Minimally Invasive Surgery for Intracerebral Hemorrhage: From Nihilism to Optimism

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Virginia Mason Neurovascular Summit
Seattle, WA
March 1, 2019
Disclosures

No personal financial disclosures

Virginia Mason is a participating site for the MIND trial for Minimally Invasive evacuation of ICH using the Artemis device, sponsored by Penumbra, INC
Objectives

• Discuss the historical context of hemorrhagic stroke

• Review the challenges faced by early attempts at surgical evacuation and the culture of nihilism created

• Discover rays of hope gleaned from prior studies

• Assess current trials using minimally invasive techniques for ICH removal and reasons for optimism
Background – Recognition to Treatment

Stroke is a syndrome of multiple etiologies

First described by Hippocrates 2400 years ago
- “apoplexy”
- “struck down by violence”

- Mechanism unknown
- Treatment supportive
Background – Recognition to Treatment

J.J. Wepfer 1650s – ‘Historiae apoplecticum’
  – Detailed cerebral vascular anatomy
  – Postulated apoplexy could result from
    • Hemorrhage
    • Blocked cerebral artery

Classifications in 1920s based on cause of “cerebral vascular accident”
  – Separated ischemic and hemorrhagic stroke
Early evaluation and treatment
# COMMON STROKE SYMPTOMS

## Right Hemispheric Stroke
- Slurred speech - dysarthria
- Weakness or numbness of left face, arm or leg
- Left sided neglect
- Right gaze preference

## Left Hemispheric Stroke
- Speech problems – what is being said or inability to get words out
- Problems with comprehension
- Weakness or numbness of right face, arm, or leg
- Left gaze preference

## Brainstem Stroke Symptoms
- Nausea, vomiting or vertigo
- Speech problems
- Swallowing problems
- Abnormal eye movements
- Decreased consciousness
- Crossed findings

## Intracerebral Hemorrhage

### Intraparenchymal Hemorrhage
- Nausea and Vomiting
- Headache
- One Sided Weakness
- Decreased Consciousness

### Subarachnoid Hemorrhage
- Worst Headache of Life
- Intolerance to Light
- Neck Stiffness or Pain
# AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress

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**TABLE 2. Stroke Chain of Survival**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection</td>
<td>Recognition of stroke signs and symptoms</td>
</tr>
<tr>
<td>Dispatch</td>
<td>Call 9-1-1 and priority EMS dispatch</td>
</tr>
<tr>
<td>Delivery</td>
<td>Prompt transport and prehospital notification to hospital</td>
</tr>
<tr>
<td>Door</td>
<td>Immediate ED triage</td>
</tr>
<tr>
<td>Data</td>
<td>ED evaluation, prompt laboratory studies, and CT imaging</td>
</tr>
<tr>
<td>Decision</td>
<td>Diagnosis and decision about appropriate therapy</td>
</tr>
<tr>
<td>Drug</td>
<td>Administration of appropriate drugs or other interventions</td>
</tr>
</tbody>
</table>
**TABLE 3. Guidelines for EMS Management of Patients With Suspected Stroke**

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Not Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manage ABCs</td>
<td>Dextrose-containing fluids in nonhypoglycemic patients</td>
</tr>
<tr>
<td>Cardiac monitoring</td>
<td>Hypotension/excessive blood pressure reduction</td>
</tr>
<tr>
<td>Intravenous access</td>
<td>Excessive intravenous fluids</td>
</tr>
<tr>
<td>Oxygen (as required $O_2$ saturation $&lt;92%$)</td>
<td></td>
</tr>
<tr>
<td>Assess for hypoglycemia</td>
<td></td>
</tr>
<tr>
<td><em>Nil per os</em> (NPO)</td>
<td></td>
</tr>
<tr>
<td>Alert receiving ED</td>
<td></td>
</tr>
<tr>
<td>Rapid transport to closest appropriate facility capable of treating acute stroke</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 4. Key Components of History

<table>
<thead>
<tr>
<th>Onset of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent events</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Comorbid diseases</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Use of medications</td>
</tr>
<tr>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Insulin</td>
</tr>
<tr>
<td>Antihypertensives</td>
</tr>
</tbody>
</table>

Pre-hospital Stroke Scale
FAST
LAMS
VAN
Adult learning

What you think is important

Relevant

What interests them
Case Example

• 71 yo right handed man, poorly controlled hypertension and DM-2

• Wife found patient in bed, aphasic and right hemiplegic, EMS to outside hospital

• Intubated for airway protection, SBP 224/110

• CT head and CTA performed together – stroke protocol
$\frac{AXBxC}{2}$

$6.5 \times 3.6 \times 5.0 / 2 = 58.5 \text{ cc}$
• CTA – no vascular lesion
• Transferred for further management
• GCS 7T (E1V1TM5), localizing on left but still hemiplegic on arrival
• To ICU, blood pressure reduced 20%

• On Aspirin, ARU 516; platelets 99 -> 84
• 6 hour stability CT (with navigation sequence) showed no significant change

• Discussed with family Apollo procedure
AxBxC/2

4.5\times1.5\times1.1/2 + 1.1\times0.9\times1/2 = 5.5 \text{ cc}

\sim 90\% \text{ reduction}
• Extubated the next morning

• Awake, more alert and localizing briskly on left, still hemiplegic on right and aphasic

• Able to be transferred to the neuro floor to initiate rehabilitation assessment
Significance of the disease

Spontaneous ICH is a devastating disease with generally poor outcomes and limited treatment options

2nd most common stroke type after ischemic, ~10-15% overall
  - Incidence 25/100000 person years, 4 million people/year worldwide (van Asch, Lancet Neurol 2010)

Outcomes much worse than ischemic stroke
  - 40% mortality at 30 days, <25% independent at 1 year (Feigin, Lancet Neurol 2003)
ICH score is a validated scale that predicts outcome

### Determination of the ICH Score

<table>
<thead>
<tr>
<th>Component</th>
<th>30-day Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICH volume, cm³</strong></td>
<td>100</td>
</tr>
<tr>
<td>≥30</td>
<td>80</td>
</tr>
<tr>
<td>&lt;30</td>
<td>60</td>
</tr>
<tr>
<td><strong>IVH</strong></td>
<td>40</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Infratentorial origin of ICH</strong></td>
<td>20</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>0</td>
</tr>
<tr>
<td>≥80</td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td></td>
</tr>
<tr>
<td><strong>Total ICH Score</strong></td>
<td>0–6</td>
</tr>
</tbody>
</table>

Effect of ICH volume on mortality

Broderick et. al  *Stroke*. 1993;24:987-993
Attempts for treatment

Medical

1. Blood pressure control
   - INTERACT (Anderson, Lancet Neurol, 2008)
   - ATTACH (Qureshi, Arch Neurol, 2010)
   - BP control is feasible and safe but no clinical benefit seen

2. Control Hematoma expansion
   - FAST Trials - rFVII (Mayer, NEJM 2005, 2008)
   - Limits clot growth but increased thromboembolic risk and no clinical benefit
Current medical guidelines

AHA/ASA Guideline

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association
Morgenstern LB, Stroke 2010

Reverse oral anticoagulation with PCC (not rFVII alone)

Patients should be monitored in an ICU
Attempts for treatment

Surgical

1. Open craniotomy
   - McKissock 1961 (Lancet) – no benefit, possible harm with surgery
   - STICH (Mendelow, Lancet 2005)
     – harm from surgery for deep ICH, ?benefit for superficial
   - STICH II (Mendelow, Lancet 2013)
     – No benefit for surgery for superficial ICH

Interpretation

The STICH II results confirm that early surgery does not increase the rate of death or disability at 6 months and might have a small but clinically relevant survival advantage for patients with spontaneous superficial intracerebral haemorrhage without intraventricular haemorrhage.
### Table: STICH II Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgery</th>
<th>Control</th>
<th>Peto odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKissock, et al(^5) (1961)</td>
<td>71/89</td>
<td>60/91</td>
<td>2.00 (1.04-3.86)</td>
</tr>
<tr>
<td>Auer, et al(^1) (1989)</td>
<td>28/50</td>
<td>37/50</td>
<td>0.46 (0.20-1.04)</td>
</tr>
<tr>
<td>Juvela, et al(^4) (1989)</td>
<td>25/26</td>
<td>21/26</td>
<td>4.39 (0.81-23.65)</td>
</tr>
<tr>
<td>Batjer, et al(^3) (1990)</td>
<td>6/8</td>
<td>11/13</td>
<td>0.55 (0.06-4.93)</td>
</tr>
<tr>
<td>Chen, et al(^9) (1992)</td>
<td>40/64</td>
<td>31/62</td>
<td>1.66 (0.82-3.34)</td>
</tr>
<tr>
<td>Morgenstern, et al(^6) (1998)</td>
<td>9/15</td>
<td>11/16</td>
<td>0.69 (0.16-2.94)</td>
</tr>
<tr>
<td>Zuccarello, et al(^7) (1999)</td>
<td>4/9</td>
<td>7/11</td>
<td>0.48 (0.09-2.69)</td>
</tr>
<tr>
<td>Chen, et al(^3) (2001)</td>
<td>86/263</td>
<td>97/230</td>
<td>0.67 (0.46-0.96)</td>
</tr>
<tr>
<td>Teernstra, et al(^8) (2001)</td>
<td>33/36</td>
<td>29/33</td>
<td>1.51 (0.32-7.12)</td>
</tr>
<tr>
<td>Hosseini, et al(^3) (2003)</td>
<td>0/1</td>
<td>0/1</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Hattori, et al(^3) (2004)</td>
<td>60/121</td>
<td>82/121</td>
<td>0.47 (0.28-0.79)</td>
</tr>
<tr>
<td>Mendelow, et al(^2) (2005)</td>
<td>346/468</td>
<td>378/496</td>
<td>0.89 (0.66-1.19)</td>
</tr>
<tr>
<td>Pantazis, et al(^4) (2006)</td>
<td>36/54</td>
<td>49/54</td>
<td>0.24 (0.10-0.60)</td>
</tr>
<tr>
<td>Wang, et al(^3) (2009)</td>
<td>87/194</td>
<td>120/181</td>
<td>0.42 (0.28-0.63)</td>
</tr>
<tr>
<td>Mendelow, et al (2013)</td>
<td>174/297</td>
<td>178/286</td>
<td>0.86 (0.62-1.20)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1695</td>
<td>1671</td>
<td>0.74 (0.64-0.86)</td>
</tr>
</tbody>
</table>

Total events: 1005 (surgery), 1111 (control)
Test for heterogeneity: \(\chi^2=39.29\), df=13 (p=0.0002), \(I^2=66.9\%\)
Test for overall effect: \(Z=4.00\) (p<0.0001)
Current surgical guidelines

For most patients with ICH, the usefulness of surgery is uncertain

Class IIb, Level of Evidence
New Recommendation

Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brain stem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible

Class I, Level of Evidence B
Revised recommendation

Initial treatment of these cerebellar hemorrhage patients with ventricular drainage alone rather than surgical evacuation is not recommended

Class III, Level of Evidence C
New Recommendation

Morgenstern LB, Stroke 2010
For patients presenting with lobar clots >30 cc and within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered (Class IIb, Level of Evidence B Updated recommendation).

The effectiveness of minimally invasive clot evacuation utilizing either stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain and is considered investigational (Class IIb, Level of Evidence B New Recommendation).

While theoretically attractive, no clear evidence at present indicates that ultra-early removal of supratentorial ICH improves functional outcome or mortality rate. Very early craniotomy may be harmful due to increased risk of recurrent bleeding (Class III, Level of Evidence B Revised from the previous guideline).
Methods for Minimally Invasive ICH Removal

1. “Pharmacologically Based”
   - Introduce a lytic and allow drainage
   - Craniopuncture – urokinase
   - MISTIE – tPA

2. “Mechanically Based”
   - Direct surgical aspiration/removal
   - Endoscopic – burr hole
   - Access sheath port – mini-crani
Pharmacologically Based MIS

Craniopuncture

- 1 million cases in China past 20 years
- Local anesthesia
- YL-1 puncture needle

Fig. 2. The YL-1 type of intracranial haematoma puncture needle

Published in: Xiaohan Chen; Wenyu Chen; Aijun Ma; Xionghong Wu; Jiangang Zheng; Xiangrong Yu; Yi Xue; J. Wang, Duoyuan Wang. British Journal of Neurosurgery 2011, 25, 369-375.
Pharmacologically Based MIS

Craniopuncture
- 1 million cases in China past 20 years
- Local anesthesia
- YL-1 puncture needle
- CT localization
- Syringe aspiration
- Urokinase infusion TID, 3-5 days

Published in: Xiaonan Chen, Wenyu Chen, Aigen Ma, Xianghong Wu, Jiangung Zheng, Xiangrong Yu, Yi Xiang J. Wang; Daoyuan Wang; *British Journal of Neurosurgery* 2011, 25, 369-375
Craniopuncture Efficacy

Minimally invasive craniopuncture therapy vs. conservative treatment for spontaneous intracerebral hemorrhage: results from a randomized clinical trial in China

Wen-Zhi Wang1,2*, Bin Jiang2, Hong-Mei Liu1, Di Li1, Chuan-Zhen Lu3, Ya-Du Zhao4, and J. W. Sander5


An effective treatment for cerebral hemorrhage: minimally invasive craniopuncture combined with urokinase infusion therapy

Haixin Sun*, Hongmei Liu†, Di Li†, Liping Liu†, Jun Yang§ and Wenzhi Wang††

1Department of Neuroepidemiology, Beijing Neurosurgical Institute, Capital Medical University, Beijing, China
2National Office for Cerebrovascular Diseases (CVD) Prevention and Control in China, Beijing, China
3Department of Neurology and 4Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Original article

- ICH 25-40 cc, GCS>9
- N =195 craniopuncture, 182 conservative
- “Independent” survival: 59.1% vs 37%
- No survival difference
- Volume reduction not mentioned

- 22 Site RCT
- ICH 30-80 cc, GCS>9
- N =159 craniopuncture, 145 mini-crani
- 90 d Barthel 21% vs 11%
- 90 d death 14.5 vs 25%
- Less rebleeding MIS
- Volume reduction not mentioned
• Typical evacuation rate ~50-60%
• Higher evacuation correlated with better outcomes
  – Wang, Clin Neurol Neurosurg 2015
• Hematoma evacuation improved with lower HU CT score
• Not widely practiced or studied outside of China but likely the largest worldwide experience with MIS for ICH
   - 1:1:1 craniopuncture : endoscopic removal: mini craniotomy
   - 900 patient target, recruiting

2. Dose-effect Relationship of Rt-PA on ICH Evacuation - 2015
   - Increasing tPA dose for craniopuncture – not recruiting

3. Stereotactic Aspiration and Thrombolysis of Intracerebral Hemorrhage: a Prospective Controlled Study (SATIH) - 2008
   - Craniopuncture vs medical management – status not known
MISTIE- Minimally Invasive Surgery Plus rtPA for Intracerebral Hemorrhage Evacuation

Does faster clot removal in ICH give better outcomes?

Multi Phase trial – I and II completed, III presented at ISC 2019 and published in Lancet

Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial

Daniel F Hanley, Richard E Thompson, John Muschelli, Michael Rosenblum, Nichol McBee, Karen Lane, Amanda J Bistran-Hall, Steven W Mayo, Penelope Keyl, Dheeraj Gandhi, Tim C Morgan, Natalie Ullman, W Andrew Mould, J Ricardo Carhuapoma, Carlos Kase, Wendy Ziai, Carol B Thompson, Gayane Yenokyan, Emily Huang, William C Broaddus, R Scott Graham, E Francois Aldrich, Robert Dodd, Crisianne Wijman*, Jean-Louis Caron, Judy Huang, Paul Camarata, A David Mendelow, Barbara Gregson, Scott Janis, Paul Vespa, Neil Martin, Issam Awad†, Mario Zuccarello†, for the MISTIE Investigators‡


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**MISTIE**

**Inclusion:** Spontaneous, supratentorial Intracerebral Hemorrhage ≥ 20ml, with a GCS ≤ 13 or a NIHSS ≥ 6

\[ n = 96 \] patients randomized

**Therapy:** 1 mg of tPA administered via drainage catheter every 8 hours for up to 72 hours (3 days)

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

**Inclusion**
- Age 18-75
- GCS ≤ 13 or NIHSS ≥ 6
- Spontaneous supratentorial ICH ≥ 20cc
- Stable clot at second CT scan performed ≥ 6 hours after diagnosis

*Hanley, et al., 2004-2015*
3D post-op & Post tPA

Hanley, et al., 2004-2015
MISTIE II Outcomes

Medical Group Estimated Clot Reduction
First 4 days, n= 39

No clot volume reduction with Medical Management alone

Hanley, et al., 2004-2015
MISTIE II Outcomes

All tPA-Dosed Group Estimated Clot Reduction
First 4 days, n= 46

60+% clot volume reduction with catheter drainage + tPA over four days.

Hanley, et al., 2004-2015
MISTIE II Long Term Outcomes

Day 365 modified Rankin Scale (mRS)

N = 25

14%

N = 23

Hanley, et al., 2004-2015
MISTIE Outcomes by residual ICH volume

- Better outcomes with greater clot reduction

Hanley, et al., 2004-2015
MISTIE II Health Economics

Length of Stay and Cost by Treatment Arm

- Medical
- Surgical

38 day LOS Reduction

- ICU
- Non-ICU

$44K savings

- ICU
- Surgery
- Non-ICU

Hanley, et al., 2004-2015
180 day mRS 0-3:
- MIS 33% vs Medical 21%
- Absolute difference proportion 0.162 (p=0.49)

Asymptomatic bleeding higher in MIS:
- 22% vs 7%, p=0.051

Symptomatic bleeding not statistically higher:
- 9% vs 2%, p=0.226

Rigorous enrollment criteria
- 4103 patients screened, only 96 (<3%) randomized
Evaluating Image-Guided, Minimally Invasive Surgery for ICH: MISTIE III Results

Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial

**Safety goal:**
Our trial evaluated the MISTIE procedure. We hoped to achieve clot evacuation without procedure-related safety events beyond the risks associated with standard care in an intensive care unit.

**Primary hypothesis:**
Does ICH reduction via the MISTIE procedure alter functional outcomes in patients with large ICH?

Hanley, ISC 2019
Clinical Protocol

Inclusion Criteria

- ICH ≥30 mL
- ICH/IVH/IVH catheter tract/BP stability
- Randomize 12 to 72 hours post onset
- Age ≥18 years
- Historical modified Rankin Scale score ≤1

Exclusion Criteria

- Vascular defect R/O by CTA
- Infratentorial hemorrhage; evidence of brain stem involvement; large IVH
- Anticoagulation required; irreversible platelet count <100,000 or INR >1.4
- Uncontrollable systemic bleeding
- Other comorbidity preventing use of thrombolytic therapy or follow-up

Hanley, ISC 2019
MISTIE III: An Investigator-Initiated Trial

Novel trial execution
• Adaptive randomization
• Standard surgical task
• Core surgical laboratory
• Blinded adjudication mRS

ClinicalTrials.gov: NCT01827046

Primary outcome
• % mRS 0–3 at 365 days
• Sensitivity analyses: ordinal; site

Secondary outcomes
• eGOS USD–UGR (4–8) at 365 days
• All-cause mortality at 365 days
• Surgical success in relation to 365-day mRS

Safety: Safety at 30 days
MISTIE III CONSORT Diagram

Assessed (n=19,942)

Randomized (n=506)

MISTIE (n=255)

5 ineligible

1 LTFU

mITT analysis (n=249)

MISTIE III CONSORT Diagram

ALLOCATION

Control (n=251)

2 ineligible

9 LTFU

mITT analysis (n=240)

Lost to follow-up: 2%

Excluded (n=19,436)

19,206 I/E criteria
162 no consent
68 other
## Treatment Variables

<table>
<thead>
<tr>
<th></th>
<th>MISTIE (n=250)</th>
<th>Control (n=249)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ictus to randomization (h)</td>
<td>47 (33-60)</td>
<td>46 (36-58)</td>
<td>0.817</td>
</tr>
<tr>
<td>Ventilation at randomization</td>
<td>107 (43)</td>
<td>102 (41)</td>
<td>0.678</td>
</tr>
<tr>
<td>MISTIE procedure duration (h)</td>
<td>1 (1-1)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Number of doses</td>
<td>4 (2-6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ictus to end of treatment (EOT) (h)</td>
<td>127 (107-151)</td>
<td>123 (113-134)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>EOT CT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH volume (mL)</td>
<td>12 (8-21)^†</td>
<td>44 (34-56)^†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVH volume (mL)</td>
<td>0.2 (0-1.5)</td>
<td>0.3 (0-1.9)</td>
<td>0.137</td>
</tr>
<tr>
<td>EOT ICH remaining ≤15 mL</td>
<td>148 (60)</td>
<td>2 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICP monitored</td>
<td>34/250 (14%)</td>
<td>38/249 (15%)</td>
<td>0.598</td>
</tr>
<tr>
<td>% subjects with any ICP ≥20 mm Hg</td>
<td>9/34 (26%)</td>
<td>22/38 (58%)</td>
<td>0.007</td>
</tr>
<tr>
<td>% subjects with any CPP &lt;70 mm Hg</td>
<td>21/34 (62%)</td>
<td>31/38 (82%)</td>
<td>0.06</td>
</tr>
<tr>
<td>% ICP readings ≥20 mm Hg</td>
<td>23/690 (3%)</td>
<td>67/711 (9%)</td>
<td>0.01</td>
</tr>
<tr>
<td>% CPP readings &lt;70 mm Hg</td>
<td>64/690 (9%)</td>
<td>159/711 (22%)</td>
<td>0.04</td>
</tr>
<tr>
<td>One or more ICP therapies</td>
<td>25/34 (73%)</td>
<td>26/38 (68%)</td>
<td>0.634</td>
</tr>
<tr>
<td>Days in ICU</td>
<td>10 (7-17)</td>
<td>10 (5-16)</td>
<td>0.460</td>
</tr>
<tr>
<td>Withdrawal of care</td>
<td>26 (10)</td>
<td>35 (14)</td>
<td>0.213</td>
</tr>
<tr>
<td>Days to return home</td>
<td>55 (34-105)</td>
<td>62 (35-100)</td>
<td>0.846</td>
</tr>
</tbody>
</table>

### Diagnostic CT (mL)

<table>
<thead>
<tr>
<th></th>
<th>ICH volume</th>
<th>IVH volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>MISTIE</td>
<td>43 (30-54)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Control</td>
<td>41 (31-55)</td>
<td>0 (0-2)</td>
</tr>
</tbody>
</table>

### Stability CT (mL)

<table>
<thead>
<tr>
<th></th>
<th>ICH volume</th>
<th>IVH volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>MISTIE</td>
<td>46 (35-60)</td>
<td>0.3 (0-3.1)</td>
</tr>
<tr>
<td>Control</td>
<td>45 (35-57)</td>
<td>0.4 (0-3.2)</td>
</tr>
</tbody>
</table>
No benefit in primary mRS outcome

Primary Result: Function at 365 Days

Modified Rankin Scale (mRS)

MISTIE

Control

Extended Glasgow Outcome Scale (eGOS)

MISTIE

Control

Proportion of participants (%)
Benefit in mRS when <15 cc achieved

mRS Distributions at Day 365 (As Treated)

Modified Rankin Scale (mRS) scores

- 0: no disability
- 1: slight disability
- 2: moderate disability
- 3: severe disability
- 4: moderate-severe disability
- 5: severe disability
- 6: death

<table>
<thead>
<tr>
<th>mRS</th>
<th>MISTIE ≤15 mL (n=145)</th>
<th>Control (n=239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (0.7%)</td>
<td>6 (2.5%)</td>
</tr>
<tr>
<td>1</td>
<td>10 (6.9%)</td>
<td>6 (2.5%)</td>
</tr>
<tr>
<td>2</td>
<td>25 (17.2%)</td>
<td>30 (12.6%)</td>
</tr>
<tr>
<td>3</td>
<td>41 (28.3%)</td>
<td>58 (24.3%)</td>
</tr>
<tr>
<td>4</td>
<td>35 (24.1%)</td>
<td>56 (23.4%)</td>
</tr>
<tr>
<td>5</td>
<td>14 (9.7%)</td>
<td>22 (9.2%)</td>
</tr>
<tr>
<td>6</td>
<td>19 (13.1%)</td>
<td>61 (25.5%)</td>
</tr>
</tbody>
</table>

10.5% difference mRS 0-3 (95% CI 1.0–20.0; p=0.03)
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

Awad, ISC 2019
### Overview of Results

#### Primary & Sensitivity Analysis

<table>
<thead>
<tr>
<th>1.1</th>
<th>Functional outcome</th>
<th>mRS 0-3 not different</th>
<th>Risk diff=4%</th>
<th>p=0.33</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2a-f</td>
<td>Ordinal mRS</td>
<td>mRS=6 less likely: MISTIE</td>
<td>AOR=0.6</td>
<td>p=0.03</td>
</tr>
<tr>
<td>1.2d-e</td>
<td>Subgroup analyses</td>
<td>No difference by treatment arm</td>
<td>No difference</td>
<td>NS</td>
</tr>
</tbody>
</table>

#### Ordered Secondary Analyses

<table>
<thead>
<tr>
<th>2.2</th>
<th>All-cause mortality</th>
<th>Lower hazard of death: MISTIE</th>
<th>HR=0.67</th>
<th>p=0.037</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3</td>
<td>Clot removal</td>
<td>Clot removal=better function</td>
<td>AOR=0.68</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>2.3a</td>
<td>EOT ≤15 mL (surgical target)</td>
<td>Increased % mRS 0-3</td>
<td>Risk diff=10.5%</td>
<td>p=0.03</td>
</tr>
<tr>
<td>2.6</td>
<td>ICU duration</td>
<td>No difference</td>
<td>10 vs 10</td>
<td>p=0.46</td>
</tr>
<tr>
<td>2.8-2.9</td>
<td>30-day mortality</td>
<td>Less mortality in MISTIE</td>
<td>9.4% vs 14.3%</td>
<td>p=0.09</td>
</tr>
<tr>
<td></td>
<td>Safety: AEs/SAEs</td>
<td>More total SAE: Control</td>
<td>126 vs 142</td>
<td>p=0.01</td>
</tr>
</tbody>
</table>
Conclusions

**Goal 1: Define functional and/or mortality change**
- For ITT, where 40% of the cases did not meet the treatment goal, MISTIE did not reach the postulated goal
- Frequency of survival is modestly improved with MISTIE without a “price” in surgical risk or vegetative state

**Goal 2: Safety of surgery-drug combination**
- MISTIE can be safely performed with simple training

**Goal 3: Impact of procedural performance on outcome**
- Improved function and increased survival is produced with Surgical reduction to $\leq 15$ mL
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.**
MISTIE Considerations

• Average clot evacuation ~70%

• Still takes ~3 days to get the clot out

• Needed to screen a high number to enroll (2.5%)

• There does seem to be survival and functional benefit when goal evacuation is achieved

• Failure to show benefit of the primary outcome means there is still not a paradigm shift in ICH treatment
Mechanically Based MIS – endoscopic or stereotactic aspiration

Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study

LUDWIG M. AUER, M.D., WOLFGANG DEINSBERGER, M.D., KURT NIEDERKORN, M.D., GÜNThER GELL, PH.D., REINHOLD KLEINERT, M.D., GERHARD SCHNEIDER, M.D., PETER HOLZER, M.D., GERTRAUDE BONE, M.D., MICHAEL MOKRY, M.D., EVA KÖRNER, M.D., GERTRUDE KLEINERT, M.D., AND SUSANNA HANUSCH, M.D.

Departments of Neurosurgery, Neurology, Radiology, and Pathology, University of Graz, Graz, Austria

Kim et al., 2009

- N = 387, ICH < 30 cc, med mgmt. vs aspiration
- Leksell frame, stereotactic placement of Archimedes aspirator
- 180 day mRS 1.2 vs 3.0

N = 100
ICH volumes>10 cc, avd ~50
Irrigation and aspiration
Evacuation rate ~50-70%
avg
6 mo Mortality: 30% vs 70%

Functional benefit: subgroups (<60yrs, <50cc starting)
“Mechanical” arm of MISTIE II trial
- Used medical group as a comparator
- Same enrollment criteria; ICH >20 cc, within 48 hours
- Evacuation rate: 68+/−21.6% on intra-op scan
- 180 and 365 d mRS 0-3: 42.9 vs 23.7%

Vespa, et al., Stroke 2016
MISPACE - Minimally invasive Subcortical Parafascicular Access for Clot Evacuation

Trans-sulcal access, neuronavigation guidance, using inner obturator to place sheath

Extracorporeal telescope and video display

Microinstruments or resection device – NICO myriad
MISPACE Experience

Endovascular-assisted surgery for the management of spontaneous intracerebral hemorrhage

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b Department of Neurosurgery, Barrow Neurological Institute, Phoenix, AZ, USA
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Initial Single-Center Technical Experience With the BrainPath System for Acute Intracerebral Hemorrhage Evacuation

Andrew M. Bauer, MD, MBA
Peter A. Rasmussen, MD
Mark D. Bain, MD, MS

BACKGROUND: Surgical intervention has been proposed as a means of reducing the high morbidity and mortality associated with acute intracerebral hemorrhage (ICH), but many previously reported studies have failed to show a clinically significant benefit. Newer, minimally invasive approaches have shown some promise.

Operative Neurosurgery 01–7, 2016

The Safety and Feasibility of Image-Guided BrainPath-Mediated Transsulcular Hematoma Evacuation: A Multicenter Study

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Mitesh Shah, MD
Amin B. Kassam, MD
Ronald Young, MD
Lloyd Zucker, MD
Anthony Maisonneuve, MD
Gavin Britz, MD
Charles Agbi, MD
JD Day, MD
Gary Gallia, MD, PhD
Robert Kerr, MD, PhD
Gustavo Pradilla, MD
Richard Roivin, MD
Charles Kulwin, MD
Julian Bailes, MD

BACKGROUND: Subcortical injury resulting from conventional surgical management of intracranial hemorrhage may counteract the potential benefits of hematoma evacuation. OBJECTIVE: To evaluate the safety and potential benefits of a novel, minimally invasive approach for clot evacuation in a multicenter study. METHODS: The integrated approach incorporates 5 competencies: (1) image interpretation and trajectory planning, (2) dynamic navigation, (3) atraumatic access system (BrainPath, NeuroGlow, Indigo Medical, Medtronic), (4) stereotacoscopic optics, and (5) automated tracking. 11 centers were trained to use this technique. Demographical, procedural, and functional outcome data were analyzed retrospectively.

Neurosurgery 00:1–10, 2017

Retrospective review, N = 11
ICH volume pre 51 cc
ICH volume post 10 cc
Evacuation rate 87%
90 mRS <2 = 36%, mRS 6 = 36%

Single center review, N = 18
ICH volume pre 52.7 cc
ICH volume post 2.2 cc
Evacuation rate 95.7%
Bleeding vessel treated 65%

11 center review, N = 39
ICH volume pre 36 cc
Evacuation rate >90% in 72%
75-89% in 23%, 50-74% in 5%
mRS >/= 3 in 63%
Multi site RCT comparing MIPS (minimally invasive parafascicular surgery) to medical management for ICH

Primary outcome: 180 day mRS

Secondary outcomes: 30 day mortality; change in ICH volume; hospital and ICU LOS

Economic analysis – cost per QALY with MIPS

Enrollment - 300
Inclusion

- Age 18-80
- ICH volume 30-80 cc
- Intervention within 24 hours
- GCS 5-14
- Historical mRS 0-1

Exclusion

- Vascular lesion, tumor, ischemic stroke causing ICH
- NIHSS < 5
- Bilateral fixed dilated pupils
- Extensor motor posturing
- Thalamus, pons, infratentorial
- NOACs
- Platelets <75000, INR >1.4
- Investigator discretion
Surgeon training in MIPS procedure

Emory University – Dr. Pradilla
Sponsor – NICO, corp.

31 sites active, target 300 patients enrolled
Neuronavigation Guided, Endoscopic Assisted ICH Aspiration

Goal: Achieve significant ICH volume reduction quickly and with minimal harm to normal brain

Used MISTIE inclusion criteria (significant ICH burden, neurologic deficit, and underlying vascular lesion excluded by CTA)

Protocol: Neuronavigation, Endoscope, and Vibrational aspiration wand
Neuronavigation Guided, Endoscopic Assisted ICH Aspiration

- Frameless stereotactic sheath placement
- Endoscope
- Apollo aspiration wand and vacuum
- Intra-op imaging to confirm evacuation
2nd Generation: Artemis

- Smaller profile
- Stroke system aspiration pump
- Longer tubing
- More aggressive hand piece
1. Pre-operative plan using neuronavigation system
   - Select trajectory along the long axis of the ICH, avoiding eloquent tracts or structures
   - Identifies the site of the burr hole
2. Surgical positioning and registration

- Head fixed in 3 point holder, patient anatomy registered to neuronavigation
- Sheath trocar and Endoscope registered to navigation system
- Neuronavigation Guided, Endoscopic Assisted ICH Aspiration
3. Sheath is advanced using navigation guidance to target at distal ICH.
   - Trocar then removed and sheath peeled back and secured with snaps.
Neuronavigation Guided, Endoscopic Assisted ICH Aspiration

Aspiration initiated within the sheath as clot delivers itself.
Neuronavigation Guided, Endoscopic Assisted ICH
Aspiration

5. Aspiration proceeds until no further clot identified circumferentially
   - Confirm position with navigation
   - Peel Sheath back 1 cm and repeat aspiration
6. Repeat aspiration in the new locations until clear cavity achieved

- Cavity inspected for hemostasis
- Liberal use of irrigation
- "SCUBA" technique
Neuronavigation Guided, Endoscopic Assisted ICH Aspiration

7. Maintain sterile field and obtain postoperative imaging
   • Ceretom portable CT scanner
   • Hybrid OR – DynaCT scan
Consecutive series of all patients with ICH/IVH treated with the Apollo system since October 2014-April 2017

Baseline characteristics, clinical performance, safety, and follow up data were assessed

Volume of hemorrhage pre- and post-procedure was calculated using the A*B*C/2 method
Results

Demographics

N = 59
Mean Age: 53.7 (25-86)
M:F 41:18

Baseline clinical scores

Mean GCS 10 (3-15)
All with contralateral motor deficits
Median ICH Score 3.0
Predicted 30 day mortality 72%
Hemorrhage characteristics

Volume
- Pre-op: 55.1 ± 30.5 cc
- Post-op: 10.2 ± 12.0 cc
- Mean Reduction: 80.6 ± 25.4 %
- Median: 90.5 (IQR 76.5-95.0)%

Midline Shift
At level of Septum Pelucidum
- Pre-op: 7.1 ± 4.5 mm
- Post-op: 4.4 ± 3.2 mm
- Reduction: 38.6 ± 30.5 %
Clinical Outcomes

Length of stay:
- ICU: 10.3±7.5 days
- Hospital: 15.7±12.9 days
- Rehab: 6.2±10.6 days

• mRS scores at 180 days
  - 1: 10%
  - 2: 7%
  - 3: 15%
  - 4: 15%
  - 5: 15%
  - 6: 37%

  - Expected mortality by ICH score: 72%
Complications/Considerations

No direct procedure related deaths

2 patients had hemorrhage re-accumulation on serial imaging
  – Both were thrombocytopenic

Wide range of post-op volume reduction
  – Related to clot characteristics and tenacity
Neuronavigation Guided, Endoscopic Assisted ICH Aspiration experience

Initial Multicenter Technical Experience With the Apollo Device for Minimally Invasive Intracerebral Hematoma Evacuation

BACKGROUND: No conventional surgical intervention has been shown to improve outcomes for patients with spontaneous intracerebral hemorrhage (ICH) compared with medical management.

OBJECTIVE: We report the initial multicenter experience with a novel technique for the minimally invasive evacuation of ICH using the Penumbra Apollo system (Penumbra Inc, Alameda, California).

METHODS: Institutional databases were queried to perform a retrospective analysis of all patients who underwent ICH evacuation with the Apollo system from May 2014 to September 2014 at 4 centers (Medical University of South Carolina, Stony Brook University, University of California at San Diego, and Semmes-Murphy Clinic). Cases were performed either in the neurointerventional suite, operating room, or in a hybrid operating room/angiography suite.

RESULTS: Twenty-nine patients (15 female; mean age, 62 ± 12.6 years) underwent the minimally invasive evacuation of ICH. Six of these parenchymal hemorrhages had an additional intraventricular hemorrhage component. The mean volume of ICH was 45.4 ± 9.6 cc (range, 25.5–70.6). The mean evacuation rate was 54.1% (range, 15.7–95.6%). The mean ICH volume decreased from preoperative 45.4 ± 9.6 cc to postoperative 21.8 ± 9 cc. The mean hematoma evacuation rate was 54.1% (range, 15.7–95.6%). The average mortality rate was 13.8% (range, 0–24%).


Multicenter review, N = 29
ICH volume pre: 45.4 cc
ICH volume post: 21.8
Evacuation rate: 54.1 %
Mortality 13.8 %
Neuronavigation-Guided, Endoscopic-Assisted ICH Aspiration

- Advantages
  - Quickly remove large volumes of ICH
  - Minimally invasive access sparing normal brain
  - Assess efficacy of treatment and repeat as needed

- Challenges
  - Small endoscopic cautery tools available but would be inadequate for large bleeding
  - Patient selection: coagulopathic patients, ? Poor platelet function, other comorbidities
  - Clinical efficacy remains to be demonstrated in a trial
Reason for Optimism

Pharmacological treatments:
- have demonstrated improved outcome vs medical management
- Are least invasive to normal brain tissue
- Have more variability in Evacuation rate
- Take time to achieve ICH volume reduction

Mechanical treatments:
- Can achieve significant volume reduction in a short time
- Require a larger path through normal tissue
- Have a less established record

Heterogeneous disease
Need comparator groups – need RCTs
**MIND Trial – Minimally Invasive Neuro Evacuation Device**

- RCT of MIS ICH evacuation vs Best medical management
- 500 patients planned
- Primary outcomes: 180 day mRS, 30 day mortality
- Secondary outcomes: 365 day mRS, QOL measures, length of stay,
Inclusion Criteria:

1. Patient age ≥ 18 and ≤ 80
2. Supratentorial ICH of volume ≥ 20 and ≤ 80 cc (measured using A x B x C/2 method)
3. Hemostasis (hemorrhage increase of < 5 cc as confirmed by 2 CT/MR taken a minimum of 6 hours apart)
4. NIHSS ≥ 6
5. Presenting GCS ≥ 5 and ≤ 15
6. Historical mRS 0 or 1
7. Symptom onset < 24 hours prior to initial CT
8. MIS must be initiated within 72 hours of ictus/bleed
9. SBP must be < 180 mmHg and controlled at this level for at least 6 hours
Virginia Mason was selected as an early participating site

We have enrolled 2 patients and screened 5, actively looking for good candidates
• 2 patients treated with Artemis system
• Both with significant neurologic deficit
• Technically successful procedures
• Awaiting longer term follow up for functional status
Conclusions – Reason for Optimism

Pharmacological treatments:
- have demonstrated improved outcome vs medical management
- Are least invasive to normal brain tissue
- Have more variability in Evacuation rate
- Take time to achieve ICH volume reduction

Mechanical treatments:
- Can achieve significant volume reduction in a short time
- Require a larger path through normal tissue
- Have a less established record

Heterogeneous disease
Need comparator groups – need RCTs
Reason for Optimism

Given the history of surgery for ICH, robust benefit in well designed trials will be required to change practice patterns.
Acknowledgments

Organizing Committee
Karen Gifford
Kellie Hurley
Stephanie Perry
Chad Gabelein
Karen McHenry
Melissa/Russo CME

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Techs and Nurses

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Neurosurgery PAs
Better Never Stops.