

Minimally invasive evacuation of spontaneous intracerebral hemorrhage using sonothrombolysis

Clinical article

DAVID W. NEWELL, M.D.,¹ M. MOHSIN SHAH, M.D.,¹ ROBERT WILCOX, M.S.,²
DOUGLAS R. HANSMANN, PH.D.,² ERIK MELNYCHUK, B.S.,³ JOHN MUSCHELLI, SC.M.,³
AND DANIEL F. HANLEY, M.D.³

¹Department of Neurosurgery, Swedish Neuroscience Institute, Seattle; ²EKOS Corporation, Bothell, Washington; and ³Brain Injury Outcomes Center, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Object. Catheter-based evacuation is a novel surgical approach for the treatment of brain hemorrhage. The object of this study was to evaluate the safety and efficacy of ultrasound in combination with recombinant tissue plasminogen activator (rt-PA) delivered through a microcatheter directly into spontaneous intraventricular (IVH) or intracerebral (ICH) hemorrhage in humans.

Methods. Thirty-three patients presenting to the Swedish Medical Center in Seattle, Washington, with ICH and IVH were screened between November 21, 2008, and July 13, 2009, for entry into this study. Entry criteria included the spontaneous onset of intracranial hemorrhage ≥ 25 ml and/or IVH producing ventricular obstruction. Nine patients (6 males and 3 females, with an average age of 63 years [range 38–83 years]) who met the entry criteria consented to participate and were entered into the trial. A ventricular drainage catheter and an ultrasound microcatheter were stereotactically delivered together, directly into the IVH or ICH. Recombinant tissue plasminogen activator and 24 hours of continuous ultrasound were delivered to the clot. Gravity drainage was performed. In patients with IVHs, 3 mg of rt-PA was injected; in patients with intraparenchymal hemorrhages, 0.9 mg of rt-PA was injected. The rt-PA was delivered in 3 doses over 24 hours.

Results. All patients had significant volume reductions in the treated hemorrhage. The mean percentage volume reduction after 24 hours of therapy, as determined on CT and compared with pretreatment stability scans, was $59 \pm 5\%$ (mean \pm SEM) for ICH and $45.1 \pm 13\%$ for IVH (1 patient with ICH was excluded from analysis because of catheter breakage). There were no intracranial infections and no significant episodes of rebleeding according to clinical or CT assessment. One death occurred by 30 days after admission. Clinical improvements as determined by a decrease in the National Institutes of Health Stroke Scale score were demonstrated at 30 days after treatment in 7 of 9 patients. The rate of hemorrhage lysis was compared between 8 patients who completed treatment, and patient cohorts treated for IVH and ICH using identical doses of rt-PA and catheter drainage but without the ultrasound (courtesy of the MISTIE [Minimally Invasive Surgery plus T-PA for Intracerebral Hemorrhage Evacuation] and CLEAR II [Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage II] studies). Compared with the MISTIE and CLEAR data, the authors observed a faster rate of lysis during treatment for IVH and ICH in the patients treated with sonolysis plus rt-PA versus rt-PA alone.

Conclusions. Lysis and drainage of spontaneous ICH and IVH with a reduction in mass effect can be accomplished rapidly and safely through sonothrombolysis using stereotactically delivered drainage and ultrasound catheters via a bur hole. A larger clinical trial with catheters specifically designed for brain blood clot removal is warranted. (DOI: 10.3171/2011.5.JNS10505)

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

SPONTANEOUS intracerebral hemorrhage occurs in more than 100,000 Americans each year and has no proven effective treatment. It is estimated that the annual incidence of ICH is 10–30 cases per 100,000 per-

sons per year, accounting for about 2 million strokes annually worldwide.⁵⁸ This condition is fatal in 30%–50% of all occurrences, and the majority of survivors have significant motor and cognitive disabilities. The severity of brain injury is related to the initial destructive effects of the ICH, the location and volume of the blood clot, and secondary events including edema, shift, and impairment of CSF drainage. Spontaneous ICH is frequently complicated by IVH, which can lead to acute and chronic hydrocephalus^{27,54,68} and increases the mortality rate to as high as 80%.

Current management for ICH consists of observation

Abbreviations used in this paper: CLEAR = Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; MISTIE = Minimally Invasive Surgery plus T-PA for Intracerebral Hemorrhage Evacuation; rt-PA = recombinant tissue plasminogen activator; SLEUTH = Safety of Lysis with EKOS Ultrasound in the Treatment of Intracerebral and Intraventricular Hemorrhage; STICH = Surgical Trial in Traumatic Intracerebral Haemorrhage.

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and medical treatment in patients with smaller hematomas and surgical evacuation with open craniotomy in those with large hemorrhages or in those with progressive mass effect judged to have a favorable prognosis if the mass effect were eliminated.^{12,58} Ventricular drainage of CSF is often performed to treat acute hydrocephalus associated with IVH.^{26,27} The effect of open surgical evacuation of an ICH has been the subject of a number of reports in the literature including a recent large multicenter randomized trial.⁴³ The results of this STICH trial demonstrated that there was no overall difference in outcome between surgical versus nonsurgical treatment. However, subgroup analysis has indicated that patients with more peripherally located lobar-type hemorrhages might benefit from early surgical evacuation.⁴⁴

Direct open surgical evacuation of an ICH can be associated with poor patient stability, additional brain injury, and frequent rebleeding during the postoperative period.^{32,49} The concept of minimally invasive evacuation of an ICH has a good rationale with the goal of reducing hemorrhage volume and mass effect enough to hasten and improve recovery. Since the advent of stereotactic localization in neurosurgery, the concept of precision-guided minimally invasive aspiration or evacuation of an ICH using a variety of approaches has been tested and reported in a number of case series.^{5,6,28,31,39,45,53,60} These approaches have included minimally invasive surgical techniques using mechanical clot disruption or endoscopic removal as well as the injection of thrombolytics for clot dissolution. Data from human studies and animal models have demonstrated that the injection of thrombolytics and catheter drainage can substantially reduce blood clot size and the area of brain tissue in direct contact with blood, resulting in patient stability, decreased tissue injury, and minimal bleeding and infection risks.^{6,39,53,65,66} These studies have also indicated that it can take several days to significantly reduce mass effect from an ICH by using thrombolytics and catheter drainage.

The impact of ultrasound in substantially increasing the effectiveness of thrombolytic substances on blood clot dissolution has been studied *in vitro*^{10,21,38} but only recently has been applied to clinical medicine. Sonothrombolysis has been used to increase the efficacy of blood clot removal from arteries and veins by applying a catheter-based approach to directly apply ultrasound and thrombolytic substances to intravascular blood clots.^{1,55,67,70} Ultrasound has also been delivered from an external source using transcranial Doppler ultrasound to successfully increase the rate of rt-PA–induced recanalization of the middle cerebral artery in acute stroke.^{2,3,20,48} We report the first use of locally delivered ultrasound with thrombolytic agents through a microcatheter stereotactically inserted directly into spontaneous ICHs in humans to facilitate accelerated evacuation of a hemorrhage.

Methods

Thirty-three patients with ICH presenting to the Swedish Medical Center Cherry Hill campus were screened between November 21, 2008, and July 13, 2009, for entry into our study, referred to as the “SLEUTH

study.” Entry criteria included the spontaneous onset of an intracranial hemorrhage > 25 ml and/or an IVH producing ventricular obstruction (third or fourth ventricular clot with hydrocephalus requiring drainage) and patient availability for treatment within 72 hours of the initial diagnostic CT. Other entry criteria consisted of systolic blood pressure < 200 mm Hg for 6 hours before entry, historical modified Rankin score of 0 or 1, and an age of 18–85 years. Exclusion criteria were an ICH meeting the standard criteria for surgical removal, an infratentorial hemorrhage, vascular lesions (including aneurysms or vascular malformations), irreversibly impaired brainstem function, uncorrectable coagulation disorders, evidence of external or internal bleeding, pregnancy, and enrollment in another study.

Nine patients who met the entry criteria consented to participate and were entered into our trial to evaluate the safety and efficacy of ICH removal using a combination of rt-PA and 24 hours of continuous ultrasound delivered directly into an ICH via a stereotactically delivered microcatheter with an ultrasound-emitting element on the tip. This catheter was designed for intraarterial thrombolysis (MicroSonic SV microcatheter, EKOS Corp.).³⁶ The distal catheter tip emits ultrasound at a frequency of 2 MHz and 0.45 W. The ultrasound intensity falls off rapidly as the distance from the catheter tip increases. Since the transducer is an unfocused acoustic source, the acoustic intensity decreases by $1/r^2$ in the immediate vicinity of the transducer and $1/r^3$ at a distance of several millimeters. It is presumed from *in vitro* studies (unpublished data, EKOS Corp.) that there is still an acceleration of lysis at least 3–4 cm from the ultrasound element. The catheter is connected to a bedside controlling unit. The device was programmed to adjust intensity if the temperature at the catheter tip exceeded 42°C. The Western Institutional Review Board approved this study, and approval was in part based on safety data from animal studies as well as data collected from patients in whom the same catheter was used in the middle cerebral artery for up to several hours for the lysis of intraarterial thrombus (unpublished data, EKOS Corp.). All patients or their next of kin gave informed consent to participate in the trial.

The patients consisted of 6 males and 3 females. Their ages ranged from 38 to 83 years, with an average age of 63 years. They were all examined with CT, and 6 patients underwent CT angiography to rule out vascular lesions as a cause of ICH. Hemorrhages were predominantly intraventricular in 3 of the patients and were primary intraparenchymal hemorrhages in the other 6. All baseline and sequential CT scans were characterized using the modified Graeb Scale to measure IVHs and the modified ellipsoid volume or “ $(A \times B \times C)/2$ ” method to measure the volume of intraparenchymal hemorrhages.¹⁴ Subsequent data analysis of hemorrhage volumes and the effect of treatment was performed at a centralized reading center set up to manage data from the CLEAR and MISTIE studies, utilizing image analysis software that allowed for heterogeneous volumetric analysis of hemorrhages during dissolution using features to define regions of interest.

Patient characteristics and hemorrhage locations are

listed in Table 1. Patients were stabilized in the neurosurgical ICU and were treated in accordance with published guidelines on the management of spontaneous ICH.^{12,57} Repeat CT scans were obtained within 24 hours of admission in all patients to establish the stability of the hemorrhage and to confirm that no active bleeding or expansion of the hematoma was occurring prior to treatment. Such a stability CT scan was compared with the initial diagnostic CT scan to determine if the hemorrhage continued to expand more than 5 ml or was stable. Of the 33 patients evaluated, 24 were excluded for the following reasons: age, size of the hematoma < 25 ml, coagulopathy, vascular lesions, failure to consent, or continued bleeding.

Comparisons were also performed between our results and the hemorrhage clearance rates in previous studies (D. Hanley, MISTIE and CLEAR studies) conducted at Johns Hopkins with identical protocols for rt-PA lysis and catheter drainage of IVH and ICH but without the use of ultrasound. The studies of intraparenchymal hemorrhage (ICH) lysis are designated “MISTIE” in this paper, and the study of IVH lysis is designated “CLEAR.” Relative to a study-defined baseline CT scan (obtained after catheter placement, before treatment), the percent of ICH or IVH volume remaining and the number of days of observation were calculated for each CT scan obtained during and subsequent to treatment. For MISTIE and SLEUTH ICHs, the baseline CT was the postoperative one obtained after catheter placement. The baseline CT for SLEUTH IVHs was the CT scan obtained after catheter placement and before the first active dose of rt-PA. For CLEAR IVHs, the baseline CT was the one obtained before the first dose of rt-PA, and the baseline volume was interpolated using the volumes from CT scans obtained directly before and after the time of the first dose. For each CT study, the percent of hemorrhage cleared per day was estimated using marginal models with robust standard errors adjusting for per-person clustering. The models were fit using an offset of 100% volume because the data were standardized to a baseline volume.

Surgical Technique for Device and Catheter Insertion

All patients were taken to an operating room, and general anesthesia was induced. Patients were registered based on CT parameters for the stereotactic placement of catheters by using the Medtronic Stealth electromagnetic navigation system. An entry point for the bur hole and a target point in the hemorrhage for the catheter tips were chosen. The Stealth guidance system was used to place a 12 Fr peel-away introducer through the bur hole into the desired location in the hemorrhage to accommodate placement of the MicroSonic SV microcatheter alongside the external ventricular drainage catheter (Fig. 1). The ventricular catheter was inserted into the peel-away introducer alongside the microcatheter, and the position was confirmed with neuronavigation. The two catheters were then tunneled out through a separate stab wound in the skin and secured. A portable CT study was performed on completion of the procedure to confirm acceptable catheter placement.

Targets for catheter placement were chosen to be most centrally located in the hemorrhage to allow the

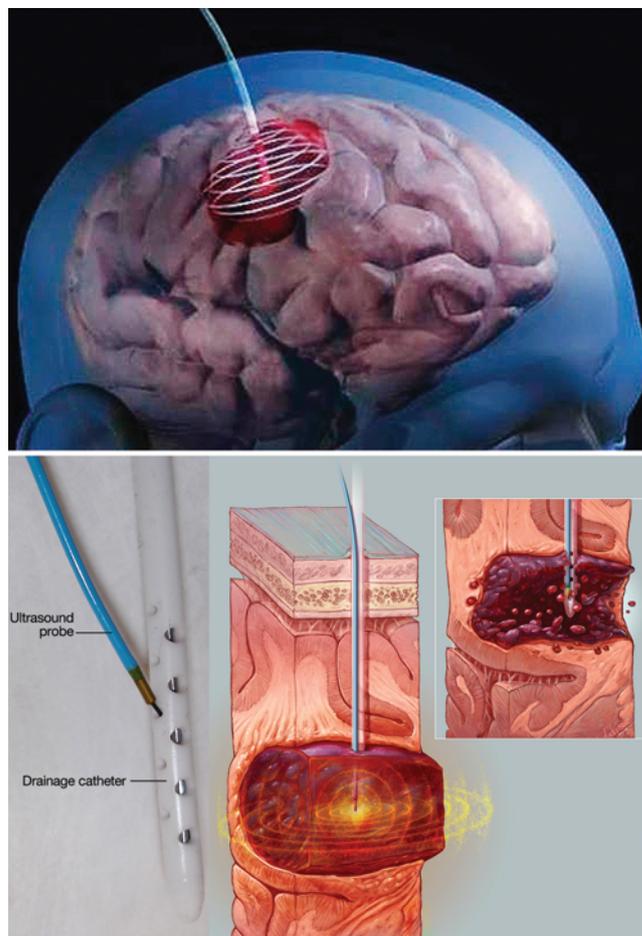


FIG. 1. **Upper:** Illustration depicting a ventricular drainage catheter and the EKOS ultrasound infusion microcatheter prior to placement in an ICH. **Lower:** Photograph showing the tip of the ultrasound catheter held in proximity to the drainage holes in the ventricular catheter using a guidewire during insertion (left), and illustrations depicting ultrasound and drainage catheter placement within an ICH during treatment (center) and later in the course of treatment after some removal of the hemorrhage (right). Reproduced with permission from D. W. Newell.

treatment zone to be central to the largest portion of the hemorrhage for maximum efficacy and for minimizing the rebleeding risk. It was permissible to have a previously placed (prior to study enrollment) external ventricular drain for the relief of acute hydrocephalus in the patients with IVH.

Sonothrombolysis Treatment Protocol

A postoperative stability CT scan was obtained 3 hours after catheter placement to confirm the absence of any additional bleeding before the treatment with ultrasound and thrombolytic substances was begun. At the initiation of treatment, rt-PA was injected into the ICH, and the catheter was flushed and clamped for 1 hour and then opened to closed drainage at 10 cm below the lesion. Based on previous dose escalation data, 1 mg of rt-PA was injected into patients with IVHs and 0.3 mg of rt-PA was injected into patients with intraparenchymal hemorrhages. Injections were repeated at 8 and 16 hours after the initial injections for a total of 3 doses over 24 hours.

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The ultrasound was turned on at the time of the first injection and was delivered at the catheter tip continuously for 24 hours. Portable CT scanning was performed at 1, 2, 4, 7, 15, and 23 hours after the initial injection and commencement of ultrasound delivery to detect any rebleeding, to measure the effect on hemorrhage size, and to assess other CT parameters including catheter location.

Results

All patients had significant reductions in the size of the treated hemorrhage as determined by a volumetric analysis comparison of the hemorrhage size prior to and after treatment (Figs. 2–5). The ultrasound catheter broke in the patient in Case 6 when she was being moved from a CT scanner during treatment, and therefore, the results of the hemorrhage reduction were excluded from the group analysis, although she was included in the clinical analysis. In the remaining 8 patients, the average treated hemorrhage size (either IVH or ICH) was reduced from 46.7 ml at the time of the postoperative stability scan to 23.4 ml at the end of 24 hours of treatment with ultrasound, rt-PA, and gravity drainage. The mean percentage volume reductions after 24 hours of treatment, as compared with pretreatment stability scans and as determined by CT, were $59 \pm 5\%$ (mean \pm SEM) for ICH and $45.1 \pm 13\%$ for IVH.

Clinical improvements as signified by a decrease in the National Institutes of Health Stroke Scale score were demonstrated at 30 days in 7 of 9 patients (average 17.6 to 8.5; Table 1). There was 1 death by 30 days after admis-

sion in a patient (Case 4) who failed to improve clinically and whose support was withdrawn according to the wishes of his family. There were no intracranial infections, and there were no significant episodes of rebleeding according to clinical or CT assessment (defined by a > 5 -ml increase in hemorrhage size).

The rate of hemorrhage lysis was compared between the 8 patients who completed treatment and the cohorts of patients treated for IVH and ICH using identical doses of rt-PA and catheter drainage without ultrasound (MISTIE [ICH lysis] and CLEAR [IVH lysis] studies, unpublished data). Marginal models were used to estimate the clearance rates for patients with IVH or ICH. An offset of 100% was used, and no constant was estimated since each patient was forced to have 100% relative to a stability (IVH) or postsurgery (ICH) scan. Robust standard errors were estimated given the small sample size.

The data were restricted to 2 days after postoperative CT scanning for the MISTIE (11 patients)/SLEUTH (5 patients) ICH patients and 2 days after the first treatment dose for the CLEAR (34 patients)/SLEUTH (3 patients) IVH patients. The relationship between time and hemorrhage clearance appeared to be linear in this time period, and it allowed the observation of hemorrhage clearance in SLEUTH patients 24 hours after the last rt-PA dose. Two CLEAR patients were excluded from analysis for lack of CT observations during the initial analysis time. There was a significant difference ($p < 0.001$) in the clearance rates between the MISTIE ICH patients randomized to the 0.3-mg dose (11 patients, $-27.9\%/day$, 95% CI -34.6% , -21.1%) and the SLEUTH ICH patients (5 patients,

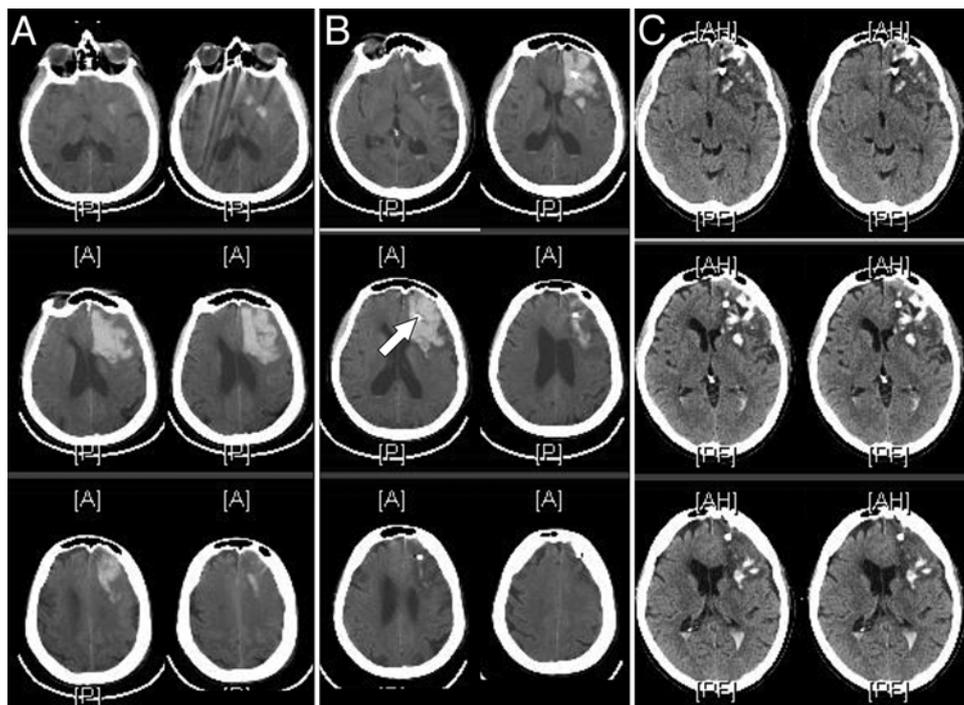


Fig. 2. Case 5. Computed tomography scans obtained in a patient who suffered a spontaneous ICH in the left frontal region. Set of images (A) showing the ICH prior to treatment. Set of images (B) showing the ICH after catheter insertion (arrow) but before treatment. Set of images (C) showing resolution of the majority of the ICH after 24 hours of ultrasound treatment and 3 doses of 0.3 mg of rt-PA administered every 8 hours during the same 24-hour interval.

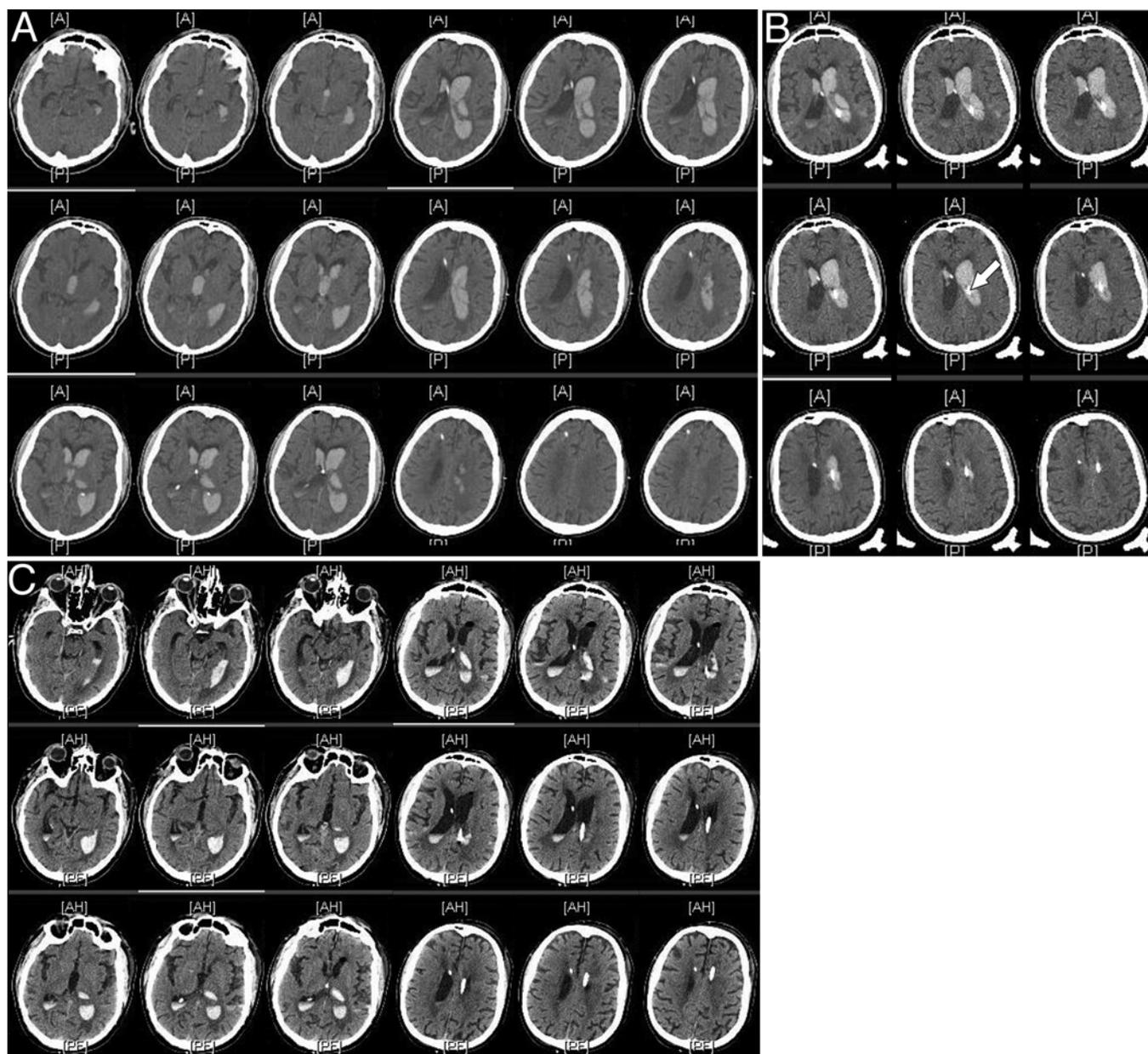


FIG. 3. Case 9. Computed tomography scans obtained in a patient who sustained a spontaneous IVH originating in the left thalamus. **A:** The hemorrhage prior to treatment is located primarily in the left lateral ventricle but is also present in the right lateral ventricle, third ventricle, and fourth ventricle (not shown). **B:** The treatment catheter is shown (arrow) after insertion into the left lateral ventricle via a frontal approach using stereotactic guidance. **C:** Scans obtained after 24 hours of treatment with continuous ultrasound and 3 doses of 1 mg of rt-PA administered every 8 hours during the same 24-hour interval. Note the near complete resolution of the left IVH and significant clearance of the remaining IVH, including clearance of the third ventricle.

-54.1%/day, 95% CI -62.2%, -46.1%. There was not a significant difference ($p = 0.428$) in the clearance rates between the CLEAR IVH patients receiving any dose of rt-PA (34 patients, -25.1%/day, 95% CI -29.9%, -20.4%) and the SLEUTH IVH patients (3 patients, -33.4%/day, 95% CI -53.2%, -13.5%). Data analyzed for these patients covered the following average number of days (\pm SD): from the first dose, CLEAR IVH 1.6 ± 0.2 and SLEUTH IVH 1.4 ± 0.5 ; from the postsurgery scan, MISTIE ICH 1.6 ± 0.3 and SLEUTH ICH 1.2 ± 0.4 .

Discussion

Outcome following ICH is dependent on a number of factors including primary injury to surrounding brain caused by the hemorrhage, secondary hemorrhage due to shearing and disruption of the small vessels and secondary edema, brain shift, and the direct toxic effects of blood products, which may occur later in the course of events.^{29,30,34,71} It is also known that recovery can be very slow in part due to the slow resolution of untreated ICH, secondary medical complications, and the perception of

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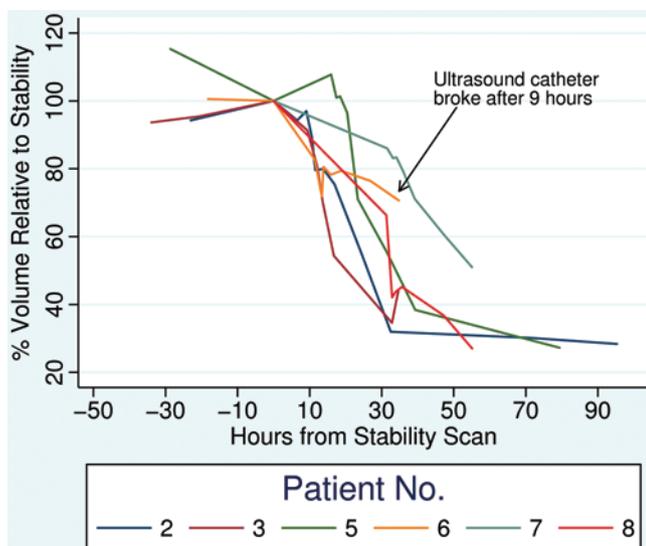


FIG. 4. Graph showing sequential ICH volume plots in the patients with parenchymal hemorrhages, expressed as the percentage reduction in hemorrhage volume relative to the stability scan obtained prior to the 24-hour treatment interval. Note that in the patient in Case 6, there is much less ICH clearance than in the remaining patients. The patient in Case 6 received the same rt-PA dose as the other patients; however, ultrasound was delivered for only 9 hours because the ultrasound catheter was fractured during patient transfer to the CT scanner for an interval control scan.

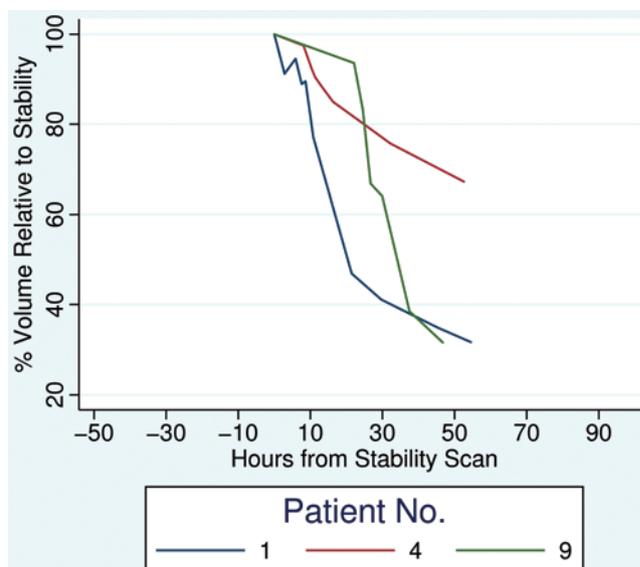


FIG. 5. Graph showing sequential IVH volume plots in the patients with primarily IVH, expressed as the percentage reduction in hemorrhage volume relative to the stability scan obtained prior to the 24-hour treatment interval.

poor prognosis, which can lead to the withdrawal of support for many patients.^{8,72} It has been shown that ICH size is a powerful determinant of outcome,¹⁴ and therefore, the concept of a timely reduction in hemorrhage size with an attendant decrease in secondary edema, shift, and the late toxic effects of blood products is appealing. Early surgery for ICH evacuation has been an attractive concept; however, severe initial damage from the ICH, additional surgical trauma, and rebleeding are factors that can limit the ability of early evacuation to improve outcome.^{43,49,64}

Recent studies have identified a number of factors that can influence the outcome of spontaneous ICH, including unstable blood pressure, continued bleeding at the time of presentation,^{7,37} rebleeding,²³ progressive edema²⁴ with shift, and herniation.

The results of well-controlled trials have not shown an overall benefit of surgery over medical management. Subgroup analysis of the STICH and other trials suggests that patients with more peripherally located hemorrhages may experience a greater benefit from surgical treatment than from medical management.⁵⁸ This finding has led to the initiation of STICH II, which will preselect patients who may be more likely to benefit from surgical treatment based on clinical factors and patients with more peripherally located hemorrhages and less central damage.^{13,44}

Since the advent of stereotactic neurosurgical methods, a number of surgeons have devised strategies using minimally invasive, stereotactically directed devices or catheters that used an Archimedes screw design to morcelize and suction pieces of solid blood clot to facilitate evacuation.⁵ Other investigators have described modi-

fications of this device to promote active mechanical ICH removal via catheters.^{28,53} Auer et al.⁴ performed a prospective randomized trial of minimally invasive endoscopic suction removal of spontaneous ICH compared with medical treatment in 100 patients and found an improved outcome in the surgically treated group. Stereotactic catheter placement and delivery of thrombolytic substances for liquefaction and drainage of intraparenchymal hemorrhage have also been reported in a number of case series.^{6,15,39,45,48,60,65,66,69} Encouraging results of minimally invasive methods for ICH removal have led to recommendations by an ICH working group appointed by the National Institutes of Health, which support the further exploration and development of these methods.⁵² The use of rt-PA to accelerate lysis and facilitate catheter drainage of IVH has also been documented in a number of case series.^{27,47,51,54,59} The encouraging results have led to a multicenter trial to randomize 500 patients with primary IVH to either ventricular drainage alone or ventricular drainage together with IVH lysis using rt-PA.⁵⁸

The method of ICH removal detailed in the present report offers some distinct advantages over previously described approaches and was made possible based on the development of several new technologies: 1) a portable navigation system that can be used at the bedside, offering the potential for accurate device placement;²⁵ 2) portable CT scanning, which promotes the advantage of placing and confirming the catheter position within the ICH and monitoring the treatment effect while minimizing patient transport;¹⁹ and 3) microcatheters that can deliver ultrasound energy to a target site in the brain. The fact that resolution of the majority of the mass effect from the hematoma occurs gently over the first 24 hours of sonothrombolysis treatment without much surgical manipulation offers some practical and theoretical advantages over other methods. Mechanical thrombectomy has the

TABLE 1: Summary of patient characteristics and clinical results of treatment*

Case No.	Age (yrs), Sex	Site Treated	NIHSS Score		Deaths w/in 30 Days	Infections	Rebleed
			Before Tx	30 Days After Tx			
1	55, M	IVH	25	11	no	no	no
2	61, M	ICH	22	22	no	no	no
3	82, F	ICH	7	4	no	no	no
4	68, M	IVH	23	died	yes	no	no
5	83, F	ICH	15	8	no	no	no
6	56, F	ICH	4	2	no	no	no
7	59, M	ICH	31	9	no	no	no
8	38, M	ICH	20	2	no	no	no
9	70, M	IVH	11	10	no	no	no
average	63		17.6	8.5	1	0	0

* NIHSS = National Institutes of Health Stroke Scale.

disadvantage of being a slow procedure with the need for continued manipulation of the tip of the thrombectomy device and incomplete collapse of a hematoma into the thrombectomy site. An advantage of the lysis procedure used in our study lies in the fact that once the sonothrombolysis device is placed, the remainder of the procedure is relatively hands free, except for the rt-PA injections, because the ultrasound runs continuously. The rapidity of ICH removal using this method also has advantages over rt-PA injections alone, including a shorter treatment time, a reduced total dose of rt-PA, and a potentially shorter time that a drainage catheter remains in place.

Ultrasound for the acceleration of hemorrhage lysis has gained increasing attention given the promising clinical results of its direct delivery via microcatheters for intraarterial and intravenous use^{16,50,55} and of its transcranial delivery for the lysis of intraarterial thrombus in acute stroke.^{1-3,20,46} Laboratory studies on its influence on thrombolysis have revealed that it has a marked effect on increasing the speed of clot lysis in a frequency- and intensity-dependent fashion.^{9-11,17,21,22,33,56,62,63} Ultrasound's beneficial effect on increasing the speed and completeness of thrombolysis via rt-PA is not created by altering the speed of the chemical reaction causing thrombin breakdown.¹⁰ Instead, ultrasound appears to increase the permeability of the formed clot to the rt-PA molecules, allowing the drug to penetrate to binding sites within the clot structure, facilitated by a phenomenon called "acoustic streaming," which is thought to mix thrombolytic substances within the structure of the thrombus.²¹ A safety study in animals has indicated that tissues appear to tolerate prolonged high-frequency ultrasound exposure without evidence of damage to vascular structures.⁶¹

Several limitations to our approach in treating ICH should be noted. We did not include patients whose condition was rapidly deteriorating from the early progression of ICH or mass effect and who were candidates for immediate surgical evacuation. We also excluded patients with continued expansion of the ICH from active bleeding until their condition stabilized, which limited the application of our method to a subset of patients with stabilized hemorrhages. It has been reported that a significant

proportion of patients have active bleeding at the time of presentation to the hospital as documented on contrast-enhanced CT.^{7,18,35,36,40,41} Efforts to address this issue have included the treatment of coagulation disorders and the investigation of treatment with systemic recombinant factor VII for ICH; however, a larger prospective randomized trial did not reveal an overall benefit in survival after ICH in patients treated with factor VII versus placebo, despite the fact that expansion of the ICH was reduced by treatment overall.⁴⁰ There is some indication that patients with active bleeding at the time of presentation may constitute a subgroup with an increased chance of benefiting from treatment with factor VII.⁴² Therefore, our patients were in a selected group that became stable but had the potential to progress to a poor outcome due to secondary deterioration from edema and secondary injury as well as from medical complications, which are frequent occurrences in patients with ICH volumes > 25 ml.

We included patients who had IVHs since they might also greatly benefit from the rapid removal of hemorrhage from the ventricle.⁵¹ Lysis and clearance of the hemorrhage in the lateral ventricle by using ultrasound and rt-PA allowed for the control of CSF drainage in 2 of our patients as well as clearance of the blood clots in the third and fourth ventricles within 24 hours. One of our patients had IVH primarily in the right trigone and temporal horn and a smaller amount of IVH in the lateral ventricle. Clearance of the IVH was not as complete in this patient because of the initial use of only one catheter and the extensive nature of the hemorrhage.

This initial safety study has demonstrated that the direct delivery of ultrasound and thrombolytic substances into ICH or IVH for lysis and drainage appears to be well tolerated and results in a markedly increased rate of clot resolution, as compared with the natural history of clot absorption or as compared with the delivery of rt-PA in the same dose schedule and catheter drainage without ultrasound (D. Hanley and CLEAR and MISTIE studies, unpublished data). It should be noted, however, that the comparison of our results with those of the CLEAR and MISTIE studies was not controlled for factors that might influence the lysis rates including the size of the hemor-

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rhage and the location of the catheter. Moreover, the patients in the CLEAR and MISTIE groups were from multicenter studies and were retrospectively compared with our patients. We also acknowledge that we had a small number of patients in each category, which makes direct comparisons problematic.

Conclusions

Additional trials with a redesigned catheter are needed to confirm our results in a larger population and to study the effect of minimally invasive accelerated clot removal using sonothrombolysis to improve outcomes in patients with ICH and IVH.

Disclosure

This work was supported by a grant from the Life Sciences Discovery Fund of the state of Washington. Support in the form of donated disposable materials, including the ultrasound catheters, was provided by the EKOS Corporation. The Medtronic Corporation Navigation Division kindly provided a portable electromagnetic Stealth unit.

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

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References

- Alexandrov AV: Ultrasound enhancement of fibrinolysis. **Stroke** **40** (3 Suppl):S107–S110, 2009
- Alexandrov AV, Demchuk AM, Felberg RA, Christou I, Barber PA, Burgin WS, et al: High rate of complete recanalization and dramatic clinical recovery during tPA infusion when continuously monitored with 2-MHz transcranial doppler monitoring. **Stroke** **31**:610–614, 2000
- Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, et al: Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. **N Engl J Med** **351**:2170–2178, 2004
- Auer LM, Deinsberger W, Niederkorn K, Gell G, Kleinert R, Schneider G, et al: Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. **J Neurosurg** **70**:530–535, 1989
- Backlund EO, von Holst H: Controlled subtotal evacuation of intracerebral haematomas by stereotactic technique. **Surg Neurol** **9**:99–101, 1978
- Barrett RJ, Hussain R, Coplin WM, Berry S, Keyl PM, Hanley DF, et al: Frameless stereotactic aspiration and thrombolysis of spontaneous intracerebral hemorrhage. **Neurocrit Care** **3**:237–245, 2005
- Becker KJ, Baxter AB, Bybee HM, Tirschwell DL, Abouelsaad T, Cohen WA: Extravasation of radiographic contrast is an independent predictor of death in primary intracerebral hemorrhage. **Stroke** **30**:2025–2032, 1999
- Becker KJ, Baxter AB, Cohen WA, Bybee HM, Tirschwell DL, Newell DW, et al: Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. **Neurology** **56**:766–772, 2001
- Blinc A, Francis CW: Transport processes in fibrinolysis and fibrinolytic therapy. **Thromb Haemost** **76**:481–491, 1996
- Blinc A, Francis CW, Trudnowski JL, Carstensen EL: Characterization of ultrasound-potentiased fibrinolysis in vitro. **Blood** **81**:2636–2643, 1993
- Blinc A, Keber D, Lahajnar G, Stegnar M, Zidansek A, Demsar F: Lysing patterns of retracted blood clots with diffusion or bulk flow transport of plasma with urokinase into clots—a magnetic resonance imaging study in vitro. **Thromb Haemost** **68**:667–671, 1992
- Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al: Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. **Stroke** **38**:2001–2023, 2007
- Broderick JP: The STICH trial: what does it tell us and where do we go from here? **Stroke** **36**:1619–1620, 2005
- Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G: Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. **Stroke** **24**:987–993, 1993
- Carhuapoma JR, Barrett RJ, Keyl PM, Hanley DF, Johnson RR: Stereotactic aspiration-thrombolysis of intracerebral hemorrhage and its impact on perihematoma brain edema. **Neurocrit Care** **8**:322–329, 2008
- Chamsuddin A, Nazzal L, Kang B, Best I, Peters G, Panah S, et al: Catheter-directed thrombolysis with the Endowave system in the treatment of acute massive pulmonary embolism: a retrospective multicenter case series. **J Vasc Interv Radiol** **19**:372–376, 2008
- Cintas P, Nguyen F, Boneu B, Larrue V: Enhancement of enzymatic fibrinolysis with 2-MHz ultrasound and microbubbles. **J Thromb Haemost** **2**:1163–1166, 2004
- Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al: Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. **Neurology** **66**:1175–1181, 2006
- ECRI Institute: Mobile computed tomography evaluation of the NeuroLogica CereTom. **Health Devices** **37**:325–342, 2008
- Eggers J, König IR, Koch B, Händler G, Seidel G: Sonothrombolysis with transcranial color-coded sonography and recombinant tissue-type plasminogen activator in acute middle cerebral artery main stem occlusion: results from a randomized study. **Stroke** **39**:1470–1475, 2008
- Francis CW, Blinc A, Lee S, Cox C: Ultrasound accelerates transport of recombinant tissue plasminogen activator into clots. **Ultrasound Med Biol** **21**:419–424, 1995
- Francis CW, Onundarson PT, Carstensen EL, Blinc A, Meltzer RS, Schwarz K, et al: Enhancement of fibrinolysis in vitro by ultrasound. **J Clin Invest** **90**:2063–2068, 1992
- Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki

- O: Hematoma enlargement in spontaneous intracerebral hemorrhage. **J Neurosurg** **80**:51–57, 1994
24. Gebel JM Jr, Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S, et al: Natural history of perihematomal edema in patients with hyperacute spontaneous intracerebral hemorrhage. **Stroke** **33**:2631–2635, 2002
 25. Gralla J, Nimsy C, Buchfelder M, Fahlbusch R, Ganslandt O: Frameless stereotactic brain biopsy procedures using the Stealth Station: indications, accuracy and results. **Zentralbl Neurochir** **64**:166–170, 2003
 26. Hallevi H, Albright KC, Aronowski J, Barreto AD, Martin-Schild S, Khaja AM, et al: Intraventricular hemorrhage: anatomic relationships and clinical implications. **Neurology** **70**:848–852, 2008
 27. Hanley DF: Intraventricular hemorrhage: severity factor and treatment target in spontaneous intracerebral hemorrhage. **Stroke** **40**:1533–1538, 2009
 28. Higgins AC, Nashold BS, Cosman E: Stereotactic evacuation of primary intracerebral hematomas: new instrumentation. **Appl Neurophysiol** **45**:438–442, 1982
 29. Hoff JT, Xi G: Brain edema from intracerebral hemorrhage. **Acta Neurochir Suppl (Wien)** **86**:11–15, 2003
 30. Hua Y, Nakamura T, Keep RF, Wu J, Schallert T, Hoff JT, et al: Long-term effects of experimental intracerebral hemorrhage: the role of iron. **J Neurosurg** **104**:305–312, 2006
 31. Kandel EI, Peresedov VV: Stereotaxic evacuation of spontaneous intracerebral hematomas. **J Neurosurg** **62**:206–213, 1985
 32. Kaneko M, Tanaka K, Shimada T, Sato K, Uemura K: Long-term evaluation of ultra-early operation for hypertensive intracerebral hemorrhage in 100 cases. **J Neurosurg** **58**:838–842, 1983
 33. Kashyap A, Blinc A, Marder VJ, Penney DP, Francis CW: Acceleration of fibrinolysis by ultrasound in a rabbit ear model of small vessel injury. **Thromb Res** **76**:475–485, 1994
 34. Keep RF, Xiang J, Ennis SR, Andjelkovic A, Hua Y, Xi G, et al: Blood-brain barrier function in intracerebral hemorrhage. **Acta Neurochir Suppl (Wien)** **105**:73–77, 2008
 35. Kelley RE, Berger JR, Scheinberg P, Stokes N: Active bleeding in hypertensive intracerebral hemorrhage: computed tomography. **Neurology** **32**:852–856, 1982
 36. Khatri P, Hill MD, Palesch YY, Spilker J, Jauch EC, Carrozella JA, et al: Methodology of the Interventional Management of Stroke III Trial. **Int J Stroke** **3**:130–137, 2008
 37. Kim J, Smith A, Hemphill JC III, Smith WS, Lu Y, Dillon WP, et al: Contrast extravasation on CT predicts mortality in primary intracerebral hemorrhage. **AJNR Am J Neuroradiol** **29**:520–525, 2008
 38. Kimura M, Iijima S, Kobayashi K, Furuhashi H: Evaluation of the thrombolytic effect of tissue-type plasminogen activator with ultrasonic irradiation: in vitro experiment involving assay of the fibrin degradation products from the clot. **Biol Pharm Bull** **17**:126–130, 1994
 39. Marquardt G, Wolff R, Janzen RW, Seifert V: Basal ganglia hematomas in non-comatose patients: subacute stereotactic aspiration improves long-term outcome in comparison to purely medical treatment. **Neurosurg Rev** **28**:64–69, 2005
 40. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al: Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. **N Engl J Med** **358**:2127–2137, 2008
 41. Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE, et al: Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. **Stroke** **36**:74–79, 2005
 42. Mayer SA, Davis SM, Skolnick BE, Brun NC, Begtrup K, Broderick JP, et al: Can a subset of intracerebral hemorrhage patients benefit from hemostatic therapy with recombinant activated factor VII? **Stroke** **40**:833–840, 2009
 43. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, 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. **Lancet** **365**:387–397, 2005
 44. Mendelow AD, Unterberg A: Surgical treatment of intracerebral haemorrhage. **Curr Opin Crit Care** **13**:169–174, 2007
 45. Mohadjer M, Eggert R, May J, Mayfrank L: CT-guided stereotactic fibrinolysis of spontaneous and hypertensive cerebellar hemorrhage: long-term results. **J Neurosurg** **73**:217–222, 1990
 46. Molina CA, Barreto AD, Tsivgoulis G, Sierzenski P, Malkoff MD, Rubiera M, et al: Transcranial ultrasound in clinical sonothrombolysis (TUCSON) trial. **Ann Neurol** **66**:28–38, 2009
 47. Morgan T, Awad I, Keyl P, Lane K, Hanley D: Preliminary report of the clot lysis evaluating accelerated resolution of intraventricular hemorrhage (CLEAR-IVH) clinical trial. **Acta Neurochir Suppl (Wien)** **105**:217–220, 2008
 48. Morgan T, Zuccarello M, Narayan R, Keyl P, Lane K, Hanley D: Preliminary findings of the minimally-invasive surgery plus rtPA for intracerebral hemorrhage evacuation (MISTIE) clinical trial. **Acta Neurochir Suppl** **105**:147–151, 2008
 49. Morgenstern LB, Demchuk AM, Kim DH, Frankowski RF, Grotta JC: Rebleeding leads to poor outcome in ultra-early craniotomy for intracerebral hemorrhage. **Neurology** **56**:1294–1299, 2001
 50. Motarjeme A: Ultrasound-enhanced thrombolysis. **J Endovasc Ther** **14**:251–256, 2007
 51. Naff NJ, Hanley DF, Keyl PM, Tuhim S, Kraut M, Bederson J, et al: Intraventricular thrombolysis speeds blood clot resolution: results of a pilot, prospective, randomized, double-blind, controlled trial. **Neurosurgery** **54**:577–584, 2004
 52. NINDS ICH Workshop Participants: Priorities for clinical research in intracerebral hemorrhage: report from a National Institute of Neurological Disorders and Stroke workshop. **Stroke** **36**:e23–e41, 2005
 53. Nguyen JP, Decq P, Brugieres P, Yepes C, Melon E, Gaston A, et al: A technique for stereotactic aspiration of deep intracerebral hematomas under computed tomographic control using a new device. **Neurosurgery** **31**:330–335, 1992
 54. Nyquist P, Hanley DF: The use of intraventricular thrombolytics in intraventricular hemorrhage. **J Neurol Sci** **261**:84–88, 2007
 55. Parikh S, Motarjeme A, McNamara T, Raabe R, Hagspiel K, Benenati JF, et al: Ultrasound-accelerated thrombolysis for the treatment of deep vein thrombosis: initial clinical experience. **J Vasc Interv Radiol** **19**:521–528, 2008
 56. Prokop AF, Soltani A, Roy RA: Cavitation mechanisms in ultrasound-accelerated fibrinolysis. **Ultrasound Med Biol** **33**:924–933, 2007
 57. Qureshi AI: Antihypertensive treatment of acute cerebral hemorrhage (ATACh): rationale and design. **Neurocrit Care** **6**:56–66, 2007
 58. Qureshi AI, Mendelow AD, Hanley DF: Intracerebral haemorrhage. **Lancet** **373**:1632–1644, 2009
 59. Rohde V, Schaller C, Hassler WE: Intraventricular recombinant tissue plasminogen activator for lysis of intraventricular haemorrhage. **J Neurol Neurosurg Psychiatry** **58**:447–451, 1995
 60. Schaller C, Rohde V, Meyer B, Hassler W: Stereotactic puncture and lysis of spontaneous intracerebral hemorrhage using recombinant tissue-plasminogen activator. **Neurosurgery** **36**:328–335, 1995
 61. Soltani A, Singhal R, Garcia JL, Raju NR: Absence of biological damage from prolonged exposure to intravascular ultrasound: a swine model. **Ultrasonics** **46**:60–67, 2007
 62. Soltani A, Volz KR, Hansmann DR: Effect of modulated ultrasound parameters on ultrasound-induced thrombolysis. **Phys Med Biol** **53**:6837–6847, 2008

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63. Tachibana K, Tachibana S: Prototype therapeutic ultrasound emitting catheter for accelerating thrombolysis. **J Ultrasound Med** **16**:529–535, 1997
64. Teernstra OP, Evers SM, Kessels AH: Meta analyses in treatment of spontaneous supratentorial intracerebral haematoma. **Acta Neurochir (Wien)** **148**:521–528, 2006
65. Teernstra OP, Evers SM, Lodder J, Leffers P, Franke CL, Blaauw G: Stereotactic treatment of intracerebral hematoma by means of a plasminogen activator: a multicenter randomized controlled trial (SICHPA). **Stroke** **34**:968–974, 2003
66. Thiex R, Rohde V, Rohde I, Mayfrank L, Zeki Z, Thron A, et al: Frame-based and frameless stereotactic hematoma puncture and subsequent fibrinolytic therapy for the treatment of spontaneous intracerebral hemorrhage. **J Neurol** **251**:1443–1450, 2004
67. Tsigvoulis G, Culp WC, Alexandrov AV: Ultrasound enhanced thrombolysis in acute arterial ischemia. **Ultrasonics** **48**:303–311, 2008
68. Tuhim S, Horowitz DR, Sacher M, Godbold JH: Volume of ventricular blood is an important determinant of outcome in supratentorial intracerebral hemorrhage. **Crit Care Med** **27**:617–621, 1999
69. Vespa P, McArthur D, Miller C, O’Phelan K, Frazee J, Kidwell C, et al: Frameless stereotactic aspiration and thrombolysis of deep intracerebral hemorrhage is associated with reduction of hemorrhage volume and neurological improvement. **Neurocrit Care** **2**:274–281, 2005
70. Wissgott C, Richter A, Kamusella P, Steinkamp HJ: Treatment of critical limb ischemia using ultrasound-enhanced thrombolysis (PARES Trial): final results. **J Endovasc Ther** **14**:438–443, 2007
71. Xi G, Keep RF, Hoff JT: Mechanisms of brain injury after intracerebral haemorrhage. **Lancet Neurol** **5**:53–63, 2006
72. Zurasky JA, Aiyagari V, Zazulia AR, Shackelford A, Diringner MN: Early mortality following spontaneous intracerebral hemorrhage. **Neurology** **64**:725–727, 2005

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Address correspondence to: David W. Newell, M.D., Swedish Neuroscience Institute, 550 Seventeenth Avenue, Suite 500, Seattle, Washington 98122. email: david.newell@swedish.org.