Stereotactic Computed Tomographic–Guided Aspiration and Thrombolysis of Intracerebral Hematoma

Protocol and Preliminary Experience

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Background and Purpose—We review preliminary experience with patients harboring intracerebral hematoma (ICH) treated by stereotactic computed tomographic (CT) guided thrombolysis and aspiration and assess procedure feasibility and safety.

Methods—Twelve patients with supratentorial ICH ≥25 mL without suspected underlying structural etiology or coagulopathy and an initial Glasgow Coma Scale (GCS) score of ≥5 were treated. A catheter was directed stereotactically or manually into the ICH through a burr hole under CT guidance. Hematoma aspiration was followed by instillation of urokinase (5 000 to 10 000 IU). This was repeated every 6 to 8 hours at bedside, with interval CT imaging, until the ICH volume diminished to <25 mL, less than half of its initial volume, or after a maximum of 10 aspirations/instillations.

Results—Mean age was 69 years (range 55 to 82 years). Median initial GCS was 12 (range 5 to 14). There were 7 ganglionic and 5 lobar ICH, and baseline hematoma size ranged 29 to 70 mL (mean 46 mL). Final ICH volume ranged from 14 to 51 mL (mean 21 mL), with ICH volume reduction by an average of 57% (range 38% to 70%). One patient (8.3%) suffered hematoma expansion during the procedure. At 6 months after the procedure, 3 patients (25%) had achieved a good recovery (Glasgow Outcome Scale [GOS] score of 5), 5 patients (42%) were dependent (GOS 3), and 1 (8.3%) remained vegetative (GOS 2). Three patients (25%) died in hospital (1 from cardiac arrhythmia and 2 from respiratory failure).

Conclusions—CT-guided thrombolysis and aspiration appears safe and effective in the reduction of ICH volume. Further studies are needed to assess optimal thrombolytic dosage and must include controlled comparisons of mortality, disability outcome, time until convalescence, and cost of care in treated and untreated patients. (Stroke. 2000;31:834-840.)

Key Words: intracerebral hemorrhage ■ stereotactic aspiration ■ stroke, acute ■ surgical treatment ■ thrombolysis ■ urokinase

Intracerebral hemorrhage (ICH) is one of the most serious types of stroke. More than 700 000 new strokes occur in the United States yearly, 20% of which are hemorrhagic, with more than half representing ICH.1 The majority of cases are associated with arterial hypertension and/or elderly age, and the most common sites of hemorrhage are the striatum, cerebellum, thalamus, and pons.2 The 30-day mortality rate is 35% to 50%, and most survivors are typically left severely disabled.1–3

Current treatment strategies are aimed toward reducing intracranial pressure (ICP) and maintaining adequate cerebral perfusion.1,4 While many clinicians agree that cerebellar and superficial lobar hematomas should be evacuated if the lesions are causing symptomatic mass effect, there is no reliable information regarding the use of surgery for deep hematomas.1,5,6 Surgical evacuation as a treatment option for ICH is typically reserved for a minority of cases, typically younger patients with large lobar hemmorhages who are at risk for or who are already suffering brain herniation. A nonsurgical management stance has in part been supported by the results of several randomized, controlled clinical trials7–10 that failed to demonstrate improved outcomes with surgery compared with medical therapy alone.

Auer et al11 published in 1989 results of a randomized controlled trial with demonstrated surgical benefit compared with medical treatment alone for the management of ICH. Their surgical strategy, consisting of ultrasound-guided endoscopic clot evacuation, produced significantly lower mortality rates and improved clinical outcome. This study and several case series of thrombolysis and catheter aspiration of
ICH suggest that minimally invasive interventions may avoid major surgical morbidity and offer improved outcome for selected patients who have suffered an ICH.11–15

We report preliminary experience with consecutive cases of ICH treated by stereotactic CT-guided aspiration and thrombolysis with urokinase. Our primary aim was to assess the feasibility and safety of the technique in a pilot series in preparation for a phase I-II trial, including refinement of the clinical protocol, procedure-related complications, clinical outcome, and radiological results. We discuss the evolution of our protocol based on this experience and articulate relevant questions that must be addressed in future studies.

Subjects and Methods
From September 1995 to March 1999, 12 patients were treated and are reviewed in this report. The patients were treated according a standardized protocol as illustrated in Figure 1. Eligibility criteria for this protocol consisted of supratentorial ICH without brain stem extension, clinical onset <48 hours before intervention, age >18 years, hematoma volume ≥25 mL, Glasgow Coma Scale (GCS) score ≥5 at admission, no signs of transtentorial herniation (ie, dilated pupils or extensor posturing), no suspected underlying structural lesion to account for the hemorrhage, no systemic bleeding diathesis (abnormal prothrombin or partial thromboplastin times, or platelet count <100,000), and no severe concurrent illness with life expectancy <6 months.

Informed Consent, Advance Directives, and Medical Therapy
The patient and/or closest kin or legal guardian provided informed consent in every case. Advance directives by the patient were meticulously respected, withholding the procedure and other invasive therapy, and maintaining only comfort measures in unconscious patients who had requested no intervention in case of likely disability. Other patients underwent the procedure, with their wishes respected for withholding of endotracheal intubation, cardiopulmonary resuscitation, or mechanical ventilation in case of deterioration.

Medical therapy was administered under current guidelines, including maintenance of normotension (per patient’s premorbid range of blood pressure control), normovolemic hydration, vigorous chest physiotherapy, deep-vein thrombosis prophylaxis (pneumatic antiembolic stockings supplemented after 24 hours by subcutaneous heparin at 5000 IU BID unless contraindicated), and early mobilization and physiotherapy. Endotracheal intubation was performed (in 8 of the 12 cases) for airway protection in patients with impaired consciousness but not specifically for the procedure. Early weaning and extubation were aimed for or tracheostomy was performed for early rehabilitation (4 cases). Enteral feeding was begun in the first day as tolerated. Ventriculostomy was performed in 1 case (patient 12) with poor GCS who had hydrocephalus from ventricular extension of hemorrhage. Ventricular drainage was weaned while intracranial pressure was monitored. No other specific monitoring or treatment of intracranial pressure was instituted in this series, and osmotic diuretics were not routinely administered.

Diagnostic Evaluation
A baseline CT scan was obtained in all patients with axial images at 0.5-cm slice thickness, and the dimensions of the hematoma were assessed. Volume of the ICH in milliliters was estimated on the basis of approximate ellipse volume with the formula: $V = \pi/4 \times A \times B \times C/2$, where $A$ represents the largest diameter of the hematoma on axial CT cuts in centimeters, $B$ the diameter of hematoma perpendicular to A on the same cut, and $C$ the number of CT slices in which hematoma is visible multiplied by the slice thickness in centimeters. For the purpose of this calculation we did not count the highest or lowest CT slice in which hematoma was first and last visualized. Intravenous contrast was administered to assess for any enhancement that would be suspicious for an underlying structural lesion. Patients aged <60 years or with abnormal contrast enhancement on CT scan underwent digital subtraction angiography before hematoma aspiration and thrombolysis to exclude an underlying vascular anomaly.

Operative Technique
All operations were performed under local anesthesia and intravenous sedation unless the patient was already intubated for medical or neurological indications independent of the procedure. For the first 5 patients in this series, initial localization of the hematoma and catheter placement were performed with the aid of a Cosman-Roberts-Wells head frame (Radionics, Inc). For the latter 7 patients, initial aspiration and catheter placement were performed in the CT scan suite under real-time imaging guidance. Contiguous, nonoverlapping axial CT slices 0.5 cm thick were obtained spanning the hematoma. An ipsilateral frontal standard burr hole location (3 cm...
lateral to midline and just anterior to the coronal suture) was typically used for capsular and thalamic hemorrhages. If the hematoma was lobar in location or extended to the cortical surface, the burr hole was localized over the hematoma. A 3F to 5F rigid metal catheter was placed with the introducer cannula into the clot via CT guidance. Careful manual hematoma aspiration was attempted using a syringe. We did not use other instruments to mechanically disrupt the hematoma. The rigid cannula was removed and replaced by a soft ventriculostomy catheter (15 cm long and 1 to 2 mm internal diameter) with perforations spanning the center of the clot. The CT scan was repeated for assessment of catheter placement and residual hematoma volume. Catheter placement was adjusted under CT guidance as necessary. After satisfactory placement within the hematoma, the catheter was tunneled subcutaneously and the exit site was covered with antibiotic ointment. The catheter was connected to a single port and capped, and a sterile dressing was applied. The patient was maintained on intravenous antibiotic prophylaxis (cefoxazol 500 mg every 6 hours or vancomycin 500 mg every 12 hours) until the brain catheter was removed.

**Thrombolysis and Aspiration Protocol**

All patients were managed in a dedicated neurosciences-neurovascular intensive care unit, where subsequent thrombolysis and clot aspiration were performed at the bedside using sterile technique. Urokinase 5000 IU (Abbokinase, Abbott Laboratories) in 1 mL of preservative-free saline was injected into the catheter if the CT scan revealed a residual hematoma volume of $\geq 25$ mL. The catheter was flushed (with 1 mL of preservative-free saline in the first 6 cases, and with another 5000 IU of urokinase in the subsequent cases). After 6 to 8 hours, manual aspiration of lysed clot was attempted at the bedside, and the aspirated volume was recorded. A CT scan was repeated at least every second aspiration. If the volume of residual hematoma remained $\geq 25$ mL, catheter instillation of urokinase was repeated. The protocol of aspiration, CT scan, and urokinase instillation was repeated as necessary until the final hematoma volume was $< 25$ mL, less than half of its initial volume, and clot aspiration were performed at the bedside using sterile technique.

**Follow-Up and Outcome Assessment**

Final hematoma volume was measured on the CT scan performed after catheter removal. Follow-up clinical information was obtained on all patients 3 and 6 months after the procedure. Clinical outcomes were graded according to the Glasgow Outcome Scale (GOS), ranging from grade 5 (good recovery) to grade 1 (dead), by a single investigator not involved in the patients' clinical management.

**Results**

The Table summarizes clinical and radiographic data in the 12 cases treated during the course of 3.5 years. Only 3 patients were treated in the first 1.5 years, 2 patients in the subsequent year, and 7 patients in the most recent year. The mean age of treated patients was 69 years (range 55 to 82 years), and there were 5 males and 7 females. Nine patients (75%) had a prior history of arterial hypertension; 7 had been treated pharmacologically. There were 5 lobar and 7 ganglionic ICHs. Among the latter, the epicenter of ICH was in the caudate-putamen in 3 cases and in the thalamus in 4 cases. All patients had spontaneous, nontraumatic ICH except for 1 case (patient 4), who developed ICH immediately after stereotactic pallidotomy for Parkinson's disease. Median initial GCS score was 12 (range 5 to 14). All patients had some degree of contralateral hemiparesis or hemiplegia, and 3 patients had additional aphasia.

The mean initial hematoma volume was 46 mL (ranging from 29 to 70 mL; Figure 2). Hematoma aspiration via the inserted catheter was easily achieved in 11 patients. In 1 patient, uncomplicated repositioning of the catheter was necessary after initial placement for optimal positioning within the hematoma before thrombolysis.

The average time from symptom onset until first aspiration was 19 hours (ranging from 4 to 48 hours). The hematoma catheter was in place for a median duration of 2 days (range 1 to 3 days). During this time the average number of aspirations was 5 (range 1 to 10 times), and the amount of blood aspirated averaged 51 mL (range 22 to 85 mL). The mean number of urokinase instillations was 4 (range 1 to 9 times). Initial ICH volume was reduced by an average of 57% (range 38% to 70%) and the average final hematoma volume was 21 mL (range 14 to 51 mL) (Figure 2).

No cerebral infection or systemic hemorrhage was encountered in any patient. There was a single instance of increased cerebral hematoma volume during treatment (patient 1). This
patient originally presented with a hematoma measuring 37 mL, which spontaneously enlarged to 70 mL immediately before catheter placement. Repeat CT brain imaging performed after the first urokinase instillation revealed the clot size had further increased to 140 mL, and the patient became less responsive (GCS change from 13 to 11). No further hematoma expansion was noted during his hospital course. Final hematoma volume was 51 mL after 9 cycles of aspiration and thrombolysis. He remained severely disabled (GOS 3) after 6 months of follow-up. There were no instances of late clinical deterioration from mass effect or edema associated with residual hematoma.

Three patients (25%) died before hospital discharge (1 from cardiac arrhythmia and 2 from respiratory failure). All 3 hospital deaths involved patients with advance directives who did not wish endotracheal intubation or other resuscitation. At 3 months’ follow-up, 3 patients (25%) had achieved good recovery (1 patient GOS 4, and 2 patients GOS 5), 5 patients (42%) were severely disabled (GOS 3), and 1 patient (8.3%) remained vegetative (GOS 2). By 6 months, the patient at

Figure 2. CT scans of patients with intracerebral hemorrhage at baseline presentation (left), after first aspiration with rigid cannula and catheter placement (before thrombolysis; middle), and after completed stereotactic aspiration and thrombolysis with urokinase (right) for each case, respectively. All scans demonstrate largest size of hematoma on axial imaging.
GOS 4 had made a complete recovery to GOS 5, and the remaining patients maintained the same level of disability.

The 3 patients who achieved good recovery all harbored lobar hematomas. They returned to premorbid level of function, being completely independent. Two of the 3 patients who died also harbored lobar bleeds. No patient with ganglionic ICH in this study achieved independence at 6 months (1 vegetative, 4 dependent in nursing care facilities, and 1 dependent at home), and all had reached that level of function by 3 months after the procedure.

Discussion
Reducing ICH Volume: Rationale and Results
Optimal treatment of ICH remains a complex and controversial issue. Anecdotal reports document frequent dramatic recovery after emergent ICH evacuation in younger patients with impending brain herniation. Older patients do not fare as well with such surgical intervention. Most of the randomized controlled trials have failed to demonstrate a superiority of craniotomy for ICH evacuation over medical therapy. Minimally invasive surgical techniques may substantially decrease hematoma volume while avoiding the morbidity of major craniotomy procedure, especially in elderly and debilitated patients. In the randomized controlled trial performed by Auer et al, ultrasound-guided endoscopic clot evacuation resulted in significantly lower mortality rates and improved clinical outcomes than medical treatment alone.

Volume of ICH is consistently shown to be a powerful predictor of poor outcome regardless of clot location, patient age, and neurological condition. Larger hematomas result in more profound and longer-lasting alterations in adjacent brain parenchyma, attributed in part to mass effect and focal edema. The rationale for evacuation of ICH is that reduction of clot volume may indeed improve neurological recovery and clinical outcome. Removal of focal mass effect may improve perfusion of compromised brain parenchyma and prevent intracranial hypertension. It also may enhance the clearance of blood breakdown products, hence preventing secondary brain edema and other potential neurotoxicity. Animal studies have in fact demonstrated that edema is diminished with the early evacuation of intracerebral clot. Other experimental studies have shown that infusion of urokinase promotes clot lysis and resorption without producing neurotoxicity, histopathological alterations, or recurrent bleeding.

Application of stereotactic surgery and minimally invasive therapies to cerebrovascular surgery has led investigators to utilize such techniques toward the goal of reducing hematoma volume in the treatment of ICH. Early attempts aimed at simple clot aspiration as well as more ingenious means of mechanical evacuation have failed to accomplish satisfactory volume reduction of ICH. This has led to the adjunct use of fibrinolytic agents as a means of enhancing clot lysis and catheter drainage. Since the first report by Doi et al, in which direct instillation of urokinase was used after stereotactic aspiration to liquefy the hematoma, several reports have followed that have favorably reported its usefulness in ICH volume reduction. In this study, ICH volume was reduced from a mean of 46 mL (range 29 to 70 mL) to a mean of 21 mL (range 14 to 51 mL). Despite variations in procedure and patient selection, this relative reduction of 57% is well in line with previously reported case series, and was typically accomplished in <72 hours from clinical onset (time until initiation of procedure plus duration of catheter thrombolysis). It is not known whether this degree and time frame of ICH volume reduction will translate into relevant clinical benefit in selected patients, or whether more rapid or complete hematoma evacuation would be required. All patients in this series had a substantially decompressed hematoma cavity (Figure 2) by the time maximal mass effect from surrounding edema would have been anticipated, and there were no instances of clinical deterioration from edema or mass associated with residual hematoma.

Inclusion and Exclusion Criteria
Much of the variability in outcomes of clinical intervention can be attributed to patient selection criteria. There is a consensus from previous studies that patients with brain stem extension of hematoma or those with neurologic signs of brain stem dysfunction have a universally poor outcome, and do not likely benefit from evacuation of ICH. We did not plan to exclude patients with normal neurological function from this protocol, although we did not encounter any patient with hematoma volume ≥25 cc and a totally normal neurological examination during the period of the study. Other studies excluded patients aged >80 years. We do not find any evidence justifying exclusion based on age alone, and hence accepted adult patients in all age groups (including 2 octogenarians), as did the recent trial by Morgenthorn et al.

Eligibility criteria of ICH volume are more controversial. The recent open surgery trial by Morgenstern et al included ICH volumes of >10 mL (20 mL in patients with GCS 15). The trial by Auer et al also considered a threshold volume of >10 mL for treatment, although therapeutic benefit appeared to be limited to lobar cases with larger ICH volume. Other studies enrolled only patients with larger ICH volumes (15 to 30 mL). We limited enrollment in this pilot study to cases with ICH volume ≥25 mL, with the major aims of verifying procedure safety and feasibility of reduction of ICH volume. It is possible that more favorable clinical outcomes may have been accomplished if patients with smaller ICH volumes had been included. We favor broader inclusion criteria to include hematoma volumes ≥15 mL in future controlled studies. It is not likely that smaller volumes of ICH will benefit from the procedure, as most such patients have a favorable outcome without intervention and the technique rarely succeeds at complete evacuation of ICH below such residual threshold.
More cases were treated in the last year of this study than in the preceding 2.5 years. This is attributed to increased confidence of referring physicians and the treating team that the procedure is not likely to cause harm nor prolong an undesirable survival against patient and family wishes. The protocol evolved from frame-based stereotactic technique toward the more facile CT-guided catheter placement. Various team members and the resident staff became more familiar with eligibility criteria and peculiarities of case management. Also, a commitment by the multidisciplinary cerebrovascular program at our institution to organize a controlled trial to evaluate this technique has resulted more recently in consideration of all eligible cases. It is anticipated that greater enrollment will be accomplished once a formal controlled study is initiated, especially as we broaden inclusion criteria to cases with smaller ICH volume. A similar period of preparation in an open registry contributed to enhanced enrollment in the recent surgery trial by Morgenstern et al.\textsuperscript{10}

\textbf{Variables in Treatment Protocol}

Other variables in treatment protocol include the surgical technique, thrombolytic agent, dosage, frequency, and end point of aspiration. Most reported studies of thrombolytic aspiration of ICH have used frame-based stereotaxy, often with general anesthesia. We initiated our protocol with frame stereotaxy, but evolved in later cases to the simpler and more facile placement of catheter under real-time CT guidance. This has avoided the obstacle of operating room scheduling and associated delays, and the definite added time involved in frame placement or fiducial calculations for conventional stereotaxy. It has also allowed more patients to be operated on under local anesthesia without airway compromise.

We have used urokinase in view of the reported case experience with this agent for more than a decade. We sought to adapt the most frequently used dosages and aspiration parameters, although it is clear that these were empirically derived and largely arbitrary. In more recent cases we escalated dosage of urokinase (5000 IU to 10 000 IU) and the frequency of aspiration from every 8 to every 6 hours. Future studies should include further controlled dose escalation to optimize effectiveness of ICH volume reduction while defining the limits of safety of the technique. The end points of thrombolytic aspiration in all prior series and in our protocol remain largely arbitrary. It is not clear whether further hematoma evacuation can be accomplished or is clinically useful beyond 48 to 72 hours. Future dose-escalation protocols should be aimed preferentially at enhancing earlier hematoma clearance rather than prolonging duration of treatment.

During the writing of this report (July 1999), a serious problem emerged regarding the purity of the only commercially available urokinase in the United States (Abbokinase, Abbott Laboratories). The US Food and Drug Administration suspended sales of this product pending assurances about legal and contaminant-free preparation of the drug (Science and Medicine. \textit{Lancet}. 1999;354:310). Recombinant synthesis tissue plasminogen activator (tPA) appears to avoid problems of impurity and may have a more rapid thrombolytic action than urokinase.\textsuperscript{14,23,32} Two clinical reports document apparent safety and similar effectiveness of tPA in 10 and 14 similarly selected ICH cases, respectively.\textsuperscript{14,32} Doses of 2 to 8 mg/d were used, with the addition of open catheter drainage system for enhanced hematoma evacuation between thrombolytic instillations. We have adapted the protocol at our institution to use tPA in doses of 2 mg at 12-hour intervals, with open catheter drainage between instillations. We have used this preliminary protocol successfully in 3 recent cases since July 1999 (Montes et al, unpublished data). Further dose-escalation studies will be required to optimize dosage and administration of this agent for hematoma evacuation and to better assess its safety.

\textbf{Thrombolysis and Hemorrhagic Risk}

The risk of recurrent hemorrhage from intracerebral infusion of urokinase has been estimated by previous authors\textsuperscript{31,33} to range from 7\% to 15\% of treated patients. Because the rebleeding risk can potentially be increased by early aspiration, several authors\textsuperscript{24,33} have suggested avoiding aspiration and thrombolysis in the initial 6 to 24 hours after ICH onset. Yamanaka and Satoh\textsuperscript{22} and Hondo et al\textsuperscript{29} reported a rebleed risk of only 3\% and 4\%, respectively, when aspiration had been carried out between 5 and 48 hours after the hemorrhage.

It is not clear whether the incidence of expanding hematoma in these above series represents any added risk from thrombolytic therapy. Frequent CT scan surveillance in the first 24 hours documents spontaneous hematoma growth in >20\% of cases, and an even greater prevalence if the first scan is performed in the first hour.\textsuperscript{17,18} Despite CT surveillance in the first day, we documented only 1 instance (8.3\%) of hematoma growth in this series, including 10 cases treated within 24 hours and 5 cases treated within 12 hours of symptomatic onset. The risk of hematoma expansion during treatment must be closely monitored in future studies, including any associated untoward clinical sequelae, but this should also be compared with the substantial risk of spontaneous hematoma expansion in the first day among untreated patients.

\textbf{Outcome Assessment: Survival Versus Disability}

Mortality has been the primary end point of therapeutic studies in most published studies, and it has ranged from 30\% to 70\%.\textsuperscript{1−3,5,10} This reflects in part patient inclusion and exclusion criteria, and to a lesser extent the treatment rendered in individual studies. In our series, there was 25\% mortality at 6 months among a cohort of patients with relatively large hematoma volume (≥25 mL). These were admittently selected, excluding deeply comatose patients and those with advance directives against heroic interventions. In fact, the 3 deaths in our series represented cases in which family wished treatment withdrawn or not escalated (denied intubation in 2 cases and cardiac pacing for arrhythmia in 1) per such advance directives. In our opinion, prior clinical trials have not articulated this issue openly, and hence the perception that invasive treatment of ICH may be used to prolong survival against family and patient wishes.
Disability levels among surviving patients may be more relevant in assessment of management outcome. It is not clear from countless cases in published uncontrolled series whether ICH evacuation in fact enhances functional recovery. Three patients (25%) in our series achieved full recovery to premorbid independent functional existence, but all harbored lobar clots, none was aged >60 years, and 2 had presented with GCS of 14 (the third presented with GCS 8). It is not clear whether these patients would have achieved similar recovery without evacuation of ICH volumes of 50, 54, and 60 mL, respectively.

None of the treated patients with ganglionic hemorrhage achieved recovery to independent existence (GOS >3), and only 1 patient was living at home at 6 months. Such outcome assessment should be supplemented in future studies by documentation of quality of life domains relevant to patient and family, and these should be compared among treated and untreated cases. This information will eventually be paramount in counseling patients and families whether to consider such intervention. Also, cost of care (acute and long term) and time until recovery may be important secondary outcome parameters that are relevant to the management of this disease. It may be advantageous to minimize stay in critical care unit and acute hospital settings even if eventual survival or disability level are not significantly altered by treatment.

In summary, we describe evolving implementation of a protocol of thrombolysis and aspiration of ICH, including eligibility criteria and technical details of case management. The procedure appears effective at decreasing ICH volume and is not associated with significant management morbidity. Further studies must assess optimal thrombolytic dosage for safety and effectiveness and must include controlled comparisons of mortality, disability outcome, quality of life, time until convalescence, and cost of care in treated and untreated patients.

References

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