MISTIE III Surgical Results: Efficiency of Hemorrhage Removal Determines mRS

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Principal Investigators

On behalf of the MISTIE investigators, patients and families
Acknowledgments

• Contributions by giants in the field over many years
• NIH/NINDS funding and partnership with StrokeNet (U01 NS080824)
• Genentech donated alteplase drug
• Trial teams, centers and committees
• Surgical and neurocritical care partners throughout the world!
Surgical Center Team

- U Chicago (Awad/Stadnik) and U Cincinnati (Zuccarello/Money) on call 24/7 for every surgical enrollment during five years
- Surgical Committee Members (Camarata, Carlson, Caron, Harrigan, Mendelow, Dodd)
- U Chicago Clinical Trials Unit (Stadnik, Fam, Carrion, Polster)
- Statistics (Cao, Thompson)
Cases with ≤15 mL EOT (residual) volume had lower mortality and better functional outcome.

mRS assessed at 1 year by blinded jury review of video-recorded mRS interviews.
• Does it matter how much blood is removed (risk/benefit)?

• What factors are associated with greater or lesser hematoma evacuation?
Review of the MISTIE Surgical Task

- Stabilization and etiology screening, correction of coagulopathy
- Image guided aspiration via rigid cannula, then placement of soft drainage catheter in the epicenter of the hematoma
- Administration of alteplase (1mg in 1 mL every 8 hours) via the soft catheter, and passive hematoma clearance to < 15 mL or 9 doses of alteplase are given
- Decision to continue dosing, with or without replacing catheter, is made by the site PI/Surgeon considering risk benefit in the individual case
Optimize ICH Cannulation to Achieve Desired ICH Evacuation

Uniform surgeon performance was achieved with deliberate trajectory planning

Lessons learned from MISTIE II

Variations in hematoma evacuation

Hanley, et al. MISTIE II, Lancet Neurology 2017
Trajectory Planning

**Trajectory A**
Frontal burr hole, anterior approach, caudate putamen bleeds

**Trajectory B**
Parieto-occipital burr hole, posterior approach, thalamic bleeds

**Trajectory C**
Burr hole over cortical area of closest extension, lobar bleeds
Defining the Surgical Cohort

110 surgeons at 73 sites

506 Patients Randomized

255 Assigned to MISTIE

242 Per Protocol Analysis of MISTIE Task

251 Assigned to Medical

13 Excluded from Per Protocol Analysis*

(*) Cases excluded are those that underwent a craniotomy for any cause within 1 year of randomization (n=6), were lost to follow up (n=1), considered ineligible (n=5) or had missing data (n=1).
Hematoma Reduction in MISTIE III Surgical Subjects

Hematoma volumes curated by a dedicated Reading Center with validated volumetric analysis of DICOM images.

Percent ICH Evacuation

Randomized to MISTIE (N=248)
**Trajectory B** more likely to require catheter replacement (RR 2.22, CI 1.01-4.87) p= 0.047

**Trajectory C** least likely to achieve < 15mL EOT endpoint (often irregular shaped lobar hematomas) p=0.027
Surgeon Qualification vs. Catheter Placement Accuracy

No significant difference in catheter placement accuracy or extent of ICH evacuation
Reduction beyond the 15 mL threshold significantly increased the chance of having a good functional outcome, by 10% for each additional mL of hematoma removed $(p = 0.002)$.
Further reduction of ICH beyond 70% removal carries a significant benefit, with 6% improvement in the chance of achieving a mRS 0-3 per additional mL removed (p = 0.002)
## Multivariate Model: ICH Remaining

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EOT ICH Remain (mL) ≤15</strong></td>
<td>2.02</td>
<td>1.05 - 3.89</td>
<td>0.035</td>
</tr>
<tr>
<td>Age (yrs) 56 - &lt;67</td>
<td>0.48</td>
<td>0.23 - 1.01</td>
<td>0.054</td>
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<tr>
<td>Age (yrs) ≥67</td>
<td>0.10</td>
<td>0.04 - 0.25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GCS (9-12)</td>
<td>2.04</td>
<td>0.98 - 4.25</td>
<td>0.055</td>
</tr>
<tr>
<td>GCS (13-15)</td>
<td>3.03</td>
<td>1.30 - 7.05</td>
<td>0.010</td>
</tr>
<tr>
<td>Stab ICH (mL) 35 - &lt;45</td>
<td>0.48</td>
<td>0.19 - 1.20</td>
<td>0.116</td>
</tr>
<tr>
<td>Stab ICH (mL) 45 - &lt;55</td>
<td>0.38</td>
<td>0.14 - 0.99</td>
<td>0.047</td>
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<tr>
<td>Stab ICH (mL) ≥55</td>
<td>0.26</td>
<td>0.01 - 0.68</td>
<td>0.006</td>
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<tr>
<td>ICH Deep</td>
<td>0.11</td>
<td>0.05 - 0.23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IVH volume (mL)</td>
<td>0.92</td>
<td>0.85 - 0.99</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Control for disease severity factors

EOT ICH Vol ≤ 15 mL
**OR 2.02** (CI 1.05-3.89)
mRS 0-3, p=0.035
### Multivariate Model: ICH Percent Removed

<table>
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<tr>
<td>EOT Percent Removed ≥70%</td>
<td>2.05</td>
<td>1.09 - 3.85</td>
<td>0.025</td>
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<tr>
<td>Age (yrs) 56 - &lt;67</td>
<td>0.49</td>
<td>0.24 - 1.02</td>
<td>0.057</td>
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<tr>
<td>Age (yrs) ≥67</td>
<td>0.09</td>
<td>0.03 - 0.25</td>
<td>&lt; 0.001</td>
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<tr>
<td>GCS (9-12)</td>
<td>2.13</td>
<td>1.03 - 4.42</td>
<td>0.042</td>
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<tr>
<td>GCS (13-15)</td>
<td>2.99</td>
<td>1.26 - 7.06</td>
<td>0.013</td>
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<tr>
<td>Stab ICH (mL) 35 - &lt;45</td>
<td>0.48</td>
<td>0.19 - 1.21</td>
<td>0.117</td>
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<tr>
<td>Stab ICH (mL) 45 - &lt;55</td>
<td>0.34</td>
<td>0.13 - 0.89</td>
<td>0.028</td>
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<tr>
<td>Stab ICH (mL) ≥55</td>
<td>0.20</td>
<td>0.08 - 0.51</td>
<td>0.001</td>
</tr>
<tr>
<td>ICH Deep</td>
<td>0.10</td>
<td>0.04 - 0.22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stab IVH (per mL)</td>
<td>0.92</td>
<td>0.85 - 0.99</td>
<td>0.030</td>
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</table>
Significant survival benefit is associated with less aggressive ICH removal thresholds than were required to achieve mRS 0-3:

- **<30 mL EOT ICH volume** (OR 5.545, CI 2.362-13.019, p <0.001)
- **>53% ICH Removal** (OR 3.896, CI 1.743-8.707, p <0.001)
Percent of subjects reaching various thresholds of ICH evacuation:

- 11% EOT > 30 mL
- 25% EOT > 20 mL
- 40% EOT > 15 mL

Thresholds Defining Result of Surgical Task in Relation to EOT ICH Volume
Demographic Factors
- Age (continuous)
- Sex (male/female)
- Ethnicity (Caucasian, African-American, Asian, Hispanic, Other)

Past Medical History
- Previous Stroke (Ischemic, Hemorrhagic, Any)
- History of cancer
- History of hypertension (treated)

Hemorrhage Characteristics
- Initial ICH volume at stability scan (continuous)
- ICH location (deep or lobar, thalamic)
- Initial GCS
- Irregular-shaped hematoma (pseudopod extensions, satellites)

Hematologic Characteristics at Baseline
- Anticoagulant use (Any time prior to enrollment)
- Antiplatelet use (Any time prior to enrollment)
- Elevated PTT (>34.0) prior to correction
- Elevated INR (>1.4) prior to correction
- Thrombocytopenia (platelets < 100,000) prior to transfusion
- Any abnormalities in clotting profile

Experience by Surgeon and Site
- Pre-Qualified* (first MISTIE case in the trial)
- Qualified with Probation* (1-3 prior successful MISTIE cases in the trial)
- Fully Qualified* (> 3 successful MISTIE cases in the trial)
- Number of MISTIE procedures by the surgeon in the trial to date (continuous)
- Number of MISTIE procedures at the site in the trial to date (continuous)

Trajectories and Catheter Placement**
- Trajectory A, B, or C
- Catheter reposition/replacement – none or more than once
- Initial catheter placement*** (good, suboptimal, or poor)
- Final catheter placement*** (good, suboptimal, or poor)

Protocol Deviations
- Major protocol deviations (site reported/safety committee adjudicated) ****
- Protocol deviations (noted by Surgical Center) *****
- Surgical protocol deviation
- Catheter manipulation/dosing problem

Variables During Dosing Period
- Hematoma expansion (ICH expansion >5 mL and/or Catheter Tract Hemorrhage
- Number of alteplase doses (continuous)
- Hypertension reading (SBP > 180 mmHg)
- Elevated PTT (>34.0) or Elevated INR (>1.4)
- Thrombocytopenia (Platelets < 100,000)
- Any abnormalities in clotting profile or chemical thromboprophylaxis
Variables significantly and independently associated with achieving EOT ICH volumes at 15-, 20- and 30-ml thresholds

Multivariate logistic regression

Same significant variables were captured by Least Absolute Shrinkage and Selection Operator (LASSO) analysis

### EOT 15 mL

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>History of hypertension</td>
<td>0.207</td>
<td>0.057 - 0.745</td>
<td>0.016</td>
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<tr>
<td>Initial volume at stability scan</td>
<td>0.968</td>
<td>0.945 - 0.991</td>
<td>0.008</td>
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<tr>
<td>Irregular-shaped hematoma</td>
<td>28.741</td>
<td>1.305 - 633.187</td>
<td>0.033</td>
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<tr>
<td>Surgical center protocol deviation</td>
<td>74.580</td>
<td>3.292 - &gt;1000</td>
<td>0.007</td>
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<tr>
<td>Catheter manipulation problem</td>
<td>107.454</td>
<td>4.751 - &gt;1000</td>
<td>0.003</td>
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<tr>
<td>Number of alteplase doses</td>
<td>0.779</td>
<td>0.675 - 0.899</td>
<td>0.001</td>
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### EOT 20 mL

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<td>Initial volume at stability scan</td>
<td>0.955</td>
<td>0.926 - 0.984</td>
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<td>Irregular-shaped hematoma</td>
<td>123.803</td>
<td>4.946 - &gt;1000</td>
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<td>Surgical center protocol deviation</td>
<td>159.928</td>
<td>16.079 - &gt;1000</td>
<td>&lt;0.0001</td>
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<tr>
<td>Catheter manipulation problem</td>
<td>126.644</td>
<td>16.507 - 971.649</td>
<td>&lt;0.0001</td>
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<tr>
<td>Number of alteplase doses</td>
<td>0.644</td>
<td>0.521 - 0.797</td>
<td>&lt;0.0001</td>
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### EOT 30 mL

<table>
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<tr>
<td>Initial volume at stability scan</td>
<td>0.927</td>
<td>0.897 - 0.958</td>
<td>&lt;0.0001</td>
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<td>Catheter manipulation problem</td>
<td>6.014</td>
<td>1.184 - 30.548</td>
<td>0.031</td>
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<tr>
<td>Catheter tract hemorrhage</td>
<td>17.675</td>
<td>3.114 - 100.333</td>
<td>0.001</td>
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<tr>
<td>Number of alteplase doses</td>
<td>0.699</td>
<td>0.559 - 0.874</td>
<td>0.002</td>
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</table>
No surgeon with >4 prior trial cases, and no site with >7 prior trial cases, ever had >30 mL EOT volume.
Opportunities for enhanced ICH removal by strict adherence to the protocol goal

- Repositioning the catheter or using a second catheter were safe (no bleeding occurred with multiple catheter repositionings!)
- Secure the catheter to prevent pullback

Some hematomas with satellite extensions, may not be amenable to further evacuation
Conclusions

• With 88% new surgeons, safe uniform performance of the surgical task was achieved in MISTIE III, with better mean hematoma evacuation than in MISTIE II. Average performance to the protocol goal failed to achieve functional benefit.

• While less stringent evacuation could suffice for survival benefit, reduction of ICH to ≤ 15 mL EOT or ≥ 70% evacuation was required for good functional outcome at 1 year. This is the first description of specific thresholds of hematoma evacuation to impact functional outcome in ICH surgery trials.

• Generalization of best performance with this procedure, or other techniques of this kind, will require strict articulation and pursuit of the benchmarks of success of the surgical task, focused education emphasizing technical nuances, and better demonstrated experience.