Surgical Treatment of Intracerebral Hemorrhage

Regional Upstate Stroke and Health Summit
6/1/2018
Grahame C Gould, MD
Assistant Professor of Neurological Surgery
Disclosures

No financial interests to disclose
Objectives

• Brief overview of intracerebral hemorrhage (ICH)
• Current treatments / recommendations for ICH
• Role of traditional surgery in treatment of ICH
• Ongoing trials for minimally invasive ICH surgery
• Review tube-based retractor system for ICH surgery
• Discuss ENRICH trial
Hemorrhagic Stroke

Clinical History
Prevalence of Disease

- 795,000+ strokes in United States annually
Clinical Burden of ICH

- Hypertension is the leading cause of intracerebral hemorrhage (ICH)

- Mortality is greater than in Ischemic Stroke
  - Early Mortality is up to 32-50%

- Of those that Survive:
  - 80% are left with significant disability
  - 12-39% Independent Function

- Economically, $12.7B of the $74B in direct costs for stroke care/year is attributed to ICH
Current ICH Standard of Care

Neuro-ICU = Lower Mortality (I, LOE B)
• BP Control (<140, SAFE: I, LOE A - Improved Outcome: IIa, LOE B)
• CPP optimization & ICP monitoring
• Reversal of Coagulopathy
  • PCCs over FFP in VKA, rFVIIa not recommended (III, LOE C)
  • Protamine for Heparin (Iib, LOE C)
  • PLT transfusion in PLA?
• IVH/CSF Drainage (IIa, LOE B)
• Supportive Care & Multi-system homeostasis
  • Glc: I, LOE C, Fever Iib, LOE C

No surgical intervention UNTIL/UNLESS NEUROLOGICAL DECLINE

Only Cerebellar ICH surgery supported (8% of all ICHs): Class I, LOE B

Cerebellar hemorrhage >3 cm deteriorating neurologically or brain stem compression and/or hydrocephalus from ventricular obstruction should have emergent surgical evacuation

Supratentorial spontaneous ICH (85% of all ICHs) is generally NOT a surgical event
Supratentorial vs Infratentorial?
ICH Standards for Surgery?

**CLASS II RECOMMENDATIONS**

- For most supratentorial ICHs, usefulness of surgery NOT WELL ESTABLISHED - *(Class IIB, LOE A)*

- Early evacuation Vs After deterioration NOT CLEARLY BENEFICIAL - *(Class IIB, LOE A)*

- For supratentorial spontaneous ICH (85% of all ICHs) evacuation MAY BE CONSIDERED in deteriorating patients as a LIFE-SAVING MEASURE - *(Class IIB, LOE C)*

- Decompressive craniectomy +/-hematoma evacuation might reduce mortality for supratentorial ICH with: coma/large hematoma with MLS or refractory ICP - *(Class IIB, LOE C)*

---

**AHA/ASA Guideline**

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage
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 Academy of Neurological Surgeons, the Congress of Neurological Surgeons, and the Neurocritical Care Society

J. Claude Hambly III, MD, MAS, FAHA, Chair; Steven M. Greenberg, MD, PhD, Vice-Chair; Craig S. Anderson, MD, PhD; Kyra Becker, MD, FAHA; Bernard R. Boulé, MD, MS, FAHA; Mary Cashman, MD, MSc, FAHA; Coridon L. Fang, MD, MSc, PhD, FAHA; Joshua N. Goldstein, MD, PhD, FAHA; R. Loch Macdonald, MD, PhD, FRCS; Patricia H. Mitchell, RN, PhD, FAHA; Philip A. Scott, MD, FAHA; Magdy B. Selim, MD, PhD; Daniel Wol, MD, MSc; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology

The effectiveness of MIS evacuation utilizing stereotactic or endoscopic aspiration +/-thrombolytics is uncertain (Class IIB, LOE A)

Stroke. 2015 Jul;46(7):2032-60
Surgical Trials in ICH
1961-2004


Positive for Surgical Evacuation BENEFIT!
## Meta-Analyses: Surgical Trials

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>Studies Analyzed</th>
<th>Odds of Death/Dependency with Surgery</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hankey &amp; Hon</td>
<td>McKissock, Juvela, Auer, Batjer</td>
<td>1.23 (0.77-1.98)</td>
<td>Insufficient Evidence</td>
</tr>
<tr>
<td>Prasad et al</td>
<td>McKissock, Juvela, Auer, Batjer</td>
<td>1.99 (0.92-4.31)</td>
<td>Insufficient Evidence</td>
</tr>
<tr>
<td>Saver et al</td>
<td>Juvela, Auer, Batjer</td>
<td>0.72 (0.38-1.44)</td>
<td>Trends Toward Improved Outcome</td>
</tr>
<tr>
<td>Fernandes et al</td>
<td>McKissock, Juvela, Auer, Batjer, Chern, Morgenstern, Zuccarello</td>
<td>1.2 (0.83-1.74)</td>
<td>Trends Toward Improved Outcome</td>
</tr>
</tbody>
</table>
STICH

- **1033** patients from **83** centers in **27** countries were randomized to early surgery (503) or initial conservative treatment (530)

- Favorable Outcome: Early surgery **122 (26%)** Vs Initial conservative treatment **118 (24%)**

- **Subgroup Analysis:**
  - Patients with lobar hematoma and no IVH had **37%** favorable outcome with conservative treatment vs. **49%** with early surgery (p=0.08)
  
- STICH lacked sufficient power to address this subgroup

**Failed to demonstrate superiority of surgery over medical management**

David Mendelow, MBBCh, PhD, FRCS
Department of Neurosurgery
Newcastle General Hospital
University of Newcastle, UK
STICH II


- Craniotomy Vs. Best medical therapy for lobar spontaneous ICH 10-100 mL and no associated IVH (78 centers, 27 countries)
- 601 patients:
  - Early surgery = 307, 6-month f/u: 298, included = 297
  - Initial conservative treatment = 294, 6-month f/u: 291, included 286
  - % Unfavorable Outcome: Surgery 174/297 (59%) Vs. 178/286 (62%) in conservative treatment group (absolute difference 3.7% [95% CI -4.3 to 11.6], odds ratio 0.86 [0.62 to 1.20]; p=0.367)
  - 21% crossed-over to surgical group

**No difference in intention-to-treat analysis of primary outcomes (extended GOS) at 6 months**

Absolute difference of primary outcome dichotomy of 3.7% favored surgery

Other trends of a secondary shift in good disability scale strata and mortality also favored surgery with a 6% effect, trending but not reaching statistical significance
MISTIE II
Minimally invasive surgery plus rtPA for intracerebral hemorrhage evacuation
ISC 2013

- **Purpose**
  - To determine the safety of using a combination of MIS and rtPA to remove ICH
  - ICES arm of trial to determine safety of endoscopic surgery to remove ICH

- **Study Design**
  - Randomized, safety study, parallel assignment, open label

---

**MISTIE II TRIAL SYNOPSIS**

**STAGE 1**
40 subjects 1:3 med.surg (2 tiers: 0.3 mg and 1.0 mg rt-PA in surgical group)

- **Hypothesis 1**
  - Clot removal occurs with rt-PA and is dose dependent

- **Hypothesis 2**
  - MIS+rt-PA is safe

**STAGE 2**
50 subjects 1:1 med.surg (1.0 mg rt-PA in surgical group)

- **Hypothesis 3**
  - MIS+rt-PA improves clot removal and functional outcomes compared to medical group

**GOAL:** > 80% ICH reduction or ICH reduction to 15 mL

**RESULTS**

- Clot removal: 27 mL (surgical) vs. 7 mL (medical)
- 0.3 mg & 1.0 mg Q6h not different for clot removal
- Rebleeding is low and similar in both groups
- Infection is similar in both groups
- Early mortality is rare in both groups

- Clot removal: 30 mL (surgical) vs. 7 mL (medical)
- mRS 0-3: 35% (surgical) vs. 24% (medical) @180 days
- Causal analysis - OR 3.03 for MIS+rt-PA associated good outcome, if <15mL residual clot and >60% clot reduction

**POST HOC OBSERVATIONS**

- Mechanical removal is sufficient in approximately 15% of MIS patients (not requiring rt-PA dosing to achieve target clot reduction)
- Accuracy of catheter placement relates to volume clot removed
- 87% of surgeons mastered operative task in one pilot Not all surgeons can perform the procedure (4% failed)
- Medical + MIS subjects may require emergent craniotomy
- 2% Post procedure mortality

- Stage 2 surgical performance improved
  - 62% of clot removed on average
  - Over 3 days, clot reduction from 47 mL to 15 mL (29mL removal)

---

Daniel Hanley, MD
Department of Neurology, Anesthesiology & CCM
Johns Hopkins University, School of Medicine
Baltimore, MD

---

UPSTATE
COMPREHENSIVE STROKE CENTER
MISTIE II Outcomes

Day 365 modified Rankin Scale (mRS)

N = 25

N = 23

14%

38 day LOS Reduction

$44K savings

Hanley DF. MISTIE II Trial Results: Safety, Efficacy and Surgical Performance. Presentation at ISC 2013.
MISTIE II Outcomes

Day 180 modified Rankin Scale (mRS)

- < 10mL: 19 subjects
- 10-20mL: 33 subjects
- 20-35mL: 32 subjects
- > 35mL: 31 subjects

EOT Volumes - All Surgical and Medical

- % Subjects
- 0
- 1
- 2
- 3
- 4
- 5
- 6

Hanley DF. MISTIE II Trial Results: Safety, Efficacy and Surgical Performance. Presentation at ISC 2013.
MISTIE III

• MISTIE III is funded by NIH/NINDS, under a cooperative agreement (U01: 1U01NS080824-01A1)
  • It involved over 90 centers in the US, Europe, Israel, China and Australia
  • Last subject enrolled in August 2017

• MISTIE III intervention seeks to remove ICH through MIS and intermittent dosing of rt-PA for 3 days
  • Cathflo Activase by Genentech in the US
  • Actilyse by Boehringer Ingelheim in Europe and Asia

• The primary endpoint is the Modified Rankin Score measured at 180- and 365-days

• Goal Improvement 12%
These Trials Have Shown:

- Benefit of MIS above other approaches
- Benefit of surgery over conservative TX
- Early surgery benefit
- Positive impact on functional outcomes
- Increased acute care cost savings
- Reduced hospital LOS

Hanley et al, Minimally Invasive Surgery plus rt-PA for ICH Evacuation (MISTIE).
Challenges of Current MIS Approaches

- Requirement of clot stability for 6-12 hours
  - Prolonged clot resolution time
- Difficult to address active bleeding
- Risk of rebleeding at primary and secondary sites
- Clinical trials for surgical ICH Evacuation have **NOT consistently** shown improved patient outcomes
Current ICH Trial Limitations

• Timing of intervention – Undefined therapeutic window
• Technique – Invasive and non standardized surgical techniques
• Patient selection – limitations, impact of associated factors
Defining a Surgical Approach for ICH

- Ideal surgery for ICH would:
  - Allow for early intervention
  - Minimize injury
  - Maximize clot reduction
  - Allow for hemostasis management
  - Minimize re-bleeds
Rationale for Early Intervention

• ~ 30-40% of hematoma expansion of >1/3 of initial volume (most within 3 hours of onset)
• Targeting the spot sign (CTA)
• Rapid correction of intracranial hypertension
• Medical complications
  • PNA
  • Aspiration
  • Respiratory Failure
  • PE
  • Sepsis = 50% of deaths

Secondary Brain Injury Cascade

Cellular disruption
Glutamate release
Ca$$^{++}$$ influx

0.4 hrs
4 hrs-7 d

RBCs
HGB
Plasma proteins
DAMPs
Thrombin

Mitochondrial dysfunction

Cytotoxic edema
Necrosis

Endothel. & MG Activation

Cytotoxic
Pro-inflammatory
Pro-oxidative

BBB disruption
Vasogenic edema
Apoptosis

Courtesy: Dr. Gustavo Pradilla
Evidence for Early Intervention

**Gregson et al. Stroke 2012; 43**
- 8 RCTs
- 2186 Cases

**Zhou et al. Stroke 2012; 43**
- 12 RCTs
- 1955 Total Patients

---

**Evidence that surgery is of benefit if undertaken early, before the patient deteriorates**

Clinical outcomes showed early removal of hematoma can potentially mitigate brain injury provided surgeon can avoid damage to eloquent areas, cortical vasculature, and subcortical tracts during surgical access.
Is surgical technique important?
The Subcortical Space: Challenges with Traditional Surgical Approaches

- Deep lesions requiring access through uninvolved cortical and white matter structures
- Intraventricular lesions
- Difficult access with traditional techniques
- Accurate subcortical targeting

**CHALLENGES**

- Retraction Injury
  - Brain tissue "creep"

**Endoscopic Visualization**

- Light & Magnification
- Quality tissue collection

**Access**
Subcortical Injury

- Subcortical injury was found the primary cause of neurological deficits following awake craniotomy procedures.
- Of cases developing new intraoperative neurological deficits, 90% occurred during subcortical dissection.
- In eloquent cortex, 43% experienced worsened neurological deficits in immediate post-op period and 14% continued to have worsened deficits at 3-month follow-up.

Preserving subcortical areas during cerebral resections may reduce the severity of both immediate and late neurological deficits.
Retraction Injury

- Challenges of subcortical surgery with retraction injury
  - Dispersion of Pressure on Tissue
  - Tissue “creep”
  - Visualization at Depth

Flat Blade Retractors  Endoscopy  Radial Retractors

The quiet revolution: retractorless surgery for complex vascular and skull base lesions

Clinical article
Robert F. Spetzler, M.D., and Naier Sanai, M.D.
Division of Neurological Surgery, Barrow Neurological Institute, St. Joseph’s Hospital and Medical Center, Phoenix, Arizona
Radial Retraction

The stereotaxic retractor in computer-assisted stereotaxic microsurgery

Technical note

PATRICK J. KELLY, M.D., STEPHAN J. GOERSS, B.S., AND BRUCE A. KALL, M.S.

Departments of Neurosurgery and Information Processing and Systems, Mayo Foundation and Mayo Medical School, Rochester, Minnesota

- Dr. Pat Kelly (1980s)
- No inclusion of WMT analysis
- Manual Dissection → Placement of Radial Retractor
- SHOWED POTENTIAL FOR LESS INJURY
Radial Retraction

- Small craniotomy
  - \( \cong 30\text{mm} \) or smaller
- Small dural opening
  - \( \cong \) Size of sheath used
  - 13.5mm or 11mm
- Venting of ICP to be during cannulation
- Air-medium & bimanual microsurgical technique
Intra-operative Ultrasound

• Customized probe designed to work within retractor system:
  • Sulcal Identification
  • Vascular Flow
  • Lesion Location
  • Real Time Monitoring:
    • Extent of Resection/Evacuation
    • Proximity to Critical Structures
    • Lesion Movement
Clot removal

The Myriad Device:
- Customized aspiration system with cutting capacity
  - Side-mouth aperture
  - Variable aspiration
  - Toggle between aspiration only and aspiration with cutting
- Allows for tissue collection in sterile, closed system
Less Invasive ICH Solution?

Evidence for early intervention

• Early intervention for clot removal:
  • Can reduce ICP
  • Relieve mass effect
  • Mitigate secondary brain injury
  • Allow for earlier extubation
  • Reduce ICU LOS

<table>
<thead>
<tr>
<th>Median ICTUS TO SURGERY (Days)</th>
<th>Sujijantarat</th>
<th>Przybylowski</th>
<th>Bauer</th>
<th>Labib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.8 (0.5-1.8)</td>
<td>1.0 (0.6-1.8)</td>
<td>1.0 (0.9-1.9)</td>
<td>1.0 (0.7-2.8)</td>
</tr>
</tbody>
</table>

Why Use Radial Retractor System?

- Standardize Technique
- Direct Hemostasis
- Avoid use of thrombolytics
Why Trans-sulcal?

• Shortest distance to lesion
• Assumes all tissue is relevant
• Tissue turgor favors “closure”

Kassam et al. Part II: an evaluation of an integrated systems approach using diffusion-weighted, image-guided, exoscopic-assisted, transulcal radial corridors. Innovative Neurosurgery; 2015
Scranton et al. Transulcal parafascicular minimally invasive approach to deep and subcortical cavernomas: technical note. JNS 2016, Mar 4:1-7
Clot Reduction Matters

- Results from MISTIE have shown EOT volume correlated to mRS at 180-days
  - Patients with <10mL of clot remaining had better mRS
  - Patients with >35mL of clot remaining had worse mRS
Evidence for clot reduction

- Growing evidence to support maximal clot reduction with this approach
- Air-medium, bimanual approach for hemostasis

<table>
<thead>
<tr>
<th></th>
<th>Sujijantarat</th>
<th>Przybylowski</th>
<th>Bauer</th>
<th>Labib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Pre-op Volume (cm³)</td>
<td>50.5cc (23.9-76.6)</td>
<td>78.0cc (40.5-105.5)</td>
<td>52.0cc (41.0-66.0)</td>
<td>36.0cc (27.0-65.0)</td>
</tr>
<tr>
<td>Median Volume Clot Reduction (%)</td>
<td>91.6% (86.9-98.9)</td>
<td>87.0% (48.5-94.5)</td>
<td>98.2% (94.8-99.2)</td>
<td>NA</td>
</tr>
</tbody>
</table>


Outcomes

- Growing evidence to support decreased mortality and LOS

<table>
<thead>
<tr>
<th></th>
<th>Sujijantarat</th>
<th>Przybylowski</th>
<th>Bauer</th>
<th>Labib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Pre-Op ICH Score</td>
<td>3</td>
<td>2</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>Median In-Hospital Mortality</td>
<td>6.3%</td>
<td>33.3%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Median Length of Stay (Days)</td>
<td>24.0 (16.0-33.0)</td>
<td>7.0 (2.5-36.3)</td>
<td>16.7 (9.7-20.9)</td>
<td>NA</td>
</tr>
</tbody>
</table>


Outcomes

- Significant improvement in post-operative GCS (p<0.001)

<table>
<thead>
<tr>
<th></th>
<th>Sujijantarat</th>
<th>Przybylowski</th>
<th>Bauer</th>
<th>Labib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Pre-Op GCS</strong></td>
<td>7 (6.25-10)</td>
<td>NA</td>
<td>10 (5.75-12)</td>
<td>10 (8-14)</td>
</tr>
<tr>
<td><strong>Median Post-op GCS</strong></td>
<td>13 (10.25-14)</td>
<td>NA</td>
<td>14 (9-14.25)</td>
<td>14 (11-15)</td>
</tr>
</tbody>
</table>

Can you prove it?
ENRICH: Early MiNimally-Invasive Removal of ICH
Study Team

• Scientific Leadership Team
  • Gustavo Pradilla, MD (Neurosurgery) – Emory University
  • Daniel Barrow, MD (Neurosurgery) – Emory University
  • Jonathan Ratcliff, MD (Neurocritical Care) – Emory University
  • Jason Allen, MD (Neuroradiology) – Emory University
  • David Wright, MD (Emergency Medicine) – Emory University
  • Michael Frankel, MD (Neurology) – Emory University
  • Alex Hall, MS, RN (Clinical Research Nurse) – Emory University
  • Victoria Phillips, DPhil (Healthcare Economist) – Emory University

• Data Safety Monitoring Board & Medical Monitor
  • Mark Hadley, MD (DSMB Chair) – University of Alabama
  • Greg Campbell, PhD (Biostatistician) – GCStat Consulting, LLC
  • Opeolu Adeoye, MD (Medical Monitor) – University of Cincinnati
Study Purpose

To determine if *minimally invasive parafascicular surgery* (MIPS) using currently available and *FDA cleared technology* for early intracerebral hemorrhage evacuation results in improved functional outcome and economic benefit when compared to standard medical management
Inclusion Criteria

• Age 18 – 80
• CT showing acute spontaneous primary ICH
• GCS 5-14
• ICH Volume 30-80mL
• Study intervention can be initiated within 24 hours of last known well (TX ≤ 8 hrs is preferred)
• Historical mRS 0 of 1

Exclusion Criteria

• Aneurysm, avm, vascular anamoly etc.
• NIHSS<5
• Bilateral fixed and dilated pupils
• Extensor motor posturing
• IVH involving >50% of the lateral ventricles
• Primary thalamic ICH
• Midbrain, pontine, or cerebellar ICH
• Use of anticoagulants that can’t be rapidly reversed
• ESRD
• ESLD
• Evidence of active bleeding involving the retroperitoneal, gastrointestinal, genitourinary or respiratory tract
• Uncorrected coagulopathy or known clotting disorder
• Plt < 75k, INR > 1.4 after correction
• Life expectancy < 6 months
• Pregnant
• No reasonable expectation of recovery, DNR, comfort measures only
• Mechanical heart valve
• Need to resume anticoagulation < 5 days
• Unable to meet follow up requirements
Objectives

• Efficacy
  • Determine if MIPS for ICH evacuation results in a 10% improvement in 180-day utility-weighted modified Rankin Scale
  • Quantify the cost per quality-adjusted life-years (QALY) gained through MIPS

• Safety
  • Determine if MIPS results in increased mortality compared to standard management
  • Determine if MIPS results in an increase in Δ hemorrhage volume between index and 24 hour follow-up CT

• Secondary
  • To assess and quantify post-operative rebleeding associated with clinical deterioration following MIPS
  • Demonstrate that percent volume of ICH reduction is associated with improved functional outcome
  • Compare UW-mRS at discharge, 30 days, and 90 days between the treatment groups.
Study Design

- Multi-center, randomized, adaptive clinical trial
- Block randomization based on hemorrhage location (anterior basal ganglia vs lobar) with subsequent enrichment on location.
- Sample size: 150 - 300 subjects
- Interim Analyses: 150 then every 25 patients up to 300
- Evaluate for stopping or enrichment at each interim
- Enrichment, and early stopping rules for futility and predicted success are predetermined
Study Update

• Trial update as of December 31, 2017 presented at 2018 International Stroke Conference
  • 21 Active Sites
  • 60 Enrolled Patients
  • 50mL Median Hemorrhage Volume (48% Lobar)
  • Mean NIHSS and GCS reported as 18.3 and 11.3, respectively
  • Mean time from LKN to randomization 13:07 hours
  • Randomization to surgery of 2:30 hours
  • Follow-up completed for 29/60 enrolled patients

Conclusion

• ICH is a common, devastating form of stroke
• ICH treatment has made little progress
• Optimal clinical targets based on data
  • Treat early
  • Remove more clot
  • Protect normal brain
• Radial retractor system to hit the targets
• Could ICH be the next ELVO?