Intraoperative Computer Guided Endoscopic Surgery for Brain Hemorrhage (ICES): A Multicenter Randomized Controlled Trial

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SUPPLEMENTAL MATERIAL

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Detailed Methods

Methods

This was a multicenter, randomized controlled trial which was approved by the UCLA Institutional Review Board (IRB) and the local IRBs at each participating institution. This study was part of the overall Minimally-Invasive Surgery plus rtPA for Intracerebral hemorrhage Evacuation (MISTIE) study[14] and done in close cooperation with the main coordinating center located at the Brain Injury Outcomes Division (BIOS) within the Department of Neurology of the Johns Hopkins Medical Institutions. The inclusion and exclusion criteria are shown in Supplemental Table I. After obtaining informed consent form signatures, eligible patients with a stable ICH volume of > 20 mL were randomized 3:1 to endoscopic surgery or standard medical management and were managed per the protocol and within local institutional guidelines. Subjects randomized to endoscopic surgery underwent the procedure within 48 hours of the time of the computed tomography (CT) scan diagnosing the hemorrhage. Both medical and surgical patients received similar standard of care as outlined in a structured guideline for treatment identical in both the MISTIE and ICES studies. Surgeons underwent detailed instructional training on the stereotactic-guided endoscopic procedure including direct mentoring of the detailed step-by-step surgical protocol by the surgical PI (NAM), video educational media demonstrating the procedure (www.ices.ucla.edu), and hands on training in a dry-lab setting. In addition, we employed a novel Surgical Center (SC)-guided approach to each enrolled subject: The surgical trajectory for each subject was discussed and confirmed with the SC PIs prior to each operation. A pilot initial run-in surgical subject was performed at each site and reviewed by the SC prior to approval for randomization at each site. A standardized imaging assessment was used in each subject to determine the presence/absence of a vascular malformation, stability of

the hemorrhage volume, and stereotactic volumetric assessment of the hemorrhage. Computerized tomographic (CT) imaging was performed on admission, 6 hours after the initial CT, preoperatively, postoperatively, and then daily up to 7 days. Neurologic assessments were performed using the modified Rankin Scale at 30, 90, 180, 270, and 365 days after hemorrhage onset.

Imaging, screening and stability protocol

Patients were identified in the emergency room at participating centers using structured inclusion/exclusion criteria and underwent a diagnostic brain CT scan on admission as part of standard of care. The effect of initial hematoma growth/instability was eliminated by use of a stability protocol involving normalized coagulation parameters, BP management, and a stability CT was done six hours later to ensure that the ICH clot was not expanding, as defined by no increase in clot size > 5 mL, using the ABC/2 method between two sequential scans. The stability scan assured 1) a stable clot volume before surgery and 2) the absence of active bleeding before performing surgery. The CT could be repeated every 6 hours until the clot was stabilized or the enrollment window (48 hr. after diagnostic CT) closed, whichever came first. A volumetric stereotactic CT was obtained just prior to surgery and used for intraoperative stereotactic guidance. At this time, the planned trajectory was shared with the trial's SC for joint review.. In addition, an MRI or CTA was required to rule out underlying pathology as the bleeding source; an angiogram was encouraged with equivocal findings on vascular pathology screening.[15] An INR of <1.4, normal aPTT, and blood pressure stability were required for the six hours immediately prior to randomization.[16,17] and immediately preoperatively.

Endoscopic Surgical Protocol

Operative procedure: The planning volumetric CT scan was performed, loaded, and registered into a frameless stereotactic image guidance system (Brain Lab® (Brainlab, Feldkirchen, Germany) or StealthStation®, (Medtronic, Minneapolis, MD). The ideal trajectory, which is parallel to the long axis of the hematoma, was selected using the image guidance probe positioned over the candidate entry point. The virtual extension of the probe tip was employed to interrogate the candidate entry points to assess whether or not the endoscope sheath would transgress any critical functional areas. One of three pre-approved approaches were selected: (A) anterior frontal lobe approach, (B) posterior parietal lobe approach, (C) surface cortical approach, each of which were designed to be parallel and in the middle of the long axis of the hematoma while avoid the internal capsule, sylvian fissure, eloquent white matter tracts and ventricles (Supplemental Figure I). The approach was pre-planned and agreed to by the SC PIs before surgery. Once the appropriate entry point was identified, this area was prepped and steriley draped A 1.5-2.0 cm burr hole was made. The dura was opened, the cortical surface coagulated and incised, and the endoscope sheath (Storz, El Segundo, CA) with obturator in place was connected to the Mitaka/Storz hydraulic fixation arm (Storz, El Segundo, CA) (See Supplemental Table II). The neuronavigational guidance "star" was then fixed to the endoscope/Mitaka complex and the endoscope was introduced into the cortex manually after releasing the hydraulic brake. The endoscope sheath was introduced parallel to the long axis of the hematoma. For the typical ovoid hemorrhage, the tip of the sheath is placed 2/3 of the way along the long axis of the hematoma (point # 1). The sheath was fixed in that location by engaging the Mitaka hydraulic brake. The obdurator was removed. Suction was fixed to the suction port of the endoscope sheath. Suction was then applied using manual thumb pressure to

close suction circuit, and blood was drained into a graduated Lukens trap for volumetric measurement. Suction was then applied 1-3 times until no further clot was evacuated at this location. The endoscope sheath was then irrigated to be sure that there was no evidence of active bleeding. If active bleeding was detected then irrigation was connected to the sheath and irrigation continued until the bleeding stopped. If the bleeding did not stop adequately, the endoscope was introduced into the sheath, fixed in place, and the bleeding point identified endoscopically. Once the bleeding point was identified, the Storz endoscopic bipolar (Storz, El Segundo, CA) was employed to coagulate the bleeding point. Once hemostasis was obtained the Mitaka arm was released and the endoscope sheath backed out to a point approximately one-third of the way into the hematoma cavity (point # 2). The suctioning and irrigation process was repeated at point # 2. Suctioning was continued until 75-80% of the hematoma volume was removed. The endoscope was introduced to be sure there was no sign of any ongoing streams of blood coming from any vessels which might require coagulation. However, no rotational steering of the sheath, nor lateral exploration of the hematoma cavity, were permitted. The cortical surface was inspected carefully to be sure that there was no ongoing bleeding coming from the corticectomy. The dura and skin were closed in a routine manner. An immediate post-operative CT scan was obtained.

Scoring Surgical Protocol Compliance: Each surgery was documented using a structured report form and a standard of care operative note. Adjudication of the surgery by the SC PIs included review of the structure report form, the operative note, and post- operative CT image review to determine if the planned trajectory was used. Compliance with the surgical protocol

was evaluated and scored using an ordinal scale. The variability of surgical techniques (such as suction pressure, duration of surgery, etc.) was judged based on this review.

Medical Treatment Protocol: All subjects were managed using the American Heart Association recommendations for the treatment of spontaneous ICH.[18] Patients randomized to receive standard medical care received CT scans and other monitoring assessments on the same schedule as those randomized to receive the ICES procedure. Mean hourly intracranial pressure (ICP) values, when monitored for clinical care, were compared between surgical and medical patients.

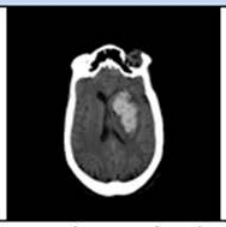
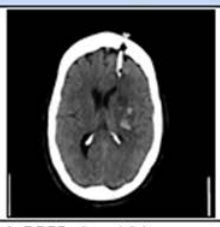
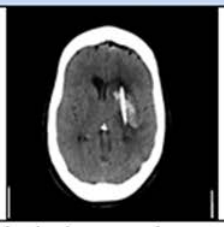
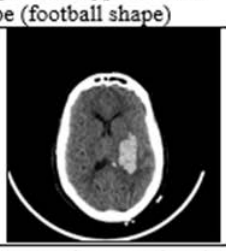
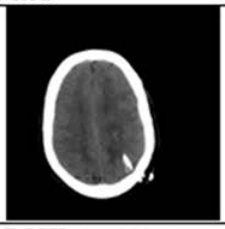
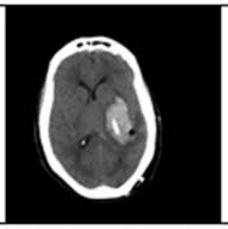
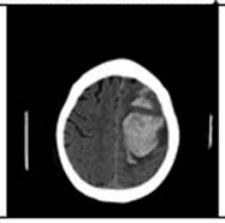
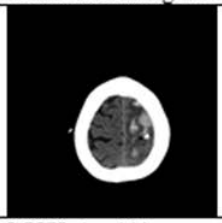
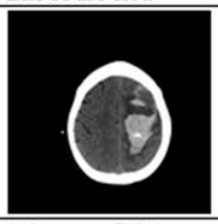
Follow-up: Subjects were followed with an MRI scan at Day 7. Subjects returned to clinic on Days 30, 180, and 365 and phone contact was made at Days 90 and 270. A certified examiner assessed mRS, Barthel Index (BI), Stroke Impact Scale (SIS), Glasgow Outcome Scale (GOS), extended GOS (eGOS), NIH Stroke Scale (NIHSS, clinic visit only) and repeat CT (days 30 and 180 only). Following a protocol amendment to extend the follow-up period after the trial started, all ICES subjects and 81% (n=29) of the 36 MISTIE subjects were followed through day 365, with the remainder of the MISTIE subjects completing the trial at day 180.. .

Image analysis: To optimize accuracy and minimize investigator bias, ICH and IVH volumes were analyzed by a core laboratory utilizing semi-automated segmentation at the threshold of 40 Hounsfield units.[19] This was performed using OsiriX software (v.4.1, Pixmeo; Geneva, Switzerland) on DICOM images of each subject's stability and treatment scans. This approach

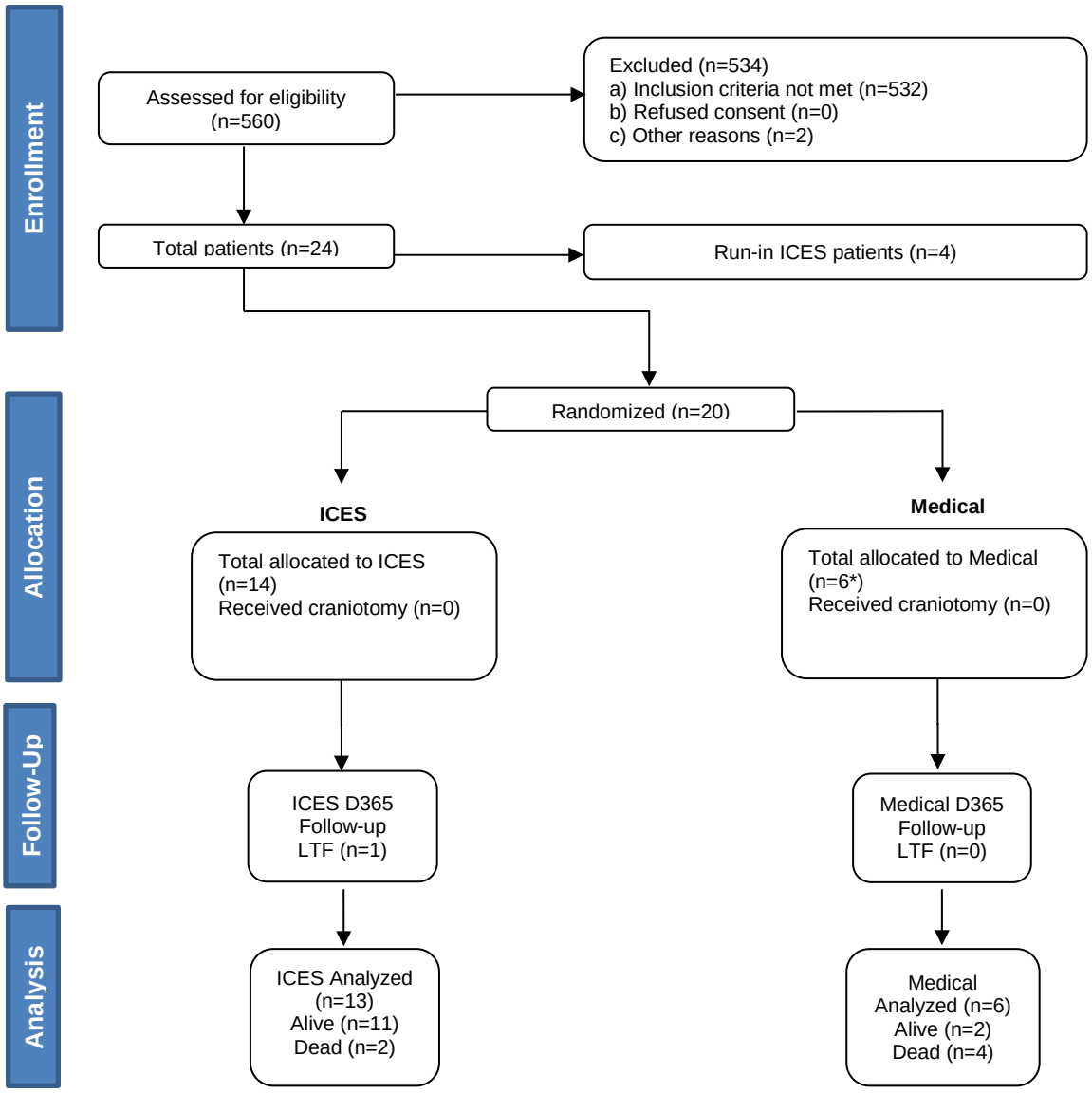
has been validated for accuracy and inter-rater reliability.[20] Core lab values were utilized in all analyses. Core lab defined location as either lobar or deep (putamen or thalamus).

1. Figures

1a. Supplemental Figure I. Trajectory planning worksheet.

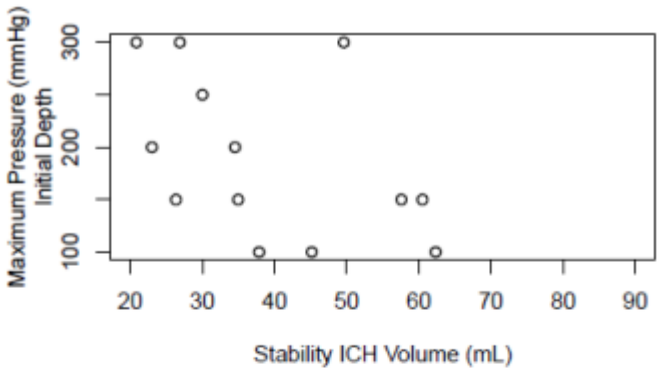
Designation	ICH Characteristics	Selected Entry Point	Chosen Trajectory
❑ Type A			
	Deep-seated occupying the anterior third of the basal ganglia with typical "oval" shape (football shape)	Type A ICH should have an entry point in the low anterior frontal area frequently close to the midline near the eyebrow, and the trajectory of the catheter has to be along the longitudinal axis of the clot.	
❑ Type B			
	Deep-seated occupying the posterior third of the basal ganglia; the shape can range from more roundish to elliptical	Type B ICH should have an entry point in the posterior parietal-occipital area frequently several cm lateral from the midline to avoid the occipital ventricular horn, and the trajectory of the catheter has to be along the longitudinal axis of the clot.	
❑ Type C			
	Superficial (lobar) with variable shape, but often more spherical	Type C ICH should have an entry point at the superficial area closest to the clot. This is usually the widest "equatorial point" of a spherical-shaped clot. The trajectory of the catheter has to be along the widest, or "equatorial", axis of the clot.	

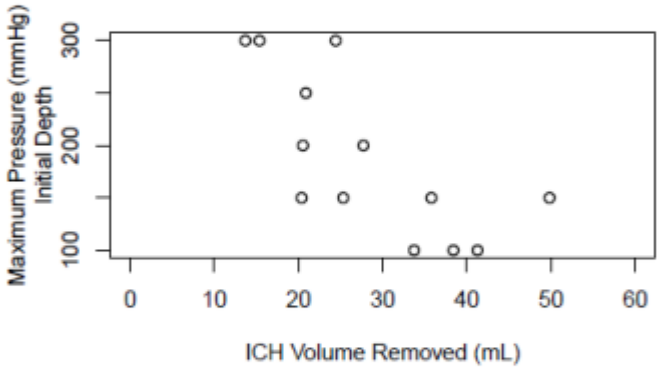
1b. Supplemental Figure II. CONSORT diagram of the ICES trial.

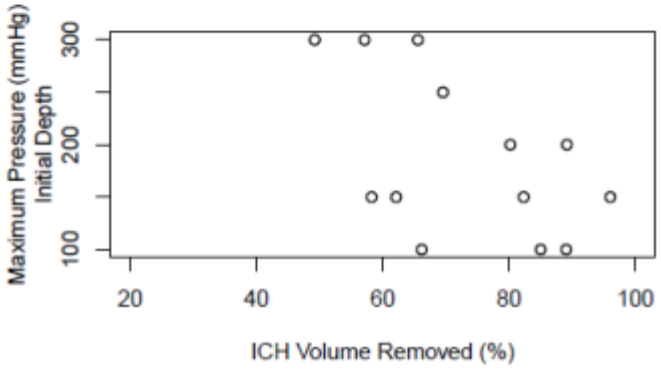


*An additional 36 medical subjects from the concurrent MISTIE II trial were included in the ITT efficacy analyses.

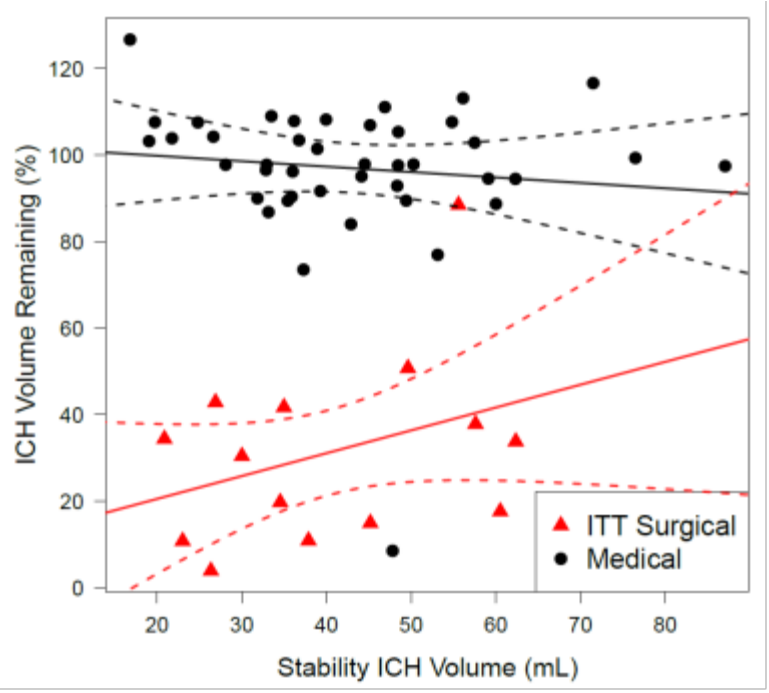
1c. Supplemental Figure III: Relationship of suction pressure to hematoma removal.



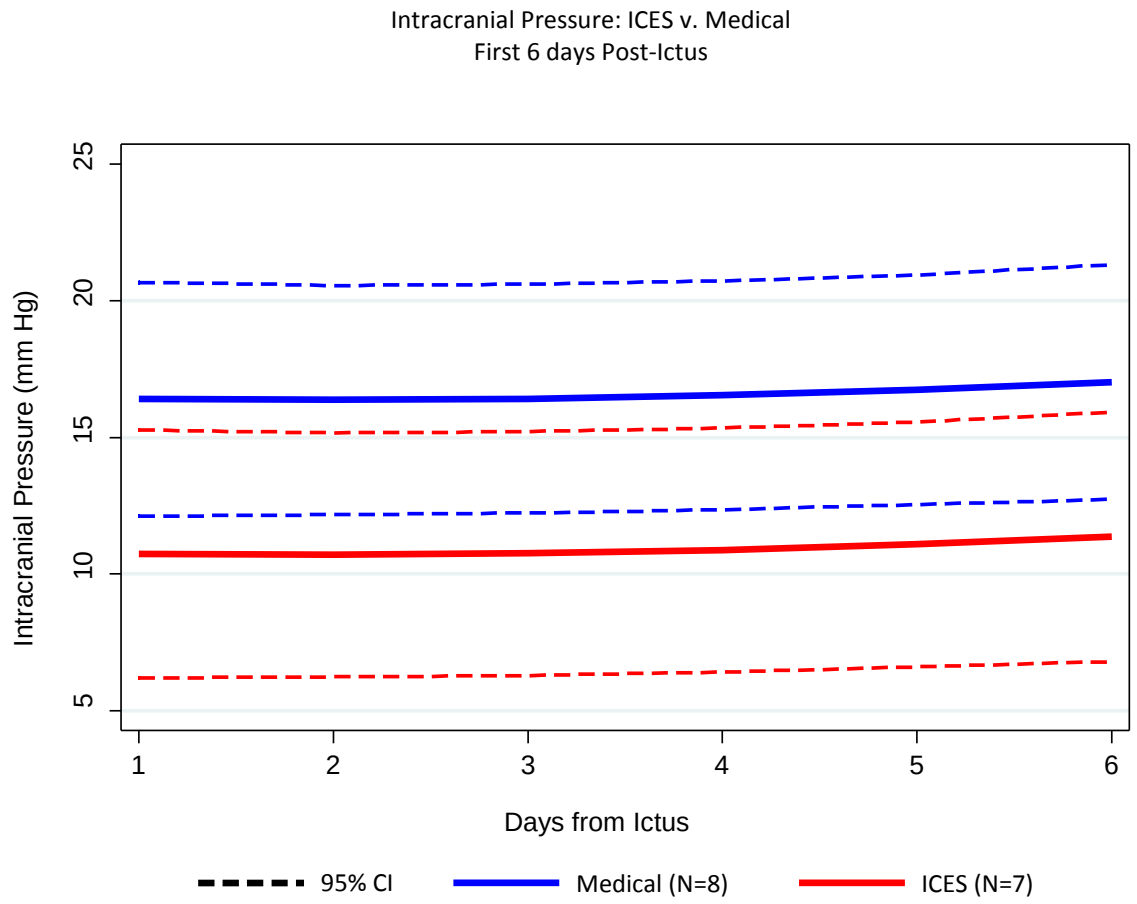




1d. Supplemental Figure IV. Distribution of clot volume as measured on the defined stability and EOT CT scans.



1e. Supplemental Figure V. Intracranial Pressure.



2. Tables

2a. Supplemental Table I. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
1. Age 18-80	1. Infratentorial hemorrhage (any involvement of the midbrain or lower brainstem as demonstrated by radiograph or complete third nerve palsy)
2. GCS ≤ 14 or NIHSS ≥ 6	2. Patients with platelet count < 100,000, INR > 1.3, or an elevated PT or APTT (reversal of Coumadin is permitted but the patient must not require Coumadin during the acute hospitalization). Irreversible coagulopathy either due to medical condition or prior to randomization (patient must have a sustained INR ≤ 1.3 using short- and long-active procoagulants [such as but not limited to NovoSeven, FFP, and/or vitamin K])
3. Spontaneous supratentorial ICH ≥ 20 mL	3. Clotting disorders
4. Symptoms < 12 hours prior to diagnostic CT scan (an unknown time of symptom onset is exclusionary)	4. Any concurrent serious illness that would interfere with the safety assessments including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic, and hematologic disease
5. Intention to initiate surgery within 48 hours after diagnostic CT	5. Patients with a mechanical valve
6. Six-hour clot size equal to the most previous clot size + 5 mL (as determined by additional CT scans at least 6 h apart (ABC/2 method)	6. Patients with unstable mass or evolving intracranial compartment syndrome
7. SBP < 200 mmHg sustained for 6 hours recorded closest to the time of randomization	7. Ruptured aneurysm, AVM, vascular anomaly, Moyamoya disease

8. Historical Rankin score of 0 or 1

9. Negative pregnancy test

8. Irreversibly impaired brainstem function (bilateral fixed, dilated pupils and extensor motor posturing), GCS ≤ 4
9. Intraventricular hemorrhage requiring external ventricular drainage
10. In the investigator's opinion, the patient is unstable and would benefit from a specific intervention rather than supportive care plus or minus endoscopic removal of ICH
11. Prior enrollment in the study
12. Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated
13. Participation in another simultaneous trial of ICH treatment

2b. Supplemental Table II. Surgical Equipment used.

Subject ID	Endoscope Sheath Used	Endoscope Holder Used	Endoscope Bipolar Used
225-502	Frazee	Mitaka/Storz	Storz
225-503	Frazee	Mitaka/Storz	Storz
225-506	Frazee	Mitaka/Storz	Storz
225-507	Frazee	Mitaka/Storz	Storz
225-510	Frazee	Mitaka/Storz	Codman Monopolar
232-513	Frazee	Mitaka/Storz	Storz
232-514	Frazee	Mitaka/Storz	Storz
225-515	Frazee	Mitaka/Storz	Storz
232-516	Gaab (model: 28162BS)	Mitaka/Storz	Storz
205-517	Frazee	Mitaka/Storz	Storz
205-519	Frazee	Mitaka/Storz	Storz
232-521	Frazee	Mitaka/Storz	Storz
225-523	Frazee	Mitaka/Storz	Storz
232-526	Frazee	Mitaka/Storz	Storz

2c. Supplemental Table III: Baseline clinical and demographic factors of patients at randomization by treatment group.

Characteristic	Medical (N=42)	ITT Surgical (N=14)
Age [IQR]	62 [49.5, 73]	59 [53.2, 68.2]
Male	28 (66.7%)	9 (64.3%)
Hypertension	34 (81%)	13 (92.9%)
Diabetes	11 (26.2%)	4 (28.6%)
Diabetes Missing	1 (2.4%)	0 (0%)
Hyperlipidemia	18 (42.9%)	5 (35.7%)
Hyperlipidemia Missing	6 (14.3%)	0 (0%)
NIHSS [IQR]	21 [17, 27]	18 [16, 23.8]
NIHSS Missing	1	0
GCS [IQR]	11 [7.2, 14]	10 [7, 11]
GCS Missing	0	1
Systolic BP (mmHg) [IQR]	140 [127, 156]	136 [132.2, 146.8]
Systolic BP (mmHg) Missing	1	0
Diastolic BP (mmHg) [IQR]	72 [61, 77]	69 [60.2, 73]
Diastolic BP (mmHg) Missing	1	0
INR [IQR]	1 [1, 1.1]	1 [1, 1.1]
INR Missing	4	1
Platelet Count [IQR]	223 [196.5, 253.5]	187.5 [173.5, 228.8]
Left hemisphere ICH no (%)	21 (50%)	8 (57%)
Deep ICH	27 (64.3%)	12 (85.7%)
Lobar ICH	15 (35.7%)	2 (14.3%)
Ictus to ER arrival (H) [IQR]	1.5 [0.9, 3.3]	0.8 [0.6, 1.5]
Ictus to Randomization (H) [IQR]	28.3 [22.5, 36.6]	24.6 [17.3, 29.7]
ICH volume: Stability [IQR]	41.4 [33.2, 50]	36.4 [27.7, 54.1]

2d. Supplemental Table IV. Details of the Intraoperative stereotactic CT-guided Endoscopic Surgery (ICES) procedure.

	Randomized Surgical (N=14)
ictus to op procedure (h) [IQR]	29.9 [24.7, 37.7]
procedure length (h) [IQR]	1.9 [1.4, 2.6]
irrigation duration (min) [IQR]	52.5 [30, 65]
active bleeding Visible	5 (35.7%)
bleed control by electrocautery	3 (21.4%)
bleeding control by ddavp	6 (42.9%)
bleeding control by irrigation	9 (64.3%)
ICH reduced by EOT (pct) [IQR]	71.2 [61, 84.7]
Luken's trap volume (mL) [IQR]	42 [31, 51]

2e. Supplemental Table V: Comparison of SAE between the surgical and medical arms.

	ITT Surgical (N=14)	Medical (N=42)
Cardiac disorders	**2**	**10**
Gastrointestinal disorders	1	2
General disorders and administration site conditions	1	7
Nervous system disorders	5	19
Other/Unclassified	1	1
Respiratory, thoracic and mediastinal disorders	1	10

2f. Supplemental Table VI. Functional outcomes among surgically and medically managed patients using the modified Rankin Score (mRS).

Functional Outcome	ITT Surgical	Medical	OR	95% CI	p-value
mRS 1-3: day 90	4 (28.6%)	3 (7.7%)	4.6	(0.67, 37.03)	0.07
Missing mRS: day 90	0 (0%)	3 (7.1%)			
mRS 1-3: day 180	6 (42.9%)	9 (23.7%)	2.4	(0.53, 10.51)	0.19
Missing mRS: day 180	0 (0%)	4 (9.5%)			
mRS 1-3: day 270	6 (46.2%)	5 (20.8%)	3.1	(0.59, 18.11)	0.14
Missing mRS: day 270	1 (7.1%)	18 (42.9%)			
mRS 1-3: day 365	6 (46.2%)	6 (23.1%)	2.8	(0.54, 14.77)	0.16
Missing mRS: day 365	1 (7.1%)	16 (38.1%)			

2g. Supplemental table VII: Comparison of surgeons/sites.

	Senior Author PI Surgeon (n=7)	Other Surgeons (n=7)
EOT Vol: mean (SD)	22.67 (18.79)	22.15 (16.53)
Percent ICH Reduction: mean (SD)	70% (29%)	65% (12%)
180 day mRS: mean (range)	5 (3-6)	4 (2-4)
# of Neuro AEs: no. (no./subject)	5 (0.71)	3 (0.43)
# of Non-Neuro AEs: no. (no./subject)	11 (1.57)	5 (0.71)