New Clinical Trials For ICH: MISTIE III
Minimally invasive techniques for hemorrhagic stroke

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Dept. of Neurology
Division of Brain Injury Outcomes
MISTIE III

• Sponsored by NINDS, R01NS046309

• Donations
  
  • Genentech - North America

  • Boehringer Ingelheim - Europe

• IND #8523 (intracerebral use of rt-PA)
StrokeNet-MISTIE III Collaboration

• MISTIE III supports the StrokeNet Network

• MISTIE III is sharing its experience with StrokeNet

• 2/3 MISTIE III leadership are StrokeNet faculty / investigators
StrokeNet – MISTIE Collaboration

<table>
<thead>
<tr>
<th>Percent</th>
<th># Stroke Net Centers</th>
<th>Stroke Net Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>38%</td>
<td>16/42</td>
<td>ACTIVE SN primary centers or satellites</td>
</tr>
<tr>
<td>52%</td>
<td>28/54</td>
<td>PROJECTED August active</td>
</tr>
<tr>
<td>22%</td>
<td>4</td>
<td>8/37 SN ENROLLMENTS</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Nonparticipating SN sites: resources, conflicts, regulatory barriers</td>
</tr>
</tbody>
</table>
10-30 cases per 100,000/Yr.  2 million ICHs annually worldwide
Surgical Clot Removal Questions & Strategies

1. Does surgical intervention help?
2. When to operate?
3. What type of surgery?
   - Craniotomy
     - Pro: Direct visualization for removal & hemostasis
     - Con: Requires corticotomy and cautery
   - MIS
     - Pro: No cortex injury, no cautery
     - Con: No direct visualization
4. How much clot should be removed?
5. Which patients benefit from which intervention?
Meta-analysis: 15 ICH Surgical Trials* (Death or Disability)

Significant advantage for surgery: OR=0.74

Significant heterogeneity by location, by surgery type

Lobar intracerebral hemorrhage and no IVH: No heterogeneity
No benefit: p=0.07

*Includes STICH I/II
Current BIOS Phase III Trials

Minimally Invasive Surgery plus rt-PA for Intracerebral Hemorrhage Evacuation

Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage
Minimally Invasive Hemorrhage Evacuation

CONCEPT

• Minimally invasive access
• Single trajectory for tissue injury
• Precision-guided, aspiration/evacuation

APPROACHES:

• Mechanical clot disruption
• Endoscopic removal
• Ultrasound
• Injection of thrombolytic
365-Day Outcome & Cost Model

MISTIE II: A Phase II Proof-of-Concept Trial
MISTIE Phase II – Overall Trial Goal

To fully test the novel idea that…

“Clot-size reduction decreases mortality and increases good outcomes”
Surgical Intervention

Pre-surgery  +20 Hr.  +42 Hr.  +52 Hrs.

3D post-op & post rt-PA
Stability CT Scan  04-Mar-10 8:41

Post-Surgery CT Scan  05-Mar-10 17:21

End of Treatment Scan  07-Mar-10 10:20

Stability Volume: 53.93
EOT Volume: 7.08
% Reduction: 86.87
Catheter Score: 116.5
Effect of ICH Volume on Mortality

Broderick et. al  *Stroke*. 1993;24:987-993
Key I/E Criteria

Exclusion
- Infratentorial ICH
- Vascular malformation or brain tumor
- Irreversibly impaired brainstem function

Inclusion
- Age 18-75
- GCS \leq 13 \text{ or NIHSS} \geq 6
- Spontaneous supratentorial ICH \geq 25cc
- Stable clot at second CT scan performed \geq 6 \text{ hours after diagnosis}
## Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medical N=42</th>
<th>Surgical N=54</th>
<th>Total N=96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>61.1 (12.3)</td>
<td>60.7 (11.0)</td>
<td>60.9 (11.5)</td>
</tr>
<tr>
<td>Male</td>
<td>66.7%</td>
<td>64.8%</td>
<td>65.6%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>54.8%</td>
<td>55.6%</td>
<td>55.2%</td>
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<tr>
<td>African American</td>
<td>26.2%</td>
<td>33.3%</td>
<td>30.2%</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>4.8%</td>
<td>3.7%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11.9%</td>
<td>7.4%</td>
<td>9.4%</td>
</tr>
<tr>
<td>HX of HTN</td>
<td>81.0%</td>
<td>90.7%</td>
<td>86.5%</td>
</tr>
<tr>
<td>HX of Diabetes</td>
<td>26.8%</td>
<td>25.9%</td>
<td>26.3%</td>
</tr>
<tr>
<td>HX of Seizure</td>
<td>12.2%</td>
<td>14.8%</td>
<td>13.7%</td>
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<tr>
<td>HX of ETOH</td>
<td>17.5%</td>
<td>31.5%</td>
<td>25.5%</td>
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<tr>
<td>HX of Tobacco</td>
<td>7.1%</td>
<td>31.5%</td>
<td>20.8%</td>
</tr>
<tr>
<td>HX of Cocaine</td>
<td>7.1%</td>
<td>7.4%</td>
<td>7.3%</td>
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</table>
# ER Presentation

<table>
<thead>
<tr>
<th>Presenting Parameter X (SD)</th>
<th>Medical N=42</th>
<th>Surgical N=54</th>
<th>Total N=96</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER Presentation SBP</td>
<td>186.7 (34.1)</td>
<td>186.4 (33.0)</td>
<td>186.5 (33.3)</td>
</tr>
<tr>
<td>ER Presentation DBP</td>
<td>101.9 (20.4)</td>
<td>106.8 (27.7)</td>
<td>104.6 (24.7)</td>
</tr>
<tr>
<td>ER Presentation MAP</td>
<td>130.2 (22.8)</td>
<td>133.2 (27.4)</td>
<td>131.9 (25.4)</td>
</tr>
<tr>
<td>ER Presentation GCS Total</td>
<td>11.6 (3.2)</td>
<td>11.4 (3.2)</td>
<td>11.5 (3.2)</td>
</tr>
<tr>
<td>Diagnostic ICH Volume</td>
<td>34.0 (15.8)</td>
<td>43.3 (22.5)</td>
<td>39.2 (20.3)</td>
</tr>
<tr>
<td>Diagnostic IVH Volume</td>
<td>1.6 (4.1)</td>
<td>4.3 (8.9)</td>
<td>3.2 (7.3)</td>
</tr>
<tr>
<td>Clot Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>35.7%</td>
<td>33.3%</td>
<td>34.4%</td>
</tr>
<tr>
<td>Deep</td>
<td>64.3%</td>
<td>66.7%</td>
<td>65.6%</td>
</tr>
</tbody>
</table>
Times from Symptom Onset*

- ER Arrival
- Diagnostic CT
- Initial Screening
- Informed Consent
- Randomization
- Operative Procedure
- First Dose

*Larger x-axis labels are days, smaller are hours*
What we learned about recovery
Day 365 modified Rankin Scale (mRS)

N = 25

N = 23

14%

Medical

Surgery

% Subjects

0

1

2

3

4

5

6
180 & 365-Day mRS

180 Day Outcomes

- Medical: N = 38
- Surgery: N = 52

- 0: 11%
- 1: 8%
- 2: 14%
- 3: 8%
- 4: 8%
- 5: 8%
- 6: 8%

365 Day Outcomes

- Medical: N = 25
- Surgery: N = 23

- 0: 14%
- 1: 21%
- 2: 8%
- 3: 8%
- 4: 8%
- 5: 8%
- 6: 8%

LTCF: 8%
30-Day Outcomes Change With MIS+rt-PA

Cincinnati 1988  MISTIE II 2013

Oxford Handicap Scale  mRankin Scale

Broderick et. al  Stroke. 1993;24:987-993
Duncan, PW: Stroke, 1999

MOBILITY

ADL

Stroke Impact Scale - Mobility Score

Stroke Impact Scale - ADL Score

Time post-stroke (days)

MIS+rt-PA
Medical management

Duncan, PW: Stroke, 1999
Length of Stay and Cost by Treatment Arm

- **Medical**
  - Length of Stay: 38 days (35%)
  - Cost: $44K (35%)

- **Surgical**
  - Length of Stay: 38 days (35%)
  - Cost: $44K (35%)

Legend:
- Red: ICU
- Blue: Non-ICU
- Green: Surgery
- Blue: Non-ICU
## Factors Affecting Functional Outcome

**ITT (n= 83)**

<table>
<thead>
<tr>
<th>ICH Severity Parameters</th>
<th>Univariate Analysis</th>
<th>Multivariate Models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio of mRS&gt;3 (p-value)</td>
<td>Model 1</td>
</tr>
<tr>
<td>Age per 1 year</td>
<td>1.05 (0.029)</td>
<td>1.08 (0.007)</td>
</tr>
<tr>
<td>Stability ICH per 10 cc</td>
<td>1.52 (0.009)</td>
<td>1.10 (0.581)</td>
</tr>
<tr>
<td>Enrollment Total GCS Score</td>
<td>0.63 (&lt;0.001)</td>
<td>0.59 (&lt;0.001)</td>
</tr>
<tr>
<td>Surgical vs. Medical arm</td>
<td>0.67 (0.407)</td>
<td>NA</td>
</tr>
<tr>
<td>End-of-treatment ≤ 15 ml ~ 3-day volume vs. &gt;15 ml</td>
<td>0.33 (0.038)</td>
<td>NA</td>
</tr>
</tbody>
</table>
Subgroup treatment effect: odds mRS >3

**MISTIE**

**Subgroups**
- **Age**
  - < 65
  - >= 65
- **GCS**
  - 3–8
  - 9–12
  - 13–15
- **Site**
  - Lobar
  - Deep
- **ICH Volume**
  - <= 50 mL
  - > 50 mL
- **Surgery Time**
  - < 36 hours
  - >= 36 hours

**Favors: MIS**

**STICH**

**Favors: Surgery**
What this means

The greater the reduction in clot size, the better the patient outcome.

Volume reduction matters!
MISTIE II – Benefits summary

**Mechanism**

- Reduction of clot burden
- “Saving tissue at risk”
- 2° injury occurs over days

**Benefits**

- Most likely MIS increases independence
- Appears to improve function & decrease cost
Upcoming MISTIE IM

On behalf of MISTIE III Trial, NIH/NINDS, and Genentech Inc., we would like to invite you to attend the

**2014 MISTIE III Investigator-Coordinator Meeting**

**Who should attend?**
PIs, Neurosurgeons, & Coordinators

**When:**
August 22-24, 2014 (Friday 6:30 PM – Sunday 3 PM)

**Where:**
Westin BWI
1110 Old Elkridge Landing Rd
Linthicum Heights, MD 21090

We have the potential to CHANGE the way we treat stroke throughout the world! We look forward to working with you over the next five to six years.
# MISTIE III Coordinating Center

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>Daniel F. Hanley</td>
<td>Study Chairman &amp; Principal Investigator</td>
</tr>
<tr>
<td>Wendy Ziai</td>
<td>Medical Monitor</td>
</tr>
<tr>
<td>Karen Lane</td>
<td>Project Director</td>
</tr>
<tr>
<td>Nichol McBee</td>
<td>Clinical Program Manager</td>
</tr>
<tr>
<td>Steve Mayo</td>
<td>Emissary International Monitoring</td>
</tr>
<tr>
<td>Janet Mighty</td>
<td>Pharmacy Manager</td>
</tr>
<tr>
<td>Andrew Mould</td>
<td>Reading Center Manager</td>
</tr>
<tr>
<td>Issam Awad</td>
<td>Co-PI, Chicago Surgical Center Director</td>
</tr>
<tr>
<td>Mario Zuccarello</td>
<td>Co-PI, Cincinnati Surgical Center Director</td>
</tr>
<tr>
<td>Kennedy Lees</td>
<td>University of Glasgow Outcomes Center</td>
</tr>
<tr>
<td>Claudia Moy</td>
<td>Program Official, NIH/NINDS</td>
</tr>
<tr>
<td>Scott Janis</td>
<td>Project Scientist, NIH/NINDS</td>
</tr>
</tbody>
</table>
MISTIE III Data Management Center

Richard Thompson  PI, Executive Director
Marie Diener-West  Senior Biostatistics Advisor
Michael Rosenblum  Biostatistician, Study Design
Elizabeth Sugar  Unblinded Biostatistician
Gayane Yenokyan  Biostatistician, Outcomes Research
Carol Thompson  Biostatistician
John Muschelli  Biostatistician/Analyst
Josh Betz  Biostatistician/Analyst
Andre Hackman  Director, Data Informatics Services Core
Rachel Dlugash  Senior Research Data Manager
Malathi Ram  Data Manager
Gwendolyn Clemens  Data Manager
Thank you