIb/IIIa receptor antagonist and mechanical thrombolysis.
- The ability to recanalize occluded vessels will continue to improve with newer agents and devices.
- RECANALIZATION IS IMPORTANT BUT IT IS NOT THE ONLY FACTOR THAT DETERMINES CLINICAL OUTCOME.
- Expedited transfers, ready availability, and appropriate selection of patients is the final determinant of the future of acute stroke treatment.
Thank you

Minnesota Stroke Initiative and Zeenat Qureshi Stroke Research Center