CASE SERIES

Long-term functional outcome following minimally invasive endoscopic intracerebral hemorrhage evacuation

Christopher P Kellner [ID] , Rui Song, Jonathan Pan, Dominic A Nistal [ID] ,
Jacopo Scaggiante, Alexander G Chartrain, Jamie Rumsey, Danny Hom,
Neha Dangayach, Rupendra Swarup, Stanley Tuhrim, Saadi Ghatan,
Joshua B Bederson, J Mocco

Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, New York City, New York, USA

Correspondence to
Dr Christopher P Kellner, Department of Neurosurgery , Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; christopher.kellner@mountsinai.org

ABSTRACT

Background and purpose Preclinical studies suggest that clot removal may mitigate primary and secondary brain injury following intracerebral hemorrhage (ICH). Although the MISTIE trial did not demonstrate an overall outcome benefit, it did demonstrate outcome benefit from effective reduction of clot burden. Minimally invasive endoscopic ICH evacuation may provide an alternative option for clot evacuation.

Methods Patients presenting to a single healthcare system from December 2015 to October 2018 with supratentorial spontaneous ICH were evaluated for minimally invasive endoscopic evacuation. Inclusion and exclusion criteria were prospectively established by a multidisciplinary group in the healthcare system. The prespecified primary analysis was the proportion of patients with modified Rankin Score (mRS) 0–3 at 6 months.

Results One hundred patients met the inclusion and exclusion criteria and underwent minimally invasive endoscopic ICH evacuation. The mean (SD) hematoma size was 49.7 (30.6) mL, the mean (SD) evacuation percentage was 88.2 (20.3)%, and 86% of patients had postoperative residual hematoma ≤15 mL. At 6 months the proportion of patients with an mRS of 0–3 was 46%.

Conclusions This study suggests that minimally invasive endoscopic ICH evacuation may produce favorable long-term functional outcomes. Further evaluation of this technique in a randomized clinical trial is necessary.

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) remains the most devastating and least treatable form of stroke. The 30-day mortality rate is approximately 40% and only 20% of survivors are functionally independent at 6 months.[1–3] Recent large-scale clinical trials have investigated a variety of medical and surgical strategies to improve outcome in patients with supratentorial spontaneous ICH, but nothing has yet proven effective. Surgical evacuation performed predominantly with conventional craniotomy was evaluated in the STICH (Surgical Trial in Intracerebral Hemorrhage) and STICH II trials, but did not show a benefit over medical therapy in either study.[4 5] Alternatively, a recent meta-analysis of randomized clinical trials evaluating minimally invasive surgery for ICH demonstrated an overall benefit to this approach.[6]

In 2016, phase 2 of the MISTIE (Minimally Invasive Surgery Plus Rt-PA for ICH Evacuation) trial demonstrated promising preliminary data for stereotactic aspiration and catheter drainage with tissue plasminogen activator.[7 8] In addition, an endoscopic evacuation arm of MISTIE II, called Intraoperative Stereotactic Computed Tomography-Guided Endoscopic Surgery (ICES), also demonstrated promising safety data.[9] Recently, phase 3 of the MISTIE trial demonstrated no functional benefit for the MISTIE procedure in selected patients, although a prespecified subgroup analysis showed improved 1-year outcome in patients with more complete evacuation (≤15 mL residual hematoma remaining after the procedure).[10] Evacuation methods have continued to evolve with the introduction of new technologies and techniques to perform this procedure.[11–15] Here we report our experience including 6-month functional outcomes with minimally invasive endoscopic ICH evacuation using the Stereotactic Intracerebral Hemorrhage Underwater Blood Aspiration (SCUBA) technique in a centralized care model.[6]

METHODS
Patient selection

The Institutional Review Board (IRB) at our institution approved this study. All patients with ICH presenting to a single health system from December 2015 to October 2018 were evaluated for minimally invasive endoscopic ICH evacuation and those eligible triaged to a single hospital that housed a dedicated ICH program. Inclusion and exclusion criteria for the procedure were agreed on prospectively by a multidisciplinary group of physicians and surgeons within the health system. Patients who were eligible presented with spontaneous supratentorial ICH ≥15 mL measured using the ABC/2 method employed in the MISTIE trial,[16] age ≥18 years, National Institute of Health Stroke Scale (NIHSS) score ≥6, and a CT angiogram (CTA) of the head demonstrating no vascular malformation. Patients were not excluded for the presence of spot sign on CTA, intraventricular hemorrhage (IVH), hematoma expansion, clinical or radiographic signs

BMJ

SNIS

Table 1 Cohort demographics and admission ICH severity measures

Variable	Mean (SD) or N
Age	62.2 (13.9)
Male	67
Race	
Hispanic	17
Asian	18
African American	35
Caucasian	30
Transferred from peripheral hospital	86
Medical history	
Prior ICH	11
CVA	15
Seizures	2
Hypertension	80
Diabetes mellitus	32
Medications	
Anticoagulant	11
Antiplatelet	28
Premorbid mRS	
0	79
1	8
2	8
3	5
Admission Glasgow Coma Score	
13–15	33
5–12	63
3–4	4
Admission NIHSS	17 (12.8–22)*
Admission ICH score	
0	5
1	28
2	40
3	22
4	5
IVH	43
Spot sign	16

*Median (IQR).
CVA, cerebrovascular accident; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

of herniation, lack of stability scan, or the presence of a reversible coagulopathy.

Endoscopic ICH evacuation technique

Minimally invasive endoscopic ICH evacuation was performed using the SCUBA technique.[6] Briefly, this technique includes stereotactic placement of a 19F (6.3 mm) vascular sheath into the hematoma, use of a three-port rigid endoscope, and an adjunctive aspiration device deployed through the working channel of the endoscope (Apollo or Artemis devices, Penumbra, California, USA). The Apollo device was used in 73 cases. In October 2017 the Artemis device became available and was used in 27 cases. A trajectory is planned along the long axis of the clot, taking care to avoid traversing eloquent brain regions. A 1.5–2 cm incision is made, a 1 cm craniectomy is drilled, and the dura is opened in a cruciate fashion. A brain biopsy is performed to aid in etiology diagnosis.[17] The vascular sheath is passed stereotactically into the clot 1–2 cm from the distal hematoma cavity wall. The introducer is removed and the endoscope is inserted with low flow irrigation. The adjunctive suction device is activated under high suction force and the hematoma is debulked from distal to proximal. After a significant portion of the hematoma has been debulked, the irrigation rate is increased. Residual clot is then targeted and retrieved. Bleeding vessels, if seen, are irrigated or cauterized. Meticulous hemostasis is achieved and maintained under direct visualization. Prior to surgical closure, an intraoperative cone-beam CT (Siemens, Munich, Germany) is performed to confirm that the surgical goal of leaving no more than 20% of the original hematoma is met.

Patient triage and perioperative management

Prior to performing the first procedure, an evidence-based ICH care plan standardizing pre-hospital, perioperative, and postoperative care was created by key stakeholders throughout the health system. A dedicated ICH hospital was established to which all patients presenting with spontaneous ICH and eligible for endoscopic evacuation were transferred. ICH-specific education was provided to ICU and floor nurses, physical therapists, rehabilitation physicians, midlevel providers, social workers, and neurosurgical residents on a weekly basis. A dedicated nurse practitioner managed all ICH patients. Key elements of the implemented care plan include an initial CTA to screen for vascular lesions associated with the hemorrhage, a CT on postoperative day 1, post-bleed day 4, and a follow-up MRI on day 7 if the patient remained in the hospital. Postoperative systolic blood pressure was maintained less than 140 mmHg for 24 hours to reduce the likelihood of hematoma expansion and postoperative rebleeding.[18 19] In addition, goals of early mobilization, aggressive ventilation weaning, early tracheostomy, daily speech and swallow assessment, and early PEG tube placement in patients in whom it is deemed necessary were discussed preoperatively when possible and always within 24 hours of admission.[20]

Outcome analysis

This study is a retrospective analysis of prospectively collected data. The prespecified primary outcome was mRS at 180 days (±1 month). Prespecified secondary outcomes included symptomatic and asymptomatic rebleeding within 72 hours and within 30 days, procedural time, 30-day mortality, neurosurgical intensive care unit (NSICU) length of stay (LOS), hospital LOS, percent hematoma reduction evaluated on the postoperative day 1 CT, and proportion of patients with postoperative hematoma volume of ≤15 mL. The hospital stay of three patients was extended far beyond others due to lack of citizenship and medical insurance (>4SD), and therefore these patients were excluded from the LOS analysis. Follow-up assessments were performed by the operating surgeon or an accredited nurse practitioner or physician's assistant guided by the mRS-9Q questionnaire.[21] For 11 patients unable to be reached for follow-up, the last known mRS was carried through for analysis as performed in the MISTIE phase III study.[10 22] Hematoma volumes were measured using the ABC/2 method.[23] Time to evacuation (TTE) was defined as time last known well or time of symptom recognition if last known well was unavailable to initiation of hematoma evacuation. The MISTIE criteria were retrospectively applied to the dataset and eight patients were found to be MISTIE-eligible by admission and preoperative clinical and radiographic

Table 2 Operative details

Variable	Mean (SD) or N
Time to evacuation (hours)	38.2 (28.7)
Positioning	
Supine	69
Supine, head turn	2
Lateral	5
Prone	24
†Number of passes (>1)	40
Side of hemorrhage	
Left	44
Right	56
Procedure time (hours)	2.5 (1.1)
Preoperative hematoma volume (mL)	49.7 (30.6)
Postoperative hematoma volume (mL)	6.2 (10.7)
≤15 mL residual	86
Evacuation percentage	88.2 (20.3)
Location	
Lobar	37
Deep	63
Distance to surface <1 cm	48
Distance to surface >1 cm	52

*Median (IQR).
†A pass is defined as repassing of the sheath through the brain under stereotactic guidance after it has been completely removed either by the same or by an additional trajectory.

Table 3 Clinical outcome measures

Variable	Mean (SD) or N
Tracheostomy	26
PEG tube placement	44
NSICU LOS (days)	8.5 (4.8–14)*
Hospital LOS (days)	17 (9–24)*
Discharge destination	
Home	4
Acute rehabilitation	58
Subacute rehabilitation	29
Hospice	4
Death or terminal extubation	3
Transfer back to transferring hospital	1
Remains inpatient for social reasons	1
Mortality at 30 days	9
Modified Rankin Score at 180 days	
0	1
1	9
2	19
3	17
4	25
5	13
6	16

*Median (IQR).
LOS, length of stay; NSICU, neurosurgical intensive care unit.

characteristics. SAS 9.3 (SAS Institute, Cary, North Carolina, USA) was used to perform statistical analyses and R 3.43 was used to create mRS distribution graphs.

RESULTS

Patient demographics

Between December 2015 and October 2018, 100 patients met the operative criteria and underwent minimally invasive endoscopic ICH evacuation. Patients had a mean (SD) age of 62.2 (13.9) years and 67% were male. Patients presented with a median NIHSS score of 17 (IQR 12.8–22.0) and Glasgow Coma Scale (GCS) score of 3–4 (4%), 5–12 (63%), 13–15 (33%). Eleven patients were on anticoagulation medication and 28 were taking antiplatelet medication. Intraventricular hemorrhage (IVH) was present in 43 patients. An external ventricular drain was required in 26 patients and IVH was evacuated in 23 (53.5% of patients with IVH). Complete demographic and admission details are shown in table 1.

ICH evacuation

Mean (SD) preoperative hematoma volume was 49.7 (30.6) mL. Thirty-seven cases were of lobar origin while 63 were of deep origin. Left-sided hemorrhage accounted for 44% of cases. Mean (SD) TTE was 38.2 (28.7) hours and mean (SD) procedure time was 2.5 (1.1) hours. Mean (SD) evacuation percentage was 88.2 (20.3)%, while the median evacuation percentage was 96.9% (IQR 85.5–99.6%). Mean (SD) postoperative hematoma volume was 6.2 (10.7) mL. Eighty-six percent of patients had a residual postoperative hematoma volume ≤15 mL while 14 patients had a residual hematoma volume of >15 mL. Complete intraoperative details are shown in table 2.

Complications

Postoperative rebleeding occurred in five cases. In four of these cases, rebleeding was asymptomatic and occurred within 72 hours. One of these patients underwent a repeat endoscopic ICH evacuation on postoperative day 1, given the radiographic appearance of the hemorrhage and lack of improvement on clinical examination despite no clinical deterioration. In one case, symptomatic rebleeding occurred on day 30 in the prior evacuation cavity in a patient with biopsy-proven amyloid angiopathy, but did not require an additional procedure. Complete details of complications are listed in online supplementary table 1.

Outcomes

Favorable long-term functional outcome, defined as mRS 0–3, was observed in 46 patients. The mortality rate at discharge, 30 days, and 180 days was 3%, 9% and 16%, respectively (table 3). Tracheostomy was performed in 26 patients and PEG tube in 44 patients. Median length of stay in the NSICU was 8.5 days (IQR 4.8–14) and median length of stay in the hospital was 17 days (IQR 9–24). A complete list of clinical outcome measures is presented in table 3.

Patients with >15 mL residual hematoma postoperatively had a rate of functional independence (mRS ≤3) of 28% while patients with a postoperative residual hematoma volume of ≤15 mL had a mRS ≤3 rate of 49% (figure 1).

Among the patients included in this study, we retrospectively identified patients who fit strict inclusion and exclusion criteria for the MISTIE III trial. Many patients satisfied multiple exclusion criteria. Sixteen patients would have been excluded for the presence of spot sign, 11 patients did not undergo repeat imaging demonstrating stable hematoma size, 36 patients did not have systolic blood pressure <180 mmHg for 6 hours prior to
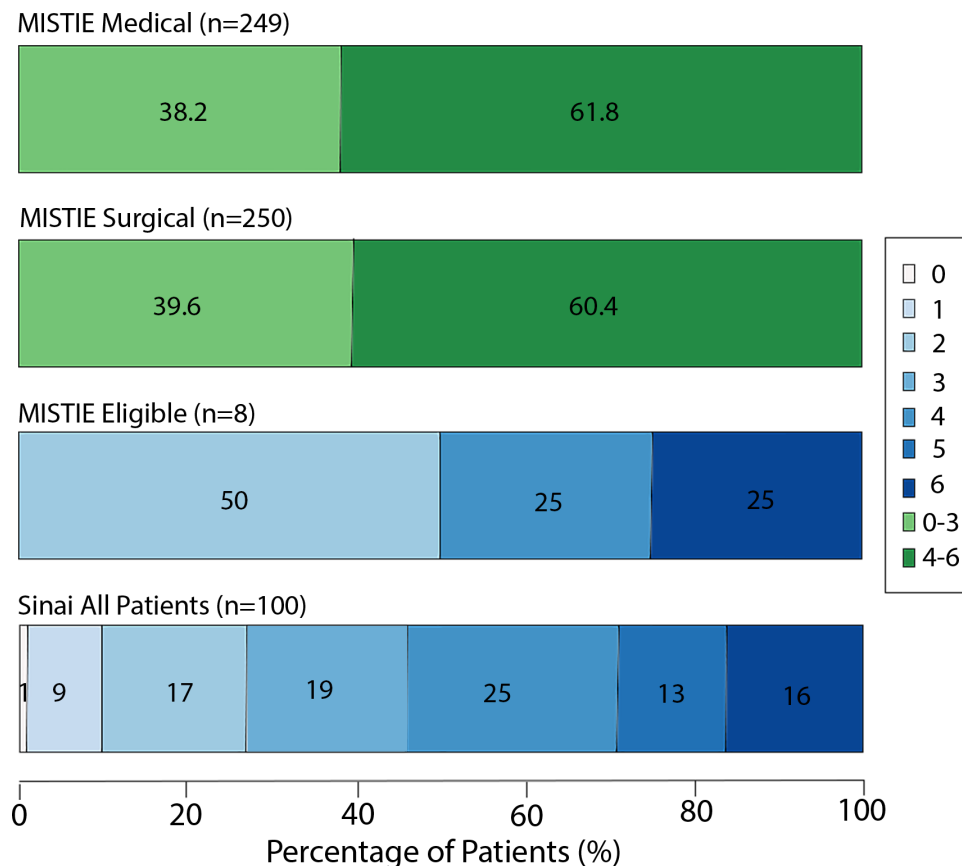
Figure 1 Distribution of long-term functional outcome. The relative proportions of patients in each modified Rankin Scale (mRS) group are shown at 180 days for the present study, the MISTIE-eligible group in the present study, and the published MISTIE III surgical and medical cohorts (detailed 180-day mRS breakdown not available).

the procedure, 12 patients had a premorbid mRS of 2 or 3, and 36 patients had a hematoma size between 15 and 30 mL. When the MISTIE-eligible subpopulation was analyzed, we found the functional independence rate at 6 months for this MISTIE-eligible group to be 50%. Given the methodological differences between the MISTIE trial and this study, statistical analysis between this group and others was not performed.

DISCUSSION
Minimally invasive endoscopic ICH evacuation
This is the first study to present long-term functional outcome data after minimally invasive endoscopic ICH evacuation performed with an adjunctive aspiration device. Among the 100 patients who underwent the procedure, 46 were found to have an mRS of 0–3 at 6 months. This procedure was found to be safe, resulting in only four rebleeding events within 72 hours, all of which were asymptomatic. Only one patient suffered a symptomatic rebleed which occurred 30 days after the initial operation and did not require surgical intervention. This procedure was found to be effective with an average evacuation percentage of 88.2% and mean postoperative hematoma volume of 6.2 mL. Eighty-six percent of patients had near-complete evacuation with ≤15 mL hemorrhage remaining postoperatively.

Minimally invasive endoscopic ICH evacuation has been previously described in numerous case series and five randomized clinical trials. In a meta-analysis of those five trials, endoscopic evacuation proved superior to medical management with an OR 0.40 (95% CI 0.25 to 0.66) predicting a poor outcome at the study endpoint. The specific surgical technique varied among

these trials, as did patient selection criteria. Throughout this clinical series the authors attempted to standardize the endoscopic surgical technique employed, which was previously published as the SCUBA technique.[6] The SCUBA technique was developed to maximize the safety and efficacy of this form of minimally invasive ICH evacuation. Key tenets of the SCUBA technique include use of an adjunctive aspiration device such as the Apollo or Artemis device to permit controlled aspiration, endoscopy performed in a wet field, and meticulous intracavitary hemostasis at the conclusion of the procedure.

Fiorella et al first demonstrated the feasibility of ICH evacuation with the Apollo system in a case series of three patients.[24] Spiotta and colleagues built on this with a larger case series of 29 patients across multiple centers.[15] In their series, however, the endoscope was used in fewer than two-thirds of cases. The evacuation percentage presented here is higher than that reported by Spiotta et al (88.2% vs 54.1%). The in-hospital mortality rate was 11.1% in the Spiotta series, which is similar to our 3% and to previously reported rates.[25] Turner and colleagues subsequently published a series of three patients with ICH of aneurysmal etiology in which the Apollo system was used for ICH evacuation after endovascular aneurysm coiling, demonstrating its applicability in a range of clinical scenarios.[26] More recently, Goyal et al reported an analysis of 19 patients who underwent endoscopic ICH evacuation with the Apollo device compared with matched contemporaneous controls and demonstrated a mortality benefit for endoscopic ICH evacuation using the Apollo device.[27] Our results build on these previous studies of endoscopic ICH evacuation by reporting long-term functional

outcome, safety data, and hospital metrics in a series in which the endoscopic technique with an adjunctive aspiration device was universally applied.

Endoscopic minimally invasive ICH evacuation in light of MISTIE III

Direct comparison between this study and other studies is not advisable, given the variation in patient selection and study protocol. However, there is value to publishing non-randomized data to communicate surgical technique and clinical care strategies between the publication events of major clinical trials.

Recently, the MISTIE III trial demonstrated no functional benefit for stereotactic thrombolysis in the intention to treat analysis comparing the proportion of patients achieving mRS ≤3 in each group at 1 year.[10] The study, did, however provide valuable information in its secondary endpoints and subgroup analyses to guide surgical goals and future clinical trial design.[28 29] Primarily, all-cause mortality at 1 year was decreased in the MISTIE group. Importantly, in the prespecified as-treated analysis including surgical patients in whom the surgical goal of ≤15 mL remaining hematoma at the end of treatment was reached, a 10.5% increase in risk difference was observed (95% CI 1.0% to 20.0%; p=0.03) in the rate of mRS ≤3 at 1 year in comparison to the medical group. Comparing patients with ≤15 mL to those with >15 mL remaining at the end of treatment in a multivariate model controlling for ICH severity factors, the authors identified an OR of 2.022 (95% CI 1.052 to 3.890, p=0.035) predicting mRS ≤3 at 1 year when ≤15 mL was achieved.[30] The investigators also demonstrated that reduction of hematoma volume beyond 15 mL remaining decreased the chance of a poor outcome with OR 0.90 (95% CI 0.85 to 0.96, p=0.002). In our dataset, the surgical goal of an end of treatment residual hematoma volume of ≤15 mL was not reached in 14 patients. These numbers are too small to perform meaningful comparisons between the two groups of successful and unsuccessful procedures. Future studies in the form of a registry or randomized controlled trial are needed to identify factors leading to procedural success in endoscopic ICH evacuation. Anecdotally, we observed that increased intracavitary bleeding during the procedure and increased clot fibrosity appeared to decrease the chance of surgical success.

A major disadvantage of stereotactic thrombolysis is the inability to mitigate hematoma expansion. Conversely, a hemorrhage must be demonstrated to be stable for a patient to be eligible for the MISTIE technique. A consistently high evacuation percentage is possible using the SCUBA technique on a broad selection of patients presenting with ICH who would have been too high risk for the MISTIE procedure. In this series, 28 patients were eligible for the SCUBA procedure who would have been excluded from undergoing the MISTIE procedure due to the presence of spot sign or hematoma expansion. The SCUBA procedure also permits early evacuation, which may prove important if time to evacuation is demonstrated to improve outcome in minimally invasive evacuation. A benefit to early evacuation in ICH surgery has been demonstrated in numerous preclinical models as well as in a patient level meta-analysis of data from surgical ICH trials showing that evacuation within 8 hours decreased the chance of a poor functional outcome with an OR of 0.59 (95% CI 0.42 to 0.84, p=0.003).

Centralized ICH care model

The initial experience described in the present study is that of a newly-established multidisciplinary program dedicated to the treatment of ICH with a predefined care pathway. All patients with supratentorial ICH in our health system, which currently provides inpatient neurosurgery services at seven hospitals, are triaged and treated at one center, while lesional forms of ICH (eg, arteriovenous malformations, dural arteriovenous fistulas, most aneurysms) are triaged elsewhere. As with cases of severe ischemic stroke, the goal of the centralized ICH care model is to funnel patients to centers with dedicated experience and resources to optimally manage ICH patients in all capacities, including medically and surgically, both minimally invasive and open, if needed.[31] Phase 3 of the MISTIE trial demonstrated the importance of surgical experience on achieving surgical goals in the MISTIE procedure, which was shown to impact functional outcome.[30]

The ICH program is supervised by a neurointensivist team at all times and has 24/7 neurosurgical coverage, both of which have been shown to improve outcomes in ICH.[32 33] In addition to the medical and surgical services, the nursing and ancillary care of this patient population appears to improve with time as the care pathways and specific needs of ICH patients are learnt by all members of the provider team. The end goal of the centralized ICH care model is to emulate the success of other centralized care models, including those for acute ischemic stroke, severe trauma, and myocardial infarction.[34–38]

Medical complications in ICH

Medical complications are unfortunately common in patients presenting with ICH, given the high rate of neurologic debilitation resulting in immobility, prolonged intubation, and the need for additional procedures such as tracheostomy, percutaneous gastrostomy, and ventriculoperitoneal shunt placement as well as others. Medical complications were common in our cohort including pneumonia (24%), acute kidney injury (9%), ventriculitis (5%), asymptomatic rebleeding (4%), ischemic stroke (3%), seizure (2%), and surgical site infection (1%) as well as others. While the rate of non-neurologic infection in the medical arm of MISTIE III was 10.4%, this number is lower than other studies have reported. In a multicenter study of patients with a diagnosis of ICH, Lord *et al* found that infections occurred in 31% of patients.[39] Risk factors for developing infection in this study were intubation, dysphagia, pulmonary edema, and deep venous thrombosis. The goal of the centralized ICH care model is to amplify both procedural experience with minimally ICH evacuation and intensive care experience with this patient population. Protocolization of the most effective evidence-based methods of prevention of each form of complication is recommended. Further studies are necessary to evaluate the efficacy of the centralized ICH care model presented in this paper.

Study limitations

The present study has several limitations. This is a single-center retrospective analysis performed using a single technique in the hands of a small group of specialized surgeons. The study lacks a non-operative arm control group with which to compare the outcomes of surgical evacuation. Outcome assessment was not blinded and was not adjudicated, although in many cases it was performed by a trained mid-level provider using a standard questionnaire. The outcomes produced throughout this initial experience are inevitably influenced by a training effect for both the surgeons performing the procedure as well as all members of the hospital team involved in the care of these complex patients. For these reasons, the authors caution the broad application of these results and encourage further development of the treatment strategies described in this study with the goal of formal evaluation in a randomized clinical trial.

CONCLUSION

This study suggests that minimally invasive endoscopic ICH evacuation with an adjunctive aspiration device can be performed safely, effectively, and consistently in a broad range of patients presenting with ICH.

ORCID iDs
Christopher P Kellner http://orcid.org/0000-0003-4604-8205
Dominic A Nistal http://orcid.org/0000-0001-9713-5873

REFERENCES

1 Dennis MS. Outcome after brain haemorrhage. *Cerebrovasc Dis* 2003;16 Suppl 1:9–13.
2 van Asch CJ, Luitse MJ, Rinkel GJ, *et al*. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol* 2010;9:167–76.
3 Flaherty ML, Haverbusch M, Sekar P, *et al*. Long-term mortality after intracerebral hemorrhage. *Neurology* 2006;66:1182–6.
4 Mendelow A, Gregson B, Fernandes H, *et al*. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *The Lancet* 2005;365:387–97.
5 Mendelow AD, Gregson BA, Rowan EN, *et al*. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *The Lancet* 2013;382:397–408.
6 Kellner CP, Chartrain AG, Nistal DA, *et al*. The Stereotactic Intracerebral Hemorrhage Underwater Blood Aspiration (SCUBA) technique for minimally invasive endoscopic intracerebral hemorrhage evacuation. *J Neurointerv Surg* 2017;2018.
7 Hanley DF, Thompson RE, Muschelli J, *et al*. Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial. *Lancet Neurol* 2016;15:1228–37.
8 Mould WA, Carhuapoma JR, Muschelli J, *et al*. Minimally invasive surgery plus recombinant tissue-type plasminogen activator for intracerebral hemorrhage evacuation decreases perihematomal edema. *Stroke* 2013;44:627–34.
9 Vespa P, Hanley D, Betz J, *et al*. ICES (Intraoperative Stereotactic Computed Tomography-Guided Endoscopic Surgery) for brain hemorrhage: a multicenter randomized controlled trial. *Stroke* 2016;47:2749–55.
10 Hanley DF, Thompson RE, Rosenblum M, *et al*. 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. *The Lancet* 2019;393:1021–32.
11 Ding D, Przybylowski CJ, Starke RM, *et al*. A minimally invasive anterior skull base approach for evacuation of a basal ganglia hemorrhage. *J Clin Neurosci* 2015;22:1816–9.
12 Fiorella D, Arthur A, Schafer S. Minimally invasive cone beam CT-guided evacuation of parenchymal and ventricular hemorrhage using the Apollo system: proof of concept in a cadaver model. *J Neurointerv Surg* 2015;7:569–73.
13 Przybylowski CJ, Ding D, Starke RM, *et al*. Endoport-assisted surgery for the management of spontaneous intracerebral hemorrhage. *J Clin Neurosci* 2015;22:1727–32.
14 Ritsma B, Kassam A, Dowlatshahi D, *et al*. Minimally invasive subcortical parafascicular Transsulcal access for clot evacuation (MI space) for intracerebral hemorrhage. *Case Rep Neurol Med* 2014;2014:1–4.
15 Spiotta AM, Fiorella D, Vargas J, *et al*. Initial multicenter technical experience with the Apollo device for minimally invasive intracerebral hematoma evacuation. *Neurosurgery* 2015;11 Suppl 2:243–51.
16 Kwak R, Kadoya S, Suzuki T. Factors affecting the prognosis in thalamic hemorrhage. *Stroke* 1983;14:493–500.
17 Anderson CS, Huang Y, Wang JG, *et al*. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol* 2008;7:391–9.
18 Anderson CS, Heeley E, Huang Y, *et al*. Rapid blood-pressure lowering in patients with acute intracerebral haemorrhage. *N Engl J Med* 2013;368:2355–65.
19 Titsworth WL, Hester J, Correia T, *et al*. The effect of increased mobility on morbidity in the neurointensive care unit. *J Neurosurg* 2012;116:1379–88.
20 Lieber AC, McNeill IT, Scaggiante J, *et al*. Biopsy during minimally invasive intracerebral hemorrhage clot evacuation. *World Neurosurg* 2019;124:e169–75.
21 Patel N, Rao VA, Heilman-Espinoza ER, *et al*. Simple and reliable determination of the modified Rankin scale score in neurosurgical and neurological patients: the mRS-9Q. *Neurosurgery* 2012;71:971–5.
22 van der Laan MJ, Gruber S. Targeted minimum loss based estimation of causal effects of multiple time point interventions. *Int J Biostat* 2012;8.
23 Kothari RU, Brott T, Broderick JP, *et al*. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* 1996;27:1304–5.
24 Fiorella D, Gutman F, Woo H, *et al*. Minimally invasive evacuation of parenchymal and ventricular hemorrhage using the Apollo system with simultaneous neuronavigation, neuroendoscopy and active monitoring with cone beam CT. *J Neurointerv Surg* 2015;7:752–7.
25 Beynon C, Schiebel P, Bösel J, *et al*. Minimally invasive endoscopic surgery for treatment of spontaneous intracerebral haematomas. *Neurosurg Rev* 2015;38:421–8.
26 Turner RD, Vargas J, Turk AS, *et al*. Novel device and technique for minimally invasive intracerebral hematoma evacuation in the same setting of a ruptured intracranial aneurysm: combined treatment in the neurointerventional angiography suite. *Neurosurgery* 2015;11 Suppl 2:43–50.
27 Goyal N, Tsivgoulis G, Malhotra K, *et al*. Minimally invasive endoscopic hematoma evacuation vs best medical management for spontaneous basal-ganglia intracerebral hemorrhage. *J Neurointerv Surg* 2019;11:579–83.
28 Kellner CP, Arthur AS, Bain M, *et al*. MISTIE III: a big step in the right direction. *J Neurointerv Surg* 2019;11:326–7.
29 Cordonnier C, Tymianski M. MISTIE III. *Stroke* 2019;50:1634–5.
30 Awad IA, Polster SP, Carrión-Penagos J, *et al*. Surgical performance determines functional outcome benefit in the minimally invasive surgery plus recombinant tissue plasminogen activator for intracerebral hemorrhage evacuation (MISTIE) procedure. *Neurosurgery* 2019;84:1157–68.
31 Chartrain AG, Mocco J. Centralization of intracerebral hemorrhage care. *World Neurosurg* 2017;97:716–7.
32 Diringer MN, Edwards DF. Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. *Crit Care Med* 2001;29:635–40.
33 Varelas PN, Eastwood D, Yun HJ, *et al*. Impact of a neurointensivist on outcomes in patients with head trauma treated in a neurosciences intensive care unit. *J Neurosurg* 2006;104:713–9.
34 Badjatia N, Carney N, Crocco TJ, *et al*. Guidelines for prehospital management of traumatic brain injury 2nd edition. *Prehosp Emerg Care* 2008;12 Suppl 1:S1–52.
35 Cameron PA, Gabbe BJ, Smith K, *et al*. Triaging the right patient to the right place in the shortest time. *Br J Anaesth* 2014;113:226–33.
36 Demetriades D, Martin M, Salim A, *et al*. The effect of trauma center designation and trauma volume on outcome in specific severe injuries. *Trans Meet Am Surg Assoc Am Surg Assoc* 2005;123:206–13.
37 Jauch EC, Saver JL, Adams HP, *et al*. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:870–947.
38 Sugerman DE, Xu L, Pearson WS, *et al*. Patients with severe traumatic brain injury transferred to a level I or II trauma center: United States, 2007 to 2009. *J Trauma Acute Care Surg* 2012;73:1491–9.
39 Lord AS, Langefeld CD, Sekar P, *et al*. Infection after intracerebral hemorrhage: risk factors and association with outcomes in the ethnic/racial variations of intracerebral hemorrhage study. *Stroke* 2014;45:3535–42.