Minimally Invasive Evacuation of ICH: The Surgical Aspect of MISTIE

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**Minimally Invasive (Stereotactic) Surgery + rt-PA for ICH Extraction (MISTIE)**

A phase II, safety, and efficacy study of ICH treatment
Sponsored by the NIH/NINDS

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MISTIE

Multicenter, randomized, controlled and stratified study comparing a surgical intervention with administration of rt-PA or mechanical aspiration to conventional medical treatment
MISTIE Trial Design

Phase I
N = 60

Minimally Invasive Surgery + 0.3 mg rt-PA
Minimally Invasive Surgery + 1.0 mg rt-PA
ICES

Phase II
n = 50

Medical Arm
Minimally Invasive Surgery + 1.0 mg rt-PA
MISTIE: Surgical Task

- Stereotactic CT/MRI Guided Navigation for the novel purpose of evacuating intracerebral hemorrhage (ICH)
Stereotactic Image Guidance

- Creation of Burr Hole w/Drill
- Insertion of a cannula large enough to pass final catheter through (14 F)
- Aspiration of the hematoma until there is no longer a fluid component of clot noted in aspirate
- Passive insertion of a catheter inside the cannula which is then removed
MISTIE

Surgical Finding #1

MIS + rt-PA is safe
Primary Endpoint Comparison
MISTIE trial – All Subjects (n= 57)

Operative Mortality (10%)
Brain Infection (15%)
Symptomatic Bleeding (35%)
30 Day Mortality (70%)

MISTIE Trial Safety Endpoints (n=57)

- Operative Mortality
- 30 Day Mortality
- Brain Infection
- Symptomatic Bleed

Randomized Tier 1 (n=20)
Randomized Tier 2 (n=20)
Run-In (n=17)
MISTIE

Surgical Finding #2

MIS + rt-PA can clear clot faster than medical management
Clot Clearance

Estimated Clot Remaining as % of Volume on Stability Scan

**Medical Patients**
First 4 days, Both Clot Sizes, n=4

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Estimated Clot Remaining as % of Volume on Stability Scan

**Surgery + rt-PA Patients (Randomized)**
First 4 days, Both Clot Sizes, n=11
MISTIE

Surgical Finding #3

The accuracy of the surgeon in the catheter placement is critical to clot size reduction
MISTIE: Surgical Task

- One goal of the MISTIE trial was to assess variability in surgical performance.
- We hypothesize that the higher is the accuracy in targeting the ICH the more complete is the clot resolution.
MISTIE: Surgical Task

- We developed a 150-point scoring system to assess whether catheter engagement with clot affected clot volume reduction.
A = 50 - % distance short* of 2/3 point

* Overshoot of the 2/3 point is acceptable as long as all side ports are within the clot

A’ = 50 – Θ**

** Θ = angle of deviation from long axis in degrees (e.g., 10° deviation, 50 -10 = 40)

B = 50 - % distance from midpoint

Total score = A + A’ + B
MISTIE: Surgical Task

- Place catheter within $\frac{2}{3}$ of clot long axis; middle $\frac{1}{3}$ of clot width
- Confirm Catheter Placement with CT prior rt-PA
- Achieve surgical endpoint: clot reduction to 10cc or 80%; whichever occurs first
MISTIE: Surgical Task

We then explored whether ideal catheter/clot interaction would be more likely using predetermined skull entry points and trajectories.
ICH Classification

- Deep-seated occupying the anterior third of the basal ganglia with typical shape been “oval” (football shape) (Type A)
- Deep-seated occupying the posterior third of the basal ganglia; the shape can range from more roundish to elliptical (Type B)
- Superficial (lobar) with variable shape (Type C)
Surgical Assessment: Catheter Location Matters

Total score = A + A' + B
Good Placement (306)

Diagnostic
10/16/06 12:25

Post-surgery
10/17/06 17:58

Post-treatment
10/19/06 12:37
Poor Placement (302)

Stability
04/06/06 17:15

Post-surgery
04/06/06 17:15

Post-treatment
04/10/06 10:27
3D Assessment

- Good Placement
- Poor Placement
MISTIE: Surgical task
Conclusions

- Importance of surgical technique
  - Importance of ICH location
  - Importance of skull entry point
  - Importance of selected trajectory
  - Importance of catheter placement
  - Importance of catheter/blood interaction
MISTIE: Surgical task
Conclusions

- Importance of surgical technique
  - Importance of ICH location
  - Importance of skull entry point
  - Importance of selected trajectory
  - Importance of catheter placement
  - Importance of catheter/blood interaction

- Clot removal treatment success in the MISTIE trial is dependent upon surgical technique.
STANDARDIZATION OF SURGERY
At one time the surgeon was almost the only skilled mechanical worker with a craft knowledge analyzed, recorded and disseminated. Now the man with the shovel and the apprentice bricklayer have outstripped him in technic, for in their activities essential motions, tools, and economy of effort have been studied and standardized and taught, while we who think ourselves open-minded scientists look askance at propositions to apply to ourselves measurements of action and efficiency and fatigue, record of errors, instructions in type, motion-training, submission to discipline and new adjustments of function and cooperation. The high average of equipment, dexterity, information, conscientious care and self-sacrificing humanity in operating-rooms, great and small, here and abroad, are matters which some years of planned travel and laborious note-taking heartily attest; but evidence is not lacking that advance is very irregular where it might be all along the line, and erratic rather than on any studied
STANDARDIZATION OF SURGERY

- Precision, Accuracy, Safety are NOT Negotiable

- Standardization of 8 Essential Elements:
  - Plan the Approach (Point of entry)
  - Choose the Trajectory
  - Aspirate the Clot
  - Place the Catheter
  - Assess catheter placement (repeat if missed axis)
  - Stabilization = Wait 6 hours
  - Administer TPA
  - Remove the Catheter
STANDARDIZATION OF SURGERY

Increased Surgical Performance by Stages

Catheter Placement Score

Patient Timeline

Stage I

Stage II

Mean Stage I

Mean Stage II
MISTIE: Surgical Task

- Mean catheter placement score (±SD) improved from 80.2 (±28.6) in stage 1 to 98.5 (±35.2) in stage 2 (p=0.017)

- Surgical patients in stage 2 experienced a 62.8% clot reduction on average compared to 52.7% in stage 1 (p<0.05)
STANDARDIZATION OF SURGERY

How We did

- **Surgical review, mentoring and guidance (Surgical Committee)**
  - Prior to surgery, the surgical team was required to choose one of the three entry points and trajectories based on the location of the bleed. This choice was prospectively reviewed by the trial’s centralized surgical center.

- **Surgical training (Webinars)**
  - Surgeons were systematically retrained via a short webinar, emphasizing the importance of catheter placement.
What does this mean?

Is the greater reduction in clot size associated with better patient outcome?

Or

Does volume reduction matter?
Day 180 modified Rankin Scale (mRS)

% Subjects

% ICH Removed from Stability to EOT

> 70%

50-70%

< 50%

N = 26

N = 20

N = 31

Legend:
- 0
- 1
- 2
- 3
- 4
- 5
- 6
Poor outcome increases with residual blood clot size (EOT)

Day 180 modified Rankin Scale (mRS)

N = 19
N = 33
N = 30
N = 29

% Subjects

<10  10-20  20-35  >35

EOT Volumes - Surgical and Medical
MISTIE II – Surgical Implications

- MIS + rt-PA is safe procedure and is effective at removing clot
- Accuracy of MIS surgery is critical to clot size reduction
- Standardized surgical performance of MIS + rt-PA has optimized catheter engagement with the clot with better catheter placement scores and increased clot removal seen
- Better surgical performance is associated with better functional outcome
MISTIE III Leadership
Mario Zuccarello & Issam Awad-Surgical Center
Richard Thompson-Statistical Center
Daniel F. Hanley, MD-Coordinating Center & IND Sponsor
Overview

- Phase III: Efficacy and Safety
- Combination MIS and Clot Lysis w/rt-PA to remove ICH
- 500 Patients
  - 1:1 Adaptive randomization
  - 250 Surgical vs 250 Medical Management
- Funding: NIH/NINDS
IDEAS TO BE TESTED PROSPECTIVELY IN MISTIE III

MISTIE III

- 14% improvement in mRS 0-2
- 38 fewer days in hospital
- $44,000 savings per subject
- 14% fewer 365-day subjects in long-term care

Provide Clinically-Directive Data

- Greater patient satisfaction
  - Utility shifts of 0.3-0.5
  - QALY shift: 5 years added for the mRS 0-2 group
MISTIE III

- RTC
- Surgery < 72 hrs
- Time for stability
- ICH > 30 cc
- BG or lobar
- Stereotactastic Aspiration
- rt-PA 1 mg q8 hrs
- Surgical endpoint: ICH volume <15 ml
- Conventional Medical Treatment
STUDY OBJECTIVES

- Primary Objective (Efficacy)

- Demonstrate that minimally invasive surgery (MIS) plus recombinant tissue plasminogen activator (rt-PA) for three days improves functional outcome by a 12% increase in the modified Rankin Scale (mRS) score 0-3 compared to medically treated subjects at 180 days.
STUDY OBJECTIVES

- Primary Objective (Safety)
- Demonstrate that early use of MIS+rt-PA for three days is safe for the treatment of ICH relative to rates of mortality, rebleeding, and infection in the medically treated subject at 30 days.
STUDY OBJECTIVES

Secondary Objective

Demonstrate that the end of treatment volume and percent of ICH reduction from MIS+rt-PA is related to improved functional outcome, as compared to medically treated subjects.
Trial Overview

- Enrollment is ongoing
- Monthly educational webinars
- Quarterly Seminars
  - Surgical Center Report
  - Safety Forum
  - Training Refresher
- DSMB: Futility Analysis (n=375) Spring 2017
M3 as of 31-Mar

Approximately:

310 @ D365 (or ET)
390 @ D180 (or ET)
Surgical Performance for First 379 M3 Surgical Subjects

- Successfully reached goal of < 15 mL: 155/219* \( \rightarrow \) 70.8%
- 5 patients not included: 4 never went to surgery and 1 emergency craniotomy before MISTIE procedure
- **One patient not shown** - EOT = 110 mL

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*EOT Goal*
THANK YOU