Current Management of Acute Ischemic Stroke

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Disclosures

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  - NIH/NINDS

Selected slides courtesy of Wade Smith, MD, PhD

Overview

- Pathophysiology of focal ischemia
- Role of acute revascularization
- Update on endovascular therapies
- Stroke centers: New challenges

Focal brain ischemia

- Time dependent
- Focal ischemia is different from global ischemia
- Energy failure -> Ca++ entry and cell death
- Glutamate toxicity
- Apoptosis

TIME IS BRAIN
Role of Time – IV rtPA
Most Recent Pooled Analysis of IV rtPA Trials

- NINDS Part 1
- NINDS Part 2
- ATLANTIS A
- ATLANTIS B
- ECASS II
- ECASS III
- EPITHET

Khatri et al., Lancet, 2010

Stroke Revascularization 2014

- IV tPA
  - Proven efficacy
  - Better outcome earlier in all subgroups
- IA lytics
  - Proven efficacy
  - Unapproved for IA tPA
  - Earlier is better, <6 hours

- Embolectomy
  - Stent retrievers better
  - Solitaire, Trevo, Merci Penumbra all able to recanalize vessels
  - No clinical efficacy data
  - Trials showing no benefit
  - SYNTHESIS- Expansion
  - IMS-III Study
  - MR RESCUE

NEJM 2013
Stroke Revascularization 2015

- IV tPA
  - Proven efficacy
  - Better outcome earlier in all subgroups
- IA lytics
  - Proven efficacy
  - Unapproved for IA tPA
  - Earlier is better, <6 hours

- Embolectomy
  - Multiple devices
    (Solitaire, Trevo, Merci Penumbra, etc.) all able to recanalize vessels
  - Stent retrievers better
  - Several new trials showing clinical efficacy

Endovascular stroke trials

- MR CLEAN  January 1, 2015
- EXTEND-IA  February 15, 2015
- ESCAPE  February 15, 2015
- SWIFT PRIME  April 17, 2015
- REVASCAT  April 17, 2015

Modified Rankin Scale (mRS)

0- Normal
1- Deficit by no disability
2- Minor disability, can walk independently
3- Needs a gait aid
4- Wheel chair bound
5- Bed bound
6- Expired
MR-CLEAN

- Netherlands, randomized pragmatic trial of IA embolectomy versus best medical therapy, IV t-PA allowed

CT/CTA: ICA/M1/M2/A2

N=267

Medical Therapy

Stroke IV t-PA if eligible < 4.5 hr

N=233

Device

Outcome: 90-Day mRS


EXTEND-IA

- Australia, randomized trial of IA embolectomy versus best medical therapy, IV t-PA required

CT/CTA/CTP: ICA or M1

Salvageable tissue

Core < 70 cc

N=35

No further Rx

N=35 Solitaire

Stroke IV t-PA 0.9 mg/kg < 4.5 hr

Outcome: Reperfusion at 3d NIHSS drop of ≥ 8

Campbell et al, NEJM 2015; 372:1009-18
EXTEND-IA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alloplase Only Group (N=35)</th>
<th>Endovascular-Therapy Group (N=35)</th>
<th>Adjusted</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median reperfusion at 24 hr (IQR)</td>
<td>31 (0-65)</td>
<td>29 (13-150)</td>
<td>0.06</td>
<td>0.02</td>
<td>0.56</td>
</tr>
<tr>
<td>Early reperfusion improvement (%)</td>
<td>17 (10-27)</td>
<td>27 (9-48)</td>
<td>0.03</td>
<td>0.01</td>
<td>0.64</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median score (IQR)</td>
<td>50 (33-67)</td>
<td>50 (35-65)</td>
<td>0.05</td>
<td>0.03</td>
<td>0.68</td>
</tr>
<tr>
<td>Safety (%)</td>
<td>92 (11-96)</td>
<td>90 (71-100)</td>
<td>0.10</td>
<td>0.08</td>
<td>0.72</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>7 (2-20)</td>
<td>6 (1-20)</td>
<td>0.06</td>
<td>0.03</td>
<td>0.68</td>
</tr>
</tbody>
</table>

EXTEND-IA

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

ESCAPE

- International, randomized trial of best medical therapy (BMT) vs. BMT + embolectomy, (IV t-PA optional)

CT/CTA/CTP: ICA or M1/M2
ASPECT 6-10 (non-con)
Good collaterals (CTA)

N=150
No further Rx

N=165
Embolectomy

Stroke
IV t-PA
0.9 mg/kg
< 4.5 hr if eligible

Outcome:
mRS at 90 day

Trial Stopped by DSMB

Goyal et al, NEJM 2015; 372:1019-30
SWIFT-Prime

- International, randomized trial of IV t-PA vs. IV t-PA + IA embolectomy, (IV t-PA required)

CT/CTA/CTP: ICA or M1 ASPECT 7-10 (non-con)

Stroke  IV t-PA  0.9 mg/kg < 4.5 hr

N=97 No further Rx
N=98 Solitaire

Outcome: mRS at 90 day (Shift analysis and mRS ≤ 2)

Trial Stopped by DSMB

Saver et al, NEJM 2015 Apr 17 e pub

Score on Modified Rankin Scale

No symptoms 1 2 3 4 5 or 6

Stent Retriever + Intravenous t-PA (N=98)

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 or 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>26</td>
<td>17</td>
<td>12</td>
<td>15</td>
<td>12</td>
<td></td>
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</table>

Intravenous t-PA (N=93)

<table>
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<th>Score</th>
<th>0</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5 or 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>11</td>
<td>16</td>
<td>17</td>
<td>22</td>
<td>26</td>
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</tbody>
</table>

N=97 No further Rx
N=98 Solitaire

Saver et al, NEJM 2015 Apr 17 e pub

OR 2.8 (1.5-4.9)

Medical Arm
Endovascular

90 mRS ≤ 2 SICH Reperfusion Mortality

Saver et al, NEJM 2015 Apr 17 e pub

ORIGINAL ARTICLE

The New England Journal of Medicine

Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

REVASCAT

- Spain (Catalonia), randomized trial of best medical therapy vs. IA embolectomy (+IV tPA if eligible)

CTA/MRA: ICA or M1
Onset within 8 hrs

Outcome: mRS at 90 day
(Shift analysis and mRS ≤ 2)

Trial Stopped by DSMB

N=103
Best medical therapy

N=103
Solitaire

Jovin TG et al, NEJM 2015 Apr 17 e pub

Summary of RCTs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Met Primary Endpoint?</th>
<th>NNT</th>
<th>Improved Mortality?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACT</td>
<td>1999</td>
<td>Yes</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>MELT</td>
<td></td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Synthesis</td>
<td>2013</td>
<td>No</td>
<td>n/a</td>
<td>No</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>2013</td>
<td>No</td>
<td>n/a</td>
<td>No</td>
</tr>
<tr>
<td>MS-III</td>
<td>2013</td>
<td>No</td>
<td>n/a</td>
<td>No</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>2015</td>
<td>Yes</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>2015</td>
<td>Yes</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>2015</td>
<td>Yes</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>SWIFT-Prime</td>
<td>2015</td>
<td>Yes</td>
<td>2.6</td>
<td>No</td>
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<tr>
<td>REVASCAT</td>
<td>2015</td>
<td>Yes</td>
<td>6</td>
<td>No</td>
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</tbody>
</table>

UCSF Acute Stroke Protocol
Stroke Centers

• System approach for stroke shown to improve outcomes
• Pre-printed orders, leadership, QA, connection to community/EMS
• Joint Commission accreditation and auditing
• Comprehensive stroke centers with endovascular capability certification started
• Increasing need in light of new trial data

Challenges

• Providing this care to everyone
• Prehospital delays
• Interfacility transfers

Conclusions

• Pathophysiology of acute focal ischemia requires emergency treatment
• Revascularization can lead to better outcomes, but needs to be achieved quickly before irreversible injury and increased risk for harm
• IA therapy for large vessel ischemic stroke now has Level 1 evidence for efficacy (7 positive RCTs)
• Current Stroke Centers are just the beginning
• Systems need to be built to provide these therapies
• We now need to get faster at treatment