Advances in Therapies for Acute Stroke: Intra-arterial Thrombolysis

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EMS Dinner
November 2nd, 2006

The presenter has no conflicts of interests to disclose.
Neuroendovascular Service @ Albany Med

- A. John Popp, MD, Chair Neurosciences Institute
- ALBANY MED STROKE TEAM
  - Gary Bernardini, MD, PhD
  - Alan Boulos, MD
  - Dileep Yavagal, MD
  - Randall Edgell, MD
  - John Dalfino, MD
Current Stroke Treatment Windows

• 0-3 h: I.V. tPA,
  – consider low dose tPA + IA lysis if M1 or large artery occlusion suspected
• 3-6 h: IA tPA
• 3-8 h: Mechanical thrombectomy, MERCI device
• 0-12h (maybe 24h) for basilar artery occlusion
Overview

- Mechanism and Pathophysiology of Ischemic Stroke
- Intra-arterial Thrombolysis
- Intra-arterial Mechanical Thrombolysis
  - MERCI
- Future directions
Stroke = Brain Attack

- Blockage of blood vessel in brain
- Lack of oxygen to the affected area
- Death of the affected brain tissue
- Loss of function (Paralysis)

Courtesy Stroke Center Org

Albany Medical Center
Ischemic Penumbra

- The ischemic penumbra is a potential target for stroke therapy
- Penumbra is defined as:
  - “potentially salvageable region of tissue surrounding the core infarct in which there is enough blood flow to survive, but not enough to function”
Need for Neuroendovascular treatment for Acute Stroke

- Extremely small number of patients receive IV tPA
  - Only 5% of eligible stroke patients receive IV tPA\(^1\)
- IV tPA recanalization rates low
  - 27 out of 54 patients in NINDS pilot study showed residual occlusion of involved vessel by angio\(^2\).
- Large vessel occlusion recanalization rates with IV tPA even lower
  - Only 10% of ICA occlusions and 25% of proximal MCA occlusions *recanalized* after IV tPA\(^3\)

Timeline in Development of Intra-arterial Thrombolysis

• 1983: Zeumer et al five cases of basilar thrombosis intra-arterial Thrombolysis

• 1998: PROACT I & II trials presented to FDA
  – Intra-arterial ProUrokinase< 6 h showed significant benefit compared to placebo
  – FDA approval not given due to low statistical power of the study
Milestones in development of AIS Rx

• August 2004: MERCI concentric device approved by FDA for intra-arterial stroke Rx
  – First device to be FDA approved for acute stroke
Acute Stroke: Diagnosis

• **Sudden** onset of focal neurologic symptoms
  – Aphasia
  – Facial assymetry
  – Arm or leg numbness
  – Arm or leg weakness
  – Gait imbalance
  – Vision loss

• Head CT and CT angiogram of head and neck
  – Safe to proceed without Serum creatinine in age < 70 and no history of kidney dz or diabetes
Intra-arterial thrombolysis: AMC

- 48 Y F w Crohn’s Dz
- Acute onset R hemiparesis and expressive aphasia
- L M1 occlusion on CTA

s/p 6.6 mg IA tPA + 4 mg ReoPro
Intra-arterial thrombolysis: AMC

- 30 day follow-up:
  - mild R facial palsy
    - No aphasia,
    - No weakness
- NIHSS: 17→2
- Back to work as store sales clerk at 4 weeks
Intra-arterial Pharmacological Thrombolysis

• PROACT I & PROACT II (1994-1998)
  – RCT for safety of IA ProUrokinase
  – IA ProUrokinase Vs Placebo (IA saline in PROACT I)
  – MCA occlusion < 6h
  – 66% recanalization for ProUK Vs 18% for control (P<0.001)
  – 40% of ProUK pts had Rankin <2 at 90 days Vs 25% control (P=0.043)
  – Relative benefit 58% and absolute benefit 15%
PROACT

- 35% of ProUK had ICH in 24 h vs 13% control
- Symptomatic ICH 10% and 2%
- No significant difference in 90 day mortality
- Downsides:
  - Time to recanalization is high
  - Risk of symptomatic hemorrhage
  - Number of pts qualifying: Out of 12,323 pts screened 474 (4%) went to angio and only 180 (1.5%) enrolled in the trial
IA thrombolysis for Stroke: Present Status

- Not FDA approved: Not reimbursed
- IA thrombolysis being done in majority of university hospitals and many community hospitals
- r-tPA IA most commonly used thrombolytic
- ASITN* endorses IA thrombolysis as accepted therapy since PROACT II
  - Change from Investigational status
Intra-arterial Mechanical Thrombolysis

- **Strategies:**
  1. Thombectomy
     - Removal of thrombus occluding the artery
  2. Thrombus disruption
     - Fragmentation of thrombus
  3. Augmented fibrinolysis
     - Mechanical enhancement of native fibrinolytic mechanism
Merci® Retriever: X6

- Flexible tapered Nitinol wire, helical shaped tip
- Platinum coil for radiopacity
- Merci® Retriever configurations:
  - X5: 5 Helical Loops/0.012” outer diameter
  - X6: 5 Helical Loops/0.014” outer diameter
Next Generation: Concentric Retriever L5

• Foreign Body Retriever
  – Sidewinder design
  – 2.5 mm diameter cylindrical design, 0.005” corewire
  – Filaments added to better entangle and prevent stretching during the retrieval process
MERCI Clot Retriever System
MERCI RETRIEVER
52 y AA female with acute onset aphasia and right arm> leg weakness
Young 82 year old lady w MVR, afib and ICA T-occlusion; presentation 2h, INR 2.3
Recanalized after two passes w L5 at 5h mark
NIHSS 22 → 7
## MERCI Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MERCI® (n = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>72 (28-93)</td>
</tr>
<tr>
<td>Female</td>
<td>46%</td>
</tr>
<tr>
<td>Median Baseline NIHSSS (range)</td>
<td>19 (8-40)</td>
</tr>
<tr>
<td>Mean Time to arterial access</td>
<td>4.3 h ± 1.7 h</td>
</tr>
</tbody>
</table>
## MERCI® Primary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Recanalization rate post retriever</th>
<th>Major Complications (Device Related)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48% (68/141) p &lt; 0.001 †</td>
<td>7.1% (10/141)</td>
</tr>
<tr>
<td>Total n=141</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† p-value for showing superiority over a 18% (PROACT II Placebo Group) success rate using the exact binomial test
Augmented Fibrinolysis: EKOS catheter

- Intra-arterial ultrasound: MicroLysUS catheter
- IMS II trial
EMS Dinner talk, November 2\textsuperscript{nd}, 2006

• THANK YOU!
Stents, Coils, Balloons, & Glue: Minimally Invasive Modalities for the Treatment of Neurological Disorders

Alan S. Boulos, MD
Herman and Sunny Stall Chair in Endovascular Neurosurgery
Director, Neurovascular Section
Neuroscience Institute
Albany, NY

AVIR, 2006
The Last Endovascular Frontier is ISCHEMIC STROKE
Stroke Statistics

- Stroke is our nation’s third leading cause of death, killing nearly 160,000 people every year.
- Each year about 600,000 Americans have a stroke. About 500,000 of these are first attacks and 100,000 of these are recurrent attacks.
- 66% hospitals do not have stroke protocols
- 2-3% of patients with stroke treated with tPA
Disability

- Stroke is a leading cause of serious long-term disability in the United States.

- About 4.5 million Americans are living with the effects of stroke.

- 71% of stroke survivors cannot return to their previous jobs when examined an average of 7 years later.
How Can We Change The Deleterious Impact of Stroke in Our Community?
Acute Stroke Team

- Stroke Specialist, ER Physician, EMT, Endovascular Surgeon
- Physicians, Fellows
- Available 24 hours, 365 days
- Evaluation within 15 minutes
- Organized system of activation and notification
<table>
<thead>
<tr>
<th>Interval</th>
<th>Time±SD (min)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last known well to study infusion start</td>
<td>206±234</td>
<td>24–703</td>
</tr>
<tr>
<td>Symptoms first observed to study infusion start</td>
<td>89±127</td>
<td>23–614</td>
</tr>
<tr>
<td>911 call to study infusion start</td>
<td>34±9</td>
<td>22–66</td>
</tr>
<tr>
<td>Paramedic arrival on scene to study infusion start</td>
<td>26±10</td>
<td>15–61</td>
</tr>
<tr>
<td>Emergency department arrival to study infusion start</td>
<td>−11±6</td>
<td>(−25)–(−1)</td>
</tr>
</tbody>
</table>
Day 90 modified Rankin scores in all trial patients (n=20), infarct patients (n=16), and <2-hour infarct patients (n=12). No patient had modified Rankin Scale scores of 4 or 5 at day 90.
Pathophysiology of Ischemic Stroke

Infarct

Ischemic Pneumbra

Occlusion of blood vessel

Brain tissue
Targets for Therapeutic Intervention in Ischemic Stroke

Infarct

Ischemic Pneumbræ

Occlusion of blood vessel

Prevent neurons from dying

Brain tissue

Restore cerebral blood flow by re-opening the vessel
FIBRINOLYTICS (INTRADEVIOUS)

tPA for acute ischemic stroke. NINDS trial

624 patients with ischemic stroke within 3 hours

Intravenous tPA (0.9 mg/kg) vs placebo

Follow-up 3 months

<table>
<thead>
<tr>
<th>Improvement at 24 h</th>
<th>tPA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>47%</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Favorable outcome at 3 m (Rankin scale)</th>
<th>tPA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>42%</td>
<td></td>
<td>27%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intracerebral hemorrhage</th>
<th>tPA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.4%</td>
<td></td>
<td>0.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Death at 3 m</th>
<th>tPA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>17%</td>
<td></td>
<td>21%</td>
</tr>
</tbody>
</table>
Strategies to improve outcome

- Deliver thrombolytics at the site of occlusion using microcatheters
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
FIBRINOLYTICS (INTRA-ARTERIAL)

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
3 months

Recanalization
Prourokinase 66%
Placebo 18%

Hemorrhagic transformation
Prourokinase 10%
Placebo 2%

Favorable outcome
Prourokinase 40%
Placebo 25%
Should Everybody be Treated using Intra-arterial Approach?

- Not available at every place
- Delay in transporting patient and initiating the procedure
- Risk associated with arterial puncture and catheterization
- May be reserved for selected patients
Neuroprotectant Studies

• We have preliminary data demonstrating a protective role for Tamoxifen (an estrogen receptor antagonist) in our stroke model.
• Our research continues to examine the role for this and other pharmaceutical agents as neuroprotectants in ischemic stroke.
New Technology for ISCHEMIC STROKE

Time Window for Treatment

Rapid Clot Removal
Concentric
<table>
<thead>
<tr>
<th></th>
<th>Revascularization Post Retriever</th>
<th>Major Complications (Device Related)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>54% (61)</td>
<td>3.5% (4)</td>
</tr>
<tr>
<td><em>n=114</em></td>
<td><em>p &lt; 0.001</em>†</td>
<td></td>
</tr>
</tbody>
</table>

† p-value for showing superiority over a 18% (PROACT II Placebo Group) success rate using the exact binomial test.
Secondary Endpoint – Modified Rankin (mRS)

90 Day mRS of Revascularized vs. Non-revascularized Patients

- **Recan**: 53% mRS 0-2, 16% mRS 3-5, 31% Death (n=51)
- **Non-Recan**: 6% mRS 0-2, 32% mRS 3-5, 62% Death (n=47)
CoAxia™ NeuroFlo™ Catheter
Safety Parameters for Pilot Study

Controlled Aortic Obstruction in Pigs

- cbfv
- MAP

% Occlusion vs. % of Baseline
Current Stroke Treatment Windows

- **0-3 h**: I.V. tPA,
  - consider low dose tPA + IA lysis if M1 or large artery occlusion suspected
- **3-6 h**: IA tPA, balloon or stent placement
- **3-8 h**: Mechanical thrombectomy, MERCI device
- **3-8 h**: Neuroflo device
- **0-12h** (up to 24h) for basilar artery occlusion
Carotid Artery Angioplasty and Stent placement

Alan S. Boulos, MD
Herman and Sunny Stall Chair of Neuroendovascular Surgery
Director of Cerebrovascular and Skull Based Surgery
Albany, NY
Who do we treat?
When do we treat?
How do we treat?

Observation
Medical Therapy
CEA
Stent
Asymptomatic Stenosis

- ACAS stenosis > 60%
- Stroke risk 5 yrs
- 11.7% medical
- 5.0% surgical
- 6.7% absolute stroke risk reduction
- 2%/yr to 1%/yr
- M&M <3.0%
Asymptomatic Stenosis

- ECST and NASCET
- Examine natural history of contralateral asymptomatic stenosis
- Risk of stroke proportional to degree of stenosis (stenosis > 80%)
- ACAS not powered to provide this information
Candidates for Carotid Endarterectomy

- Patients with 50%-99% carotid stenosis and ipsilateral cerebral ischemic symptoms (SYMPTOMATIC)
- Patients with 60%-99% carotid stenosis without ischemic symptoms (ASYMPTOMATIC)
EVERYTHING IS SOFT EXCEPT YOUR ARTERIES.
Why another carotid revascularization procedure?
Risk-Benefit Ratio

- Benefit of carotid revascularization lost if:
- The rate of perioperative stroke or death exceeds 6% for patients with SYMPTOMATIC carotid stenosis.
- The rate of perioperative stroke or death exceeds 3% for patients with ASYMPTOMATIC carotid stenosis.
Trials versus Real World

• The rate of complications exceed the specified rate in general practice.
• Medicare CEA mortality is three times greater than that reported in NASCET.
• Everybody blames the surgeon.
• Patient selection is the main determinant of perioperative complication rate.
| Neurological risks          | Progressive stroke  
<table>
<thead>
<tr>
<th></th>
<th>Recent stroke</th>
</tr>
</thead>
</table>
| Vascular specific risks     | High bifurcation    
|                             | Very long lesion (>3cm distally in ICA of 5cm into CCA) 
|                             | Clot                
|                             | Contralateral ICA stenosis or occlusion |
| Medical risks               | Intracranial stenosis or occlusion |
|                             | Hypertension, diastolic 
|                             | Coronary artery disease 
|                             | Diabetes             
|                             | Obesity              
|                             | COPD                 
|                             | Renal Insufficiency  
<p>|                             | Congestive heart failure |</p>
<table>
<thead>
<tr>
<th>Events</th>
<th>Stent (156 pts) [95% CI]</th>
<th>CEA (151 pts) [95% CI]</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.6% [-0.6%, 1.9%]</td>
<td>2.0% [-0.2%, 4.2%]</td>
<td>0.36</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.8% [0.8%, 6.9%]</td>
<td>5.3% [1.7%, 8.9%]</td>
<td>0.59</td>
</tr>
<tr>
<td>Major ipsilateral</td>
<td>0.0%</td>
<td>1.3%</td>
<td>0.24</td>
</tr>
<tr>
<td>Major Non-Ipsilateral</td>
<td>0.6%</td>
<td>0.7%</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Minor Ipsilateral</td>
<td>3.2%</td>
<td>3.3%</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Minor Non-Ipsilateral</td>
<td>0.6%</td>
<td>0.0%</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>MI (Q or NQ)</td>
<td>2.6% [0.1%, 5.0%]</td>
<td>7.3% [3.1%, 11.4%]</td>
<td>0.07</td>
</tr>
<tr>
<td>Q-Wave MI</td>
<td>0.0%</td>
<td>1.3%</td>
<td>0.24</td>
</tr>
<tr>
<td>Non-Q Wave MI</td>
<td>2.6%</td>
<td>6.0%</td>
<td>0.16</td>
</tr>
<tr>
<td>Death / Stroke</td>
<td>4.5% [1.2%, 7.7%]</td>
<td>6.6% [2.7%, 10.6%]</td>
<td>0.46</td>
</tr>
<tr>
<td>Death / Stroke / MI</td>
<td>5.8% [2.1%, 9.4%]</td>
<td>12.6% [7.3%, 17.9%]</td>
<td>0.047</td>
</tr>
</tbody>
</table>
One year data of SAPPHIRE
The right tool for the right indication

- Limitations for CAAS – Access difficulties
The right tool for the right indication

- Limitations for CAAS – Lesion sites difficulties or distal landing zone difficulties
Protection Devices

Distal Balloon

Distal Filter

Flow reversal

Negative pressure
Captured Debris

A Certain Stroke
Symptomatic Carotid occlusion

65 yo female presents with speech arrest (transient global aphasia) progressed to expressive dysphasia and transient right arm weakness (drift, fine motor control)

Placed on ASA/Plavix, CT/MRI no infarct at 24 hours, symptoms improve. Still mild expressive aphasia (NIHSS 2)
Extracranial Carotid Angioplasty and Stent Placement

- The procedure is not quite drive-thru yet
- Currently Overnight and sometimes ambulatory
- Someday?
CEA or CAS? Which would YOU Prefer?
Thank You
boulosa@mail.amc.edu

Nick and Teo Boulos
Meet the Stroke Team
NYS/DOH Stroke Center Requirements

- Recommended Stroke Evaluation Targets:
  - Door to MD evaluation          10 minutes
  - Door to stroke team contact   15 minutes
  - Door to CT scan               25 minutes
  - Door to CT interpretation     45 minutes
  - Door to RX                    60 minutes

(Based on National Institute of Neurological Disorders and Stroke=NINDS)
Identification of Potential Stroke Patient

- **EMS “in the field”**
  - Cincinnati Stroke Scale
  - Time of onset of symptoms determined
  - Stabilization of patient en-route
  - EMS calls within 5 minutes to arrival in ED with possible stroke patient

- **Triage “walk-in”**
  - History consistent with stroke
  - Time of onset of symptoms determined
Stroke Team Notification

- ED Charge Nurse informed of potential acute stroke patient with "Persistent, Sudden Onset Neurological Symptoms"
- Patient arrives into ED
- Placed in room with Stroke Packet
- ED Charge Nurse activates acute stroke page
  - ED Attending (Door to MD evaluation=10 minutes)
  - Stroke attending
  - Stroke Resident
  - Stat Nurse
  - CT tech
Stroke Page

- Stroke Attending
- ED Attending
- CT tech
- STAT RN
- Neurology Resident
Acute Stroke Protocol
# Acute Stroke Flow Sheet

## IV TPA

<table>
<thead>
<tr>
<th>YES</th>
<th>Ordered</th>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Given</td>
<td></td>
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</tr>
</tbody>
</table>

## NO

- Medical contraindication
- NIH stroke > 3hrs age
- Time of NIH onset unknown
- Patient refused

## Dysphagia Screen

- Unsafe to Swallow
- Decreased LOC, and/or inability to protect airway

- S0 of respiratory distress
- Coughing with oral intake
- High O2 requirement
- Intubated
- Feeding Tube
- Slurred speech, facial droop

- Safe to swallow
- None of the above issues

## Patient Disposition

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

## Evaluated By

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
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<tbody>
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</table>

## Date/Time of first PO

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
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**Acute Stroke Flowsheet**

**Acute Stroke**

**Flowsheet**

**THE NEUROSCIENCES INSTITUTE**

**Albany Medical Center**
Treatment/Diagnostics

• STAT Stroke Labs sent
  – Special requisition in packet
  – Contains special green top tubes with orange tape to indicate “STAT Stroke Labs”
  – Results should be given within 45 minutes

• 12-lead ECG

• STAT non-contrast head CT
  – Obtained as Priority 1
  – Door to CT scan 25 minutes

• Two 20 g PIV lines started
  – 1 for TPA
  – 1 for Blood draws
Treatment/Diagnostics

• Door to Stroke Team contact=15 minutes
• NIHSS determined
  – Sticker for NIHSS in Packet
• Neurological exam
• Patient evaluation reviewed with Stroke Attending
• Decision made of potential as rtPA candidate
  – pending results of head CT
  – Head CT reviewed with senior radiology/neuroradiology
  – Door to CT interpretation time= 45 minutes
Stents, Coils, Balloons, & Glue: Minimally Invasive Modalities for the Treatment of Neurological Disorders

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The presenter has no conflicts of interests to disclose.
Admission

• Patient admitted to appropriate unit based on care needs
  – D5E
  – D558
  – ICU

• Place on appropriate Plan of Care
  – Ischemic Stroke POC
  – Intracerebral Hemorrhage (non-traumatic) POC
  – Subarachnoid Hemorrhage POC

• Documentation of care
  – DVT prophylaxis
  – Education
  – Smoking Cessation
Stroke Unit

- 8 beds
- Advanced monitoring
- Staffed by Neuroscience Nurses
- 3 RN’s for 8 patients
- Continuous observation
- Aggressive Blood Pressure Control
Ongoing Care

- PT/OT
- Speech/Swallowing evaluation
- Completion of diagnostics
  - Echo
  - Carotid U/S
  - Hypercoag w/u
- Patient Teaching
- Discharge Planning