Minimally invasive treatment for intracerebral hemorrhage

EMUN ABDU, M.D.,¹ DANIEL F. HANLEY, M.D.,² AND DAVID W. NEWELL, M.D.¹

¹Department of Neurosurgery, Swedish Neuroscience Institute, Seattle, Washington; and ²Brain Injury Outcomes Center, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Spontaneous intracerebral hemorrhage is a serious public health problem and is fatal in 30%–50% of all occurrences. The role of open surgical management of supratentorial intracerebral hemorrhage is still unresolved. A recent consensus conference sponsored by the National Institutes of Health suggests that minimally invasive techniques to evacuate clots appear to be a promising area and warrant further investigation. In this paper the authors review past, current, and potential future methods of treating intraparenchymal hemorrhages with minimally invasive techniques and review new data regarding the role of stereotactically placed catheters and thrombolytics. (http://thejns.org/doi/abs/10.3171/2012.1.FOCUS11362)

KEY WORDS • intracerebral hemorrhage • sonothrombolysis tissue plasminogen activator • intraventricular hemorrhage

S PONTANEOUS ICH is a serious public health problem accounting for 10%–15% of strokes.³⁴ In the United States, 60,000–120,000 patients suffer from hemorrhagic strokes each year, and the incidence has been increasing due to an aging population in addition to an increased use of anticoagulation and antiplatelet agents for thromboembolic diseases. On average, only 20%–40% of those who suffer an ICH are expected to have functional outcomes at 6 months.⁹ Moreover, the cost of care for patients with ICH is among the highest of all brain disorders.³⁹ Half of the patients with ICH will die in the hospital after requiring expensive ICU care, and an additional 30% will survive as dependents requiring long-term care and rehabilitation.

Common causes of spontaneous ICH include hypertension, anticoagulation, and amyloid angiopathy. The presenting neurological signs and symptoms are depen-

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dent on the size, location, and degree of mass effect of the clot. In an autopsy study of hypertensive hemorrhages, the common locations were external capsule in 42%, pons in 16%, thalamus in 15%, cerebellum in 12%, and white matter in 10%.¹² The 1-year mortality rates for ICH vary depending on location: 65% for brainstem, 57% for lobar, 51% for deep, and 42% for cerebellar.¹¹ Frequently, ICH is complicated by IVH, which can lead to obstructive hydrocephalus, thereby independently increasing the mortality rate to as high as 80%.^{14,30,41}

Unlike cerebellar hemorrhages in which there are more defined medical and surgical management pathways, surgical treatment of supratentorial ICH, specifically deep subcortical and basal ganglia hemorrhages, is controversial. The principal aims of treatment are preventing further hemorrhage, reducing ICP, controlling cerebral perfusion pressure, and reducing mass effect when possible.

Deep lesions (that is, those in the basal ganglia or brainstem) have a dismal prognosis, and open surgical evacuation does not appear to improve the patient's outcome compared with medical management. Historically, there has been no role for open surgery in such cases.³² Surgery is believed to save lives by decreasing ICP in select patients, but it does not necessarily result in restoration of meaningful functional status. In cases in which supratentorial ICH is surgically treated, removal of the ICH reduces mass effect, and it also removes the neurotoxic blood products, helping to prevent edema and secondary brain injury.³⁴

Abbreviations used in this paper: CLEAR = Clot lysis: Evaluating accelerated resolution of intraventricular hemorrhage; EVD = external ventricular drainage; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; ICP = intracranial pressure; IVH = intraventricular hemorrhage; MIS = minimally invasive surgery; MISTIE = Minimally Invasive Surgery plus T-PA for Intracerebral Hemorrhage Evacuation; mRS = modified Rankin Scale; NIH = National Institutes of Health; NIHSS = NIH Stroke Scale; rt-PA = recombinant tissue plasminogen activator; SLEUTH = Safety of Lysis with EKOS Ultrasound in the Treatment of Intracerebral and Intraventricular Hemorrhage.

Open surgery is relatively contraindicated due to the frequent medical comorbidities that these patients have. Moreover, surgeons are often reluctant to make an extensive corticotomy through uninjured brain to evacuate deep ICHs. An ideal technique for ICH evacuation would be one that minimizes brain manipulation and one that could also be performed under minimal anesthesia, preferably at the bedside. This approach may offset the added morbidity of surgery, especially for deep lesions and those that are too unstable to undergo any major operative intervention.

Current NIH Consensus

In 2007, a consensus conference was sponsored by the NIH to try to establish priorities for further investigation into the most promising therapies for the management of spontaneous ICH. A number of different medical and surgical therapies were examined. The mainstay of medical management for intracranial hemorrhage includes reversal of anticoagulation (international normalized ratio < 1.4), treatment of hypertension, treatment of increased ICP with osmotic diuretics or hypertonic saline. and placement of an EVD catheter for IVH.⁶ The primary goal of lowering blood pressure is to prevent continued hemorrhage and rehemorrhage without drastically lowering cerebral perfusion pressure in those patients who have high ICP. There is incomplete evidence to support specific blood pressure parameters; therefore, until such randomized studies exist to suggest a specific goal, the American Stroke Association guidelines recommend maintaining blood pressure lower than 180 mm Hg in the acute period with short-acting antihypertensive agents while concurrently paying attention to cerebral perfusion pressure in patients in whom clear signs of increased ICP are shown both clinically and on images.^{30,33} Furthermore, for those without clear clinical signs of increased ICP, aggressive lowering of blood pressure is recommended.

Treatment with procoagulants, such as factor VIIa, were thought to be theoretically beneficial by promoting hemostasis at sites of vascular injury and by limiting further enlargement of hemorrhage.²⁰ The FAST (Factor VIIa for Acute Hemorrhagic Stroke) study was a Phase III prospective randomized trial to determine the efficacy of factor VIIa in patients with ICH who presented within 3 hours of symptoms onset. Although this was a promising theory, this large multicenter study did not confirm better functional outcomes despite producing significant reduction in the rate of hematoma expansion.¹⁹ Therefore, the use of factor VIIa is currently not recommended in the treatment of patients with ICH.

Surgical Therapy

Evaluation of outcomes in most large studies of open surgery can be difficult because of the lack of subcategorization of patients depending on location, size, degree of brain destruction, and comorbidity, as well as other factors. Evacuation of ICH via craniotomy is the most commonly used surgical treatment for ICH. However, its benefits are marginal at best, and its uses remain controversial.^{32,36} A meta-analysis of multiple prior surgical trials has not shown benefit for ICH evacuation over nonsurgical treatment. The largest among these, the STICH trial, was a prospective study of 1033 patients from 107 centers over an 8-year period in which patients were randomized to surgery or best medical management.²¹ Its results indicated that surgical evacuation did not appear to be helpful in treating supratentorial ICH.²¹ However, in a subset of patients presenting with superficial hematomas without IVHs, 49% of patients achieved favorable outcomes compared with 37% of those treated conservatively.²² Since the initial trial was not sufficiently powered to examine this subgroup, the STICH II study is now ongoing to further determine whether open surgical evacuation is beneficial in cases of superficially located ICH.

Despite the fact that surgical studies to date have shown that craniotomy is not the mainstay of treating unselected cases, the current nonsurgical management is insufficient, especially in cases with mass effect and secondary deterioration. There is growing evidence that there is value in evacuating the clot and decreasing mass effect, subsequently reducing a further cascade of injury due to the presence of hemorrhage (edema, apoptosis, necrosis, and inflammation).^{34,35} Hence, one of the outcomes from the 2007 NIH consensus statement was that minimally invasive techniques to evacuate clots seemed to be a promising area for further investigation based on favorable results in various studies and case series.⁶ Minimally invasive therapeutic modalities have become more attractive in treating ICH over craniotomy for various reasons, including short operative time, the potential for performing them at the bedside, and minimizing the potential exacerbation of secondary brain trauma through the avoidance of larger corticotomies and brain retraction.

Minimally Invasive Therapy: Mechanical and Pharmacological Approaches

The earliest work on mechanical thrombectomy was conducted using a stereotactic approach to drain clots via a cannula.⁵ This was done prior to the CT era, and localization was based on the clinical examination and evaluation of vessel displacement on cerebral angiography.⁵ Knowing that the lateral lenticulostriate arteries were responsible for most hypertensive ICHs, the authors aimed a rigid cannula to the lateral lenticulostriate arteries using plain skull radiographs and a stereotactic apparatus. Although the clinical outcome was poor, the authors were able to localize the ICH and perform drainage in 12 of 13 patients.

This minimally invasive technique has been further developed since the advent of CT scanning. The introduction of stereotactic systems such as the Leksell frame further improved accuracy of localizing the clot. However, because most acute hematomas are solid, clots clogging the drainage system were noted to be a problem. Several modifications of clot-evacuating instruments have been made to overcome this issue. Backlund and von Host⁴ used CT scanning for the stereotactic localization of hematomas and used a device that evacuated the clot by the Archimedes principle, in which an outer cannula is attached to suction and an inner screw is rotated to mechanically break the clot. This was a novel technique that facilitated mechanical clot lysis, and since the advent of this device, others have reported larger case series showing that mechanical lysis facilitates clot removal.^{16,17} Hondo et al.¹⁵ tried to overcome this using an ultrasound aspirator to facilitate mechanical clot lysis. Nizzuma and Suzuki^{28,29} left a drain in the cavity after the aspiration of a hematoma and injected urokinase to facilitate pharmacological lysis. They reported promising outcomes at 6 months.

Endoscopy-guided aspiration has also been investigated with use of a single bur hole and endoscope. In 1989, Auer et al.³ reported the first randomized controlled trial comparing the difference between endoscopically assisted aspirations and pure medical management. At 6 months, there was decreased mortality and a trend toward better outcomes in the surgical group, but these benefits were limited to lobar hematomas and to patients younger than 60 years.

Urokinase²⁶ and streptokinase were the initial common agents for thrombolysis, but recently the use of rt-PA has become more prevalent. Rohde et al.³⁸ reported that IVH cleared earlier with rt-PA than urokinase by 5 days. Hanley and colleagues have extensively studied the role of rt-PA in ICH and IVH (unpublished data). These authors performed multiple prospective studies to assess safety, optimum dose, and interval for treatment using rt-PA for IVH (CLEAR studies) and ICH (MISTIE studies).

These studies laid out the principles for successful minimally invasive operative intervention, which included subtotal evacuation to relieve mass effect but enough to tamponade and prevent rehemorrhage, avoid injury to normal brain, provide accurate localization using stereotaxy, and facilitate lysis of clot either mechanically, via thrombolytics, or both. Table 1 outlines these initial case reports and series depicting the method of clot evacuation and outcomes.

Intraventricular Hemorrhage Trials

The CLEAR study is a multicenter blinded prospective safety trial comparing best medical/ICU care with aggressive ventricular drainage with rt-PA injected into ventricular catheters at a dose of 3 mg every 12 hours.²⁵ The study enrolled 48 patients. Symptomatic bleeding was noted in 23% of the rt-PA group and in 5% in the placebo group (p = 0.1). Mortality was 19% in the rt-PA group and 23% in the placebo group. The clot resolution rate was significantly increased in the rt-PA group (18% vs 8%, p < 0.001). The rt-PA group also underwent earlier removal of the EVD catheter and relied less on exchanging EVD catheters due to clot obstruction of catheters. They also noted clinical improvement by an increase in GCS scores at 4 days within the rt-PA group.

This initial safety study was not designed to assess long-term functional outcome. Patients with significant impairment at presentation could take more than 30 days to recover consciousness; therefore, functional outcomes are better studied at longer time intervals.^{24,42} The CLEAR III trial is a current ongoing trial that will assess functional performance in a 90- to 180-day time frame.

Lippitz¹⁸ and Schaller⁴⁰ and their colleagues conducted a study for thrombolytic treatment of ICH by injecting rt-PA every 12-24 hours via a drain stereotactically placed in the hematoma cavity. Lippitz et al. used 3 mg rt-PA delivered through a stereotactically placed catheter; depending on residual ICH on CT at 24 hours, rt-PA treatment was repeated for 1-3 days. Schaller et al. further calculated the dose of rt-PA relative to the maximum hematoma diameter of 1 cm for 1 mg rt-PA. Doses were repeated every 24 hours for a total of 3 days of treatment if necessary. Morgan et al.²³ conducted a prospective study consisting of ICH aspiration via a stereotactically placed catheter and rt-PA injection starting 12 hours after onset of symptoms in patients with supratentorial ICH regardless of the depth of ICH. Aspiration was repeated after 24 hours. If subsequent CT scanning showed significant hematoma, the procedure was repeated for up to 3 days or until the hematoma was smaller than 15 cm³.

The MISTIE trial was a Phase II study for ICH treatment.¹³ The trial evaluated the safety, efficacy, and surgical performance, including accuracy of catheter placement and volume of ICH reduction at the end of treatment. Forty patients were randomized to MIS plus rt-PA or medical therapy. The rt-PA dose used was 0.3, 1, or 3 mg. The patients' profiles included a mean age of 62 ± 11 years, location in the basal ganglia (in 58%) and lobar area (in 42%), GCS score lower than 14, NIHSS score greater than 6, and an ICH larger than 25 cm³ on CT scanning. Patients who were excluded from the study were those with infratentorial hemorrhage, IVH, coagulopathy, and an underlying vascular lesion. The group randomized to surgery had a 14-Fr cannula placed stereotactically into the center of the clot. Using a 10-ml syringe, the surgeon first aspirated the clot until resistance was met. Then a soft ventricular catheter was placed, and accurate placement was confirmed using CT scanning. Thrombolytics were given, and the catheter was initially closed, but it was later opened to allow for drainage. This was done every 8 hours for up to 9 doses or until the clinical end point was reached. Clinical end points were reduction of clot by 80% of the original size, clot size reduction to 15 cm³ or smaller, or new hemorrhage.

Mortality rates at 7 and 30 days were 0% and 10.5%, respectively. Rebleeding was observed in 10.5% of patients (in the MIS group), and there were no instances of brain infection. Clot removal rates were significantly higher in the treatment group than in the medically treated patients (19%/day for patients receiving 0.3 mg and 16%/day for those receiving 1.0 mg). The amount of residual volume correlated strongly with the accuracy of catheter placement, but patient demographics, clot location, and duration of treatment did not appear to be associated. Baseline factors (GCS and NIHSS scores) and ICH/IVH clot volumes at presentation and at the end of end of treatment were predictors of good functional outcome (mRS Score 0-3) at 180 days. Surgical extraction of the clot was associated with an mRS score of 0-3. These authors concluded that a minimally invasive approach appears to be safe compared with medical therapy and can

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Authors & Year	Study Type	No. Pts	Method	Vol (cm ³)	FU Duration	Location	Outcome	Re- hemorrhage
Benes et al., 1965	case series	13	stereotactic apparatus w/ clinical exam & cerebral angiographic signs of shift	hun	NS	basal ganglia	localized & drained in 12/13 pts	NR
Backlund & von Holst, 1978	case report	~	CT-guided stereotactic device w/ Archimedes screw principle; novel device	~100	NS	NS	drained 70 ml from estimated 100 ml clot	NR
Niizuma & Suzuki, 1987	case series	145	CT-guided w/ Leksell stereotactic sys- tem for 1st evacuation followed by urokinase infusion via cath placed in ICH	NS	6 mos	basal ganglia, thalamus, Iobar	8% full recovery, 29% independent, 43% depen- dent, 13% poor	NR
Auer et al., 1989	randomized control trial	100	endoscopic evacuation of ICH vs best medical management	>10	6 mos	basal ganglia, thalamus, Iobar	lobar hemorrhage w/ minimal initial neurological deficits, <50-cm ³ clot, <60 yrs old had favor- able outcome compared w/ medically man- aged pts; no difference in functional outcome in basal ganglia or thalamic hemorrhages	NR
Kandel & Peresedov, 1990	case series	74	CT-guided stereotactic device w/ Archimedes screw principle	24–115	9 yrs	basal ganglia, thalamus, lobar	9 (12%) had recurrent clots; 48 (64%) had com- plete recovery; 36 (49%) had residual hemi- paresis	12%
Hondo et al., 1990	case series	437	CT-guided stereotactic device w/ US aspirator followed by urokinase infusion via cath placed in ICH	NS	NS	basal ganglia, thalamus, Iobar	mortality 26% thalamic, 23% lobar, 27% cere- bellar, 33% pontine	NR
Lippitz et al., 1994	case series	6	CT-guided stereotactic insertion of cath into hematoma followed by scheduled rt-PA infusion & closed system drainage	30–100	4-17 mos	basal ganglia, thalamus, Iobar	84% of hematoma removed; 6/10 pts indepen- dent at FU	%0
Schaller et al., 1995	case series	14	CT-guided stereotactic insertion of cath into hematoma followed by scheduled rt-PA infusion & closed system drainage	36–196	3–13 mos	basal ganglia, thalamus, Iobar	fast improvement in level of consciousness in 5 pts who presented w/ poor GCS scores	%0
Newell et al., 2011	case series	ດ	CT guided insertion of cath & US mi- crocatheter into hematoma followed by tPA infusion & closed drainage system	>25	3 mos	basal ganglia, thalamus, Iobar	45% vol reduction of ICH in 24 hrs; clinical im- provement in NIHSS in 8/9 pts; faster rate of clot lysis compared w/ current MISTIE trial pts	%0
Hanley et al., ongoing	MISTIE: randomized control trial Phases I & II	40	CT or MRI guided insertion of cath into hematoma followed by scheduled t-PA infusion & closed system drainage	>25	6 mos	basal ganglia, thalamus, Iobar	10.5% mortality at 30 days in MIS group; 46% clot resolution in acute phase in the rt-PA group vs 4% in medical group	10%

* cath = catheter; FU = follow-up; NR = not reported; NS = not specified; pts = patients; unk = unknown; US = ultrasound.

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accomplish clot evacuation without craniotomy and that catheter localization is critical to optimizing hematoma resolution. 13

Carhuapoma et al.7 also studied the effect of stereotactic aspiration and rt-PA on perihematomal edema. Perihematomal edema is thought to occur from local mass effect of the clot and secondary injury from blood degradation products. The impact of perihematomal edema on neurological function of patients who survive the acute phase is unknown.7 Some studies have reported a reduction in perihematomal edema with clot removal regardless of the surgical approach.^{20,31} However, there are also reports suggesting that while thrombolytic agents administered within clots accelerate the rate of lysis, they can also poten-tially worsen associated edema.^{10,37} To test whether thrombolytics exacerbate perihematomal edema, Carhuapoma et al. investigated 15 patients with ICH who underwent frameless stereotactic aspiration of the clot followed by insertion of a catheter into the hematoma. Recombinant tissue plasminogen activator was given every 12 hours until clot resolution or until the catheter fenestrations were no longer in the clot. The rate of ICH and perihematomal edema volume resolution was determined using CT findings. The authors observed a significant rate of hematoma resolution (9.65%/day) and perihematomal edema resolution (4%/day) with in the first 8 days of treatment.⁷

Combined Mechanical and Pharmaceutical Approach

As mentioned above, mechanical devices and thrombolytics have achieved positive effects on clot lysis. It would therefore make sense to have a device that can incorporate both modalities to safely augment the rate of lysis. The efficacy of thrombolytics has been shown to be augmented by the adjunct use of ultrasound in both in vivo and in vitro studies.^{1,2,8} The mechanism by which ultrasound enhances thrombolysis is believed to be the result of acoustical streaming where ultrasound facilitates delivery of drug through the clot structure. Newell et al.²⁷ first reported the use of locally delivered ultrasound and thrombolytics to sites of hematoma by stereotactic insertion of microcatheters with ultrasound-emitting elements in the SLEUTH study.

The inclusion criteria for this study were ICH larger than 25 cm³, IVH producing obstructive hydrocephalus, treatment within 72 hours of initial CT, blood pressure lower than 200 mm Hg, mRS Score 0 or 1, and age 18–85 years. Nine patients (6 females and 3 males) who met the criteria entered the trial. A microcatheter emitting ultrasound waves as well as a drainage catheter was placed stereotactically into an ICH or IVH (Fig. 1). The rt-PA protocol was identical to that in the MISTIE II trial. The distal catheter tip emitted ultrasound at a frequency of 2 MHz and 0.45 W. This was delivered for 24 hours. The hemorrhages were predominately IVHs in 3 patients and ICHs in 6 patients. Compared with the MISTIE and CLEAR studies, a faster rate of clot lysis was observed. This approach seems to be very promising, but the study was conducted in only 9 patients. Larger study groups are needed to confirm these findings. Furthermore, the ultrasound-emitting catheter was designed for intraarterial placement and clot lysis for the treatment of ischemic strokes. Catheters specifically devised for intracranial use may provide better clot lysis, and they are currently in development by the EKOS Corp. (Fig. 2).



Fig. 1. Apparatus for the SLEUTH study. Left: A standard EVD catheter with a small ultrasound-emitting probe (EKOS) inserted in the catheter tip fenestration. Right: Illustration showing stereotactic insertion of the ventricular catheter with the EKOS US microcatheter (*upper*). The tip of the catheter assembly is seen within the intraparenchymal clot (*lower*). Printed with permission from the Swedish Neuroscience Institute.



Fig. 2. New design of an ultrasound-emitting drainage catheter designed to deliver ultrasound directly into the center of an ICH and allow continuous drainage of the liquefied clot. Reprinted from EKOS Corp., internal document.

Conclusions

A minimally invasive approach to evacuate ICH has been well documented to be a safe practice. Thus far, the CLEAR and MISTIE studies have supported this assertion. An increased rate of clot lysis could potentially be achieved with a combination of mechanical and pharmaceutical approaches. However, more extensive studies need to be conducted to determine whether the additional mechanical effects via ultrasound further yield beneficial long-term outcome versus pharmacological lysis alone. Currently, catheters are being redesigned for this purpose and will be evaluated in additional future clinical trials.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Hanley, Newell. Acquisition of data: Hanley, Newell. Analysis and interpretation of data: all authors. Drafting the article: Newell. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Abdu. Statistical analysis: Hanley, Newell. Administrative/ technical/material support: Abdu, Newell.

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Address correspondence to: Emun Abdu, M.D., Swedish Neuroscience Institute, 550 Seventeenth Avenue, Suite 500, Seattle, Washington 98122. email: emun.abdu@swedish.org.