Neurocritical Care

ISSN 1541-6933/05/3:237–245
DOI: 10.1385/Neurocrit. Care 2005;03:237–245

Perspectives in Thrombolysis and ICH

Frameless Stereotactic Aspiration and Thrombolysis of Spontaneous Intracerebral Hemorrhage

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Abstract

Introduction: To test the feasibility and safety of a minimally invasive technique, we report our experience in treating spontaneous intracerebral hemorrhage (ICH) patients by using frameless stereotactic clot aspiration-thrombolysis and its effects on their 30-day survival. We compared the observed cohort mortality with its predicted 30-day ICH mortality, by using previously validated methods.

Methods: Selection criteria were diagnosis of hypertensive ICH ≥35 cc, reduced level of consciousness, and no brainstem compression. Frameless stereotactic puncture/clot aspiration followed by intraclot external catheter placement was performed. Two milligrams of recombinant tissue plasminogen activator (rtPA) was administered q12 hours until ICH volume ≤10 cc, or the catheter fenestrations were no longer in continuity with the clot.

Results: Fifteen patients were treated, mean age was 60.7 years. Hemorrhage locations included basal ganglia (13), thalamic (1), and lobar (1); mean systolic blood pressure; and admission ICH volumes were 229.3 mmHg and 59.1 cc, respectively. Median time from ictus to clot aspiration/thrombolysis was 1 (range 0–3) day. Mean hematoma volume was reduced to 17% of pretreatment size. Complications were ventriculitis (6.6%) and clot enlargement (13.3%). Two patients were dead at 30 days. Median Glasgow Coma Scale (GCS) scores were 10.5 (4–15) at admission and 11.0 (3–15) at discharge. By using the most conservative estimate for analysis, probability of observing two or fewer deaths among 15 patients with an overall probability of dying calculated at 0.33 was $p = 0.079$.

Conclusions: In this selected cohort of patients with ICH, stereotactic aspiration and thrombolytic washout seemed to be feasible and to have a trend towards improved 30-day survival, when using their predicted mortality data as "historical control." Complications did not exceed expected incidence rates. Based on the experience presented here as well as previous similar reports, a larger, randomized study addressing dose escalation, patient selection, and best therapeutic window is needed.

Key Words: Intracerebral hemorrhage; intraventricular hemorrhage; thrombolysis; rtPA; clot aspiration; minimally invasive surgery.

(Neurocrit. Care 2005;03:237–245)

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Introduction

Nontraumatic, spontaneous intracerebral hemorrhage (ICH) accounts for 10 to 15% of all strokes and affects 37,000 to 52,000 people annually in the United States. The estimated overall 30-day mortality rate approaches 50% in these patients, with 62% mortality at 1 year. Of those who survive, only 20% show functional recovery at 6 months *(1,2)*. With the incidence of this disease predicted to double over the next 50 years (changing racial demographics, increasing longevity of the population), the medical and social pressure to find better therapies for these patients is growing *(1)*.

Although contemporary clinical research in the medical treatment of this subgroup of stroke victims seems to be reemerging, directed effective therapies for ICH are still lacking *(3)*. Conceptually, hematoma evacuation could positively influence the outcome of ICH patients by different mechanisms: (1) Reduction of the hematoma volume/mass could reduce the risk of abnormal cerebral elastance with subsequent elevated intracranial pressure *(4)*. (2) Because ICH volume seems to have a direct association with the volume of perihematoma brain edema, early blood clot evacuation also could help reduce the volume of perihematoma tissue swelling and its associated mass effect *(5,6)*. (3) Other noninflammatory toxic influence of blood and its degradation products on viable brain tissue adjacent to the blood clot could be minimized if hematoma evacuation is successful in reducing the exposure between these two elements (*7–19*).

For several decades, efforts to determine which is the "best" primary therapy of spontaneous supratentorial ICH, surgical or medical management, have monopolized clinical research in vascular neurology and neurosurgery *(20–26)*. In spite of substantial effort devoted to addressing this aspect of the care of patients with ICH, no clinical trial has clearly demonstrated that one form of therapy is superior to the other. Recently, this lack of a proven superior treatment has resurfaced with the release of the results from a large European multicenter trial comparing best medical therapy and best medical therapy plus surgical hematoma evacuation *(27,28)*.

In recent years, growing interest has developed in testing minimally invasive surgery (MIS) techniques to remove intracerebral hematomas *(24,29)*. Different procedures have included simple aspiration with mechanical devices such as the Archimedes screw; endoscopic evacuation of the clot; and most recently, the application of fibrinolytic agents into the hematoma after the sterotactic placement of a soft catheter *(30–38)*. Several small case series in the United States have suggested the safety and efficacy of fibrinolytic agents such as urokinase, streptokinase, and recombinant tissue plasminogen activator (rtPA) adjunctively used to enhance hematoma drainage. Although other countries have reported preliminary experience with adjunctive thrombolytic therapy for patients with ICH *(31, 39–41)*, ICH aspiration and thrombolysis in the United States remains a treatment modality largely restricted to centers specialized in the advanced treatment of stroke patients. This difference may result, in part, from the lack of randomized trial testing of this high-risk therapy versus other more conventional/standard forms of therapy in ICH patients.

The objective of the present study was to report feasibility and safety data gathered at the Sinai-Grace Hospital/Detroit Medical Center in treating selected patients with spontaneous ICH by using frameless, stereotactic aspiration and thrombolysis of the intraparenchymal clot with rtPA. As endpoints, we compared observed 30-day mortality with the predicted 30-day ICH cohort mortality independently obtained using two previously validated methods *(42,43)*.

Subjects and Methods

The cohort consisted of selected patients with ICH treated with a protocol of clot aspiration and thrombolysis by using a frameless, stereotactic method over 2.25 years. This treatment was considered an acceptable alternative to unproven open craniotomy with hematoma evacuation and best medical therapy in selected cases at Sinai Grace Hospital/Detroit Medical Center. The decision to perform clot aspiration and thrombolysis was made by a senior neurosurgeon (R.R.J.), if the following criteria were identified within 72 hours from the ictus:

1. Computed tomographic (CT) diagnosis of nontraumatic, spontaneous supratentorial ICH of ≥35 cc of volume; this ICH volume cut-off was derived from previous independent studies by Tuhrim and Broderick suggesting that mortality after ICH increases significantly when hematoma volume reaches 30 cc and larger *(42,44,45)*.
2. Reduced level of consciousness leading to incapacity to follow commands (score of 2 in the NIH Stroke scale item 1a).
3. No evidence of brainstem compression/herniation syndrome for at least 8 hours from ICH onset (to ensure neurological stability before the procedure).
4. Patient's age ≥18 years (because children are not part of the center's usual patient population).
5. No clinical or radiological evidence of primary vascular abnormality (e.g., aneurysm and arterio-venous malformation) as cause of ICH.
6. No clinical/laboratory evidence of a systemic bleeding disorder.

Although no predefined time window was used between the time the patients were first seen in the emergency department and aspiration/lysis therapy was administered, the treating team of physicians allocated every effort in expediting this complex process.

The Wayne State University Institutional Review Board approved this project. Data are retrospectively collected onto standardized abstraction forms.

Operative Technique

After initial resuscitation and radiographic evaluation, potentially eligible patients underwent repeat CT scan with fiducials by using a stereotactic protocol that used 1- or 2-mm slices that were then loaded onto a Stealth Station (Medtronic, Minneapolis, MN). The following surgical procedures were performed under general anesthesia. The patient's head was rigidly fixed in a Mayfield clamp, and a reference arc was attached to the apparatus. The fiducials were identified as landmarks on the CT scan by using the Stealth planning software. The goal of placement was to center the catheter along the main (long) axis of the clot with the tip

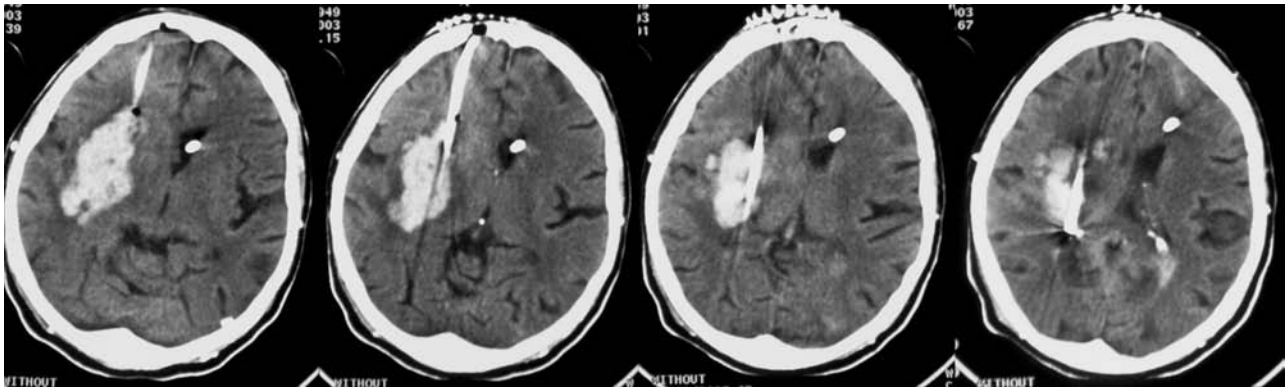

Fig. 1. Head CT scan showing intraclot catheter placement in a patient with a right basal ganglia ICH (patient 5). Note the spatial relationship between the catheter and the long axis of the blood clot.

of the catheter near the posterior end of the hematoma (Figure 1). The objective of this maneuver was to allow maximum exposure of the clot to the ports of the drainage catheter and fibrinolytic agent. Virtual elongation of the pointer was then used to determine burr hole placement and the optimal trajectory and depth to the target. Placement of the burr hole over presumed eloquent cortex was avoided in every case, and catheter trajectory through brain tissue seeming to be normal on CT was limited as much as possible. After placement of the burr hole with a perforator, the virtual pointer was placed on the dura to reconfirm the trajectory and depth. The dura was then opened and a rigid brain cannula (Medtronics) was placed along the predetermined trajectory to the desired depth. After placement of the rigid catheter, careful manual hematoma aspiration was performed. No other methods to mechanically disrupt the clot were attempted. After measuring the volume of aspirate, no more than one-half the pretreatment hematoma volume was removed due to concerns that overly aggressive aspiration could precipitate further hemorrhage. The rigid cannula was then removed, and a soft ventriculostomy-type catheter (15 cm in length; 1 to 2 mm internal diameter) (Codman, Raynham, MA) was placed along the same trajectory. In the standard fashion, a contralateral external ventricular drain (EVD) was placed at Kocher's point. Both the intraclot catheter and EVD were tunneled under the scalp and sutured in place, at the tunneling exit, with tack sutures to the scalp.

Thrombolysis Protocol

In the operating room, after confirming catheter placement by aspiration of blood, 14 of 15 patients received 2 mg rtPA (Alteplase, Genentech, San Francisco, CA) reconstituted in 2 cc of preservative-free 0.9% saline. The catheter then was irrigated with 2 cc of preservative-free 0.9% saline and then clamped from drainage for 1 hour. If the intracranial pressure (ICP) increased to 20 mmHg or more for longer than 10 minutes, the EVD was reopened with an appropriate pressure gradient while adjunctive medical therapies to control ICP were instituted. All patients were managed in a dedicated intensive care unit (ICU). Subsequent drug administration was performed using identical and sterile technique at bedside in the ICU.

Information on the ideal dose of rtPA in this clinical paradigm was extrapolated from available safety information *(37,46,47)*, such that we administered 2 mg rtPA into the clot cavity every 12 hours in the manner described above. Serial CT scans (daily or on alternate days) were performed to assess the arbitrarily chosen desired radiographic endpoint for adjunctive thrombolysis, ≤10 cc of residual ICH volume. Treatment was discontinued if the catheter fenestrations were no longer in continuity with the clot. Throughout the treatment protocol, all patients underwent close neurological and ICP monitoring by using standard EVD placed in the lateral ventricular system. The medical management of these patients followed the current recommendations formulated by the American Heart Association *(48)*. As is our usual practice, patients received daily coagulation parameter testing (e.g., prothrombin and partial thromboplastin times, platelet count). After our usual practice, patients did not receive routine antibiotic prophylaxis.

Statistical Analysis

The predicted mortality in ICH patients with or without IVH was obtained using the model designed by Tuhrim and coworkers *(42)*. Using logistic regression analysis, the 30-day survival probability (P) of ICH patients treated after standard neurocritical care practices (e.g., mechanical ventilation, osmotic therapy, EVD, blood pressure control) may be calculated with the following formula:

$$P = \frac{e^{3.125+2.7859GCS+0.0180ICH+.5832PP-.9567HYDRO+0.097IVH}}{1+e^{3.125+2.7859GCS+0.0180ICH+.5832PP-.9567HYDRO+0.097IVH}} \quad (1)$$

where PP (pulse pressure) can assume values of 0 (≤85 mmHg) or 1 (>85 mmHg); GCS (Glasgow Coma Scale) score can assume values of 0 (>8) or 1 (≤8); ICH is measured in cubic centimeters, HYDRO is expressed as 0 if hydrocephalus is absent, 1 if it is present; and IVH represents the size of the intraventricular hemorrhage in cubic centimeters. For validation purposes, a separate and independent calculation of the predicted 30-day mortality of this patient cohort was performed using the ICH score, as reported by Hemphill and coworkers *(43)*. In brief, this method assigns a 30-day mortality probability based on the following variables: GCS score, ICH volume, presence of IVH, infratentorial location of ICH, and the age of the patient. After calculating the 30-day mortality and assessing the actual

Table 1
Clinical Characteristics of Treatment Cohort

Patient	*Age/Sex*	*ICH to treatment (days)*	*Admission GCS*	*Admission ICH (cc)*	*Admission IVH (cc)*	*PP*	*HC*	*30-Day predicted mortality (Tuhrim model)*	*30-Day predicted mortality (Hemphill model)*	*30-Day actual mortality*
1	73/M	1	9	62.1	0	1	1	7.12%	26%	Alive
2	40/M	0	6	53.9	0	1	1	51.75%	26%	Alive
3	50/M	1	10	109.04	18.6	1	1	52.43%	72%	Alive
4	58/F	1	12	28.79	0	1	0	0.99%	13%	Alive
5	53/F	0	14	56.4	0	1	1	6.47%	13%	Alive
6	62/M	3	15	40.08	0	0	1	2.89%	13%	Alive
7	79/M	N/A	N/A	94.06	0	N/A	1	N/A	N/A	Dead
8	59/M	3	5	56.7	53.8	1	1	99.54%	72%	Alive
9	80/M	1	13	107.7	37.8	0	1	79.93%	72%	Alive
10	86/F	1	11	77.06	0	1	1	2.51%	72%	Alive
11	64/F	2	6	43.8	5.05	0	1	45.00%	72%	Alive
12	28/M	1	14	54.1	0	1	1	6.23%	13%	Alive
13	54/F	2	4	36.55	14.91	1	1	54.90%	97%	Dead
14	64/M	2	9	41.83	0	0	1	2.88%	26%	Alive
15	60/M	1	11	23.5	0	1	1	3.69%	13%	Alive

PP, pulse pressure: 0, ≤85 mmHg; 1, > 85 mmHg; HC, hydrocephalus: 0, absent; 1, present; M, male; F, female; N/A, not available.

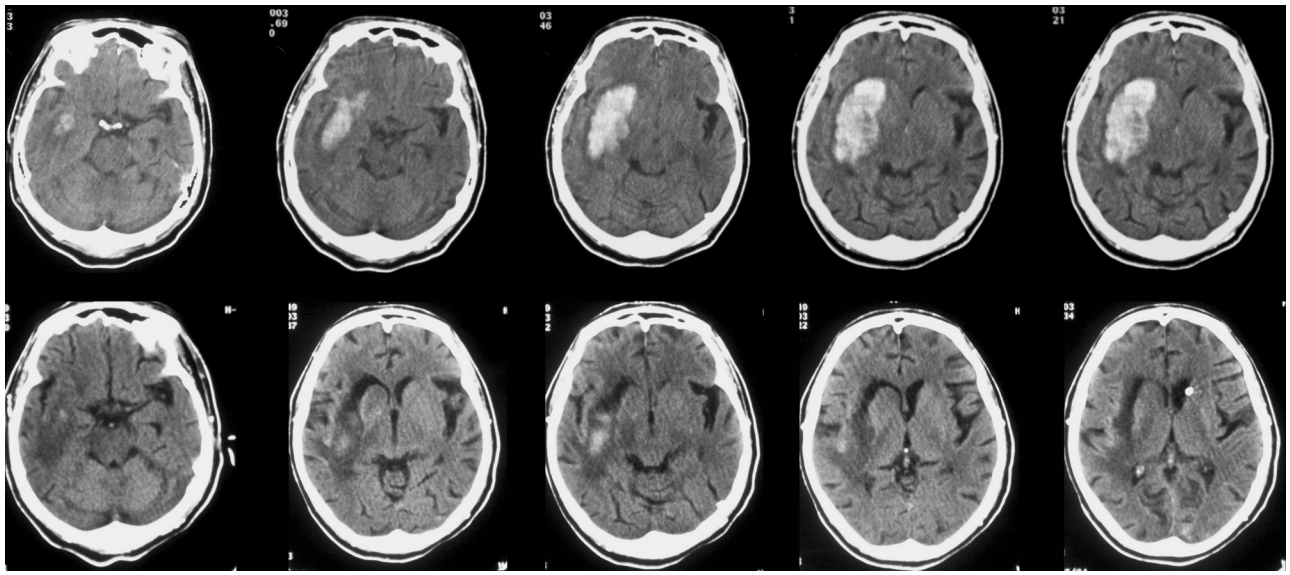

Fig. 2. (Top) Admission head CT scan in a patient with a right basal ganglia hypertensive ICH (patient 5). **(Bottom)** Head CT scan 13 days later, after clot aspiration and thrombolysis, demonstrating near-complete clot resolution.

mortality rate for the cohort, comparison was performed using the exact hypothesis test for binomial random variables to calculate the probability of obtaining the number of deaths observed, or fewer, under the predicted mortality rate, and accepting statistical significance only if $p < 0.05$.

Measurement of Intraparenchymal and Intraventricular Hematoma Volumes

Using the software ImageJ for Macintosh (version 1.32e, Wayne Rasband, National Institutes of Health, Bethesda, MD), volume measurements of blood clots were performed according to their specific signal density on head CT slices. The boundaries of the hematoma areas were traced by hand on each slice by one of the investigators (J.R.C.). The cross-sectional area of each slice was then multiplied by the slice thickness and added to give the total hematoma volume.

All image analyses were performed on a Powerbook G4 computer (Apple Computer, Cupertino, CA).

Results

Relevant demographic, clinical, and neuroradiological characteristics of the study cohort are summarized in Table 1.

Demographic Features

Over 28 consecutive months, approximately 110 patients with diagnosis of ICH were screened. Fifteen patients were treated using the described protocol. Ten patients were male and five female, and their mean age was 60.7 (range 28–86; SD ± 15.2) years.

Clinical Features

Limited clinical information was available for review in one patient (patient 7). All 15 patients had premorbid hypertension. The location of the hematoma was thalamic (1 patient), lobar (1 patient), and basal ganglia (13 patients). The median GCS on admission was 10.5 (range 4–15; SD ± 3.6), 4 patients had a GCS ≤8 and 11 patients had a GCS >8. The mean systolic blood pressure on admission was 229.3 mmHg (range 160–300; SD ± 44.7); mean diastolic blood pressure was 125.5 mmHg (range 90–170; SD ± 24). One patient developed ventriculitis. The ICH drain remained in place 7.9 days (range 4–15; SD ± 3.6). One patient (patient 3) required repositioning of the ICH drain during the study period. There were two deaths in the entire cohort. Care was not withdrawn or withheld in any of the 15 patients. The median GCS at the time of discharge was 11.0 (n = 14; range 3–15; SD ± 3.5).

Laboratory Features

None of the patients had a bleeding diathesis. The mean coagulation parameters throughout the study behaved as follows: International Normalized Ratio (INR) 1.3 (n = 12; range 1.0–2.3; SD ± 0.3); platelet count 264.0×10^3/cc (n = 15; range 200–335; SD ± 44.6), and partial thromboplastin time (PTT) 25.4 seconds (n = 12; range 13.2–29.4; SD ± 4.6) in nine patients in whom serial coagulation studies were available for analysis.

Neuroradiological Features

The mean ICH volume was 59.1 cc (range 23.5–109; SD ± 26.8). Intraventricular hemorrhage was present in five patients, with a mean IVH volume of 8.7 cc (range 0–53.8; SD ± 16.4). No intraventricular thrombolysis was administered in this patient cohort. Radiological and clinical evidence of ICH enlargement occurred in patients 7 and 15 (13.3% of the entire cohort). Mean residual hematoma was 69.3% (range 16–126.1; SD ± 30) of the pretreatment hematoma volume at 24 hours and 17% (range 1–57.5; SD ± 16.2) at the end of treatment (Figures 2 and 3). Two patients (patients 6 and 8) demonstrated radiological evidence of nonenlarging, peri-intraventricular catheter tract contusion/hematoma during the study period (Figure 4); however, no such instances were recorded in the vicinity of the intraclot drain.

Treatment

All 15 patients received rtPA for a mean of 4.8 days (range 2–10; SD ± 2.3). The median time from ictus to clot aspiration and thrombolysis treatment was 1 day (range 0–3; SD ± 0.92). During the treatment period, patients received a mean of 14.7 mg (range 6–30; SD ± 8.6) rtPA. Besides two patients with enlargement of the ICH, no other clinical or laboratory-based evidence of central nervous system or systemic bleeding was encountered throughout the study period in the remainder of the patient cohort.

30-Day Outcome

First we calculated the overall predicted probability of dying as follows: If a patient's calculated probability of dying (expressed as a percentage) was ≤50%, this patient was predicted to survive; if the patient's probability of dying was >50%, this patient was predicted to die. After dichotomizing outcomes in this manner, and by using a conservative approach (in view of insufficient clinical data to reliably calculate the predicted 30-day mortality) in assuming that patient 7, who died, would have been predicted to survive, we obtained predicted 30-day mortality >50% in 5 of 15 patients (cohort probability of dying at 30 days of 33.3%) by using Tuhrim's model. Using the same dichotomized outcomes approach, an even larger 30-day predicted mortality (40%) was independently obtained using the prediction model reported by Hemphill and coworkers (Table 1). Because of the methodological limitations of our study (small sample size and retrospective nature), we decided to use the most conservative estimate (30-day mortality prediction 33.3%) for the subsequent statistical analysis. By using the exact hypothesis tests for binomial random variables, the probability of observing two or fewer deaths among 15 patients if their overall probability of dying was 0.333 is $p = 0.079$.

Discussion

We report preliminary feasibility and safety data based on our experience with frameless, stereotactic aspiration and thrombolysis of spontaneous ICH in 15 patients treated at a university-affiliated hospital. There was a trend towards improved 30-day survival. The possible complications of this form of treatment (ventriculitis and hematoma enlargement) did not exceed their expected incidence.

Current therapies available to ICH patients include general critical care for airway protection and ventilator management (if needed) as well as aggressive and invasive blood pressure control and monitoring *(48)*. When clinically relevant, cerebral edema is routinely treated with hyperosmolar therapy (e.g., mannitol) and hyperventilation (if the patient

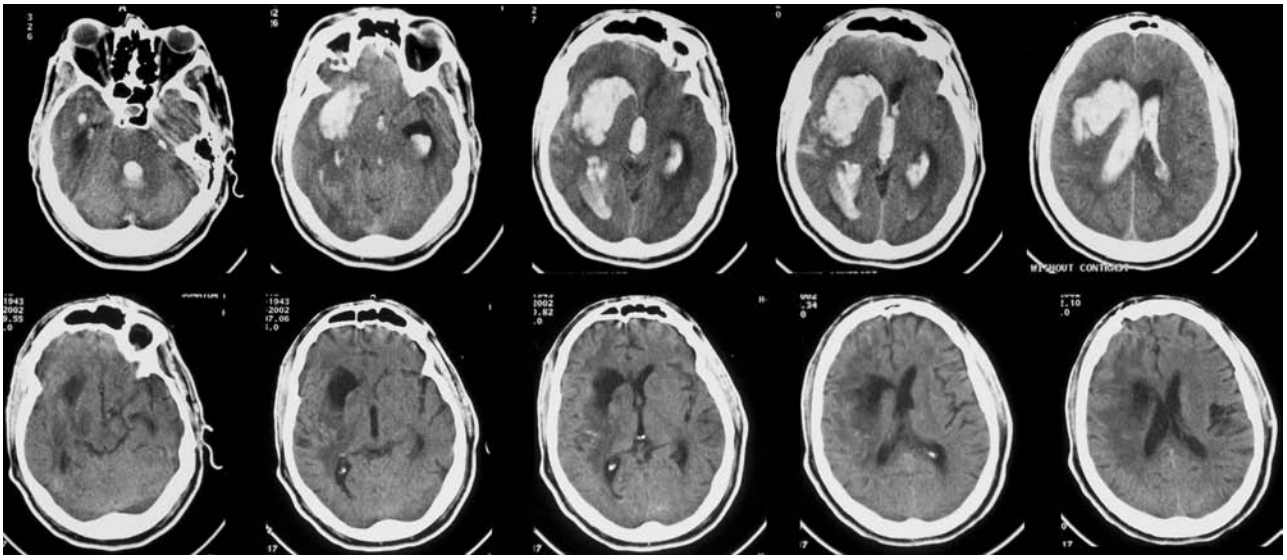

Fig. 3. (Top) Admission head CT scan in patient 8 demonstrating a right basal ganglia ICH with IVH involving the entire ventricular system. **(Bottom)** Head CT scan 14 days later after clot aspiration and lysis with rtPA. Note the complete resolution of the ICH and IVH. No intraventricular thrombolysis was administered in any of the 15 patients reported here.

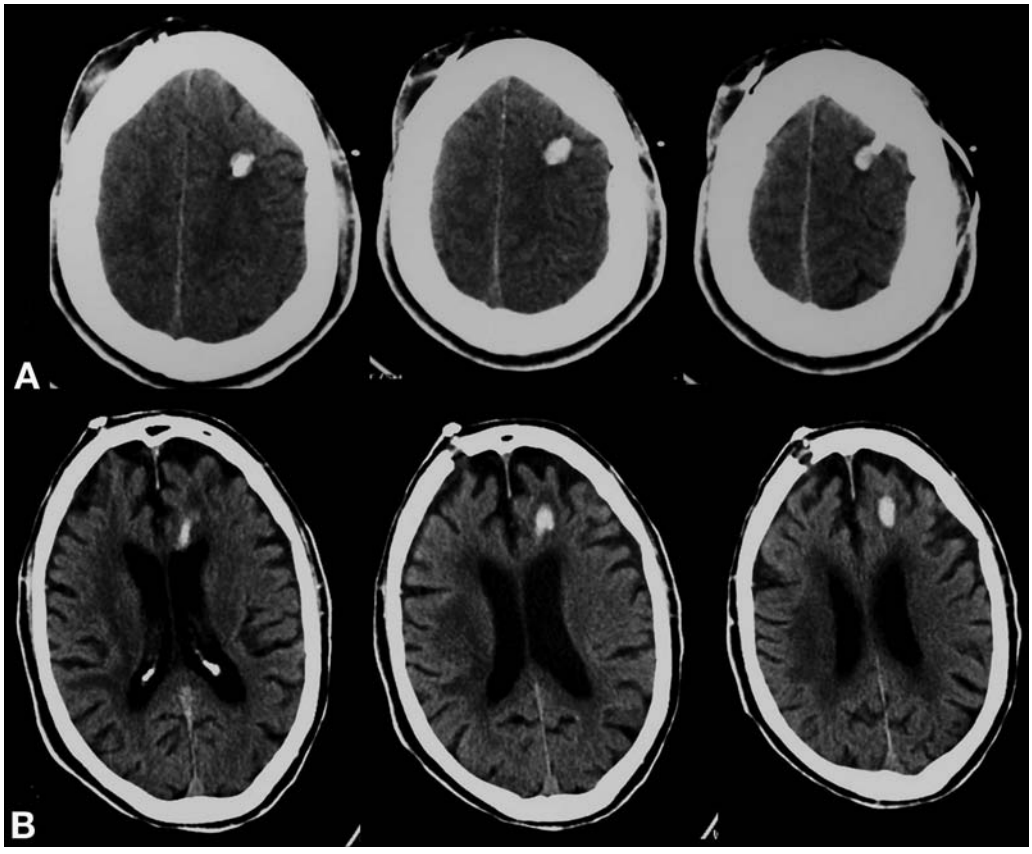

Fig. 4. Head CT scans demonstrating *de novo* development of periventriculostomy contusions in two patients (**A**, patient 6; **B**, patient 8). Of note, the contusions were contralateral to the intraparenchymal hemorrhage and to the intraclot catheter.

is intubated and ventilated) *(4)*. Elevated intracranial pressure is monitored and treated using EVD. Although surgical treatment for supratentorial hematomas has been tested as an individual neurosurgeon's "best available treatment" option for several decades, individual study results as well as recent meta-analyses comparing surgical hematoma evacuation and best medical therapy alone have failed to define a beneficial role for surgery in patients with spontaneous ICH *(49)*. Any possible benefits of ultraearly craniotomy were overshadowed by an alarmingly elevated rate of hematoma expansion in a clinical trial conducted in the United States comparing these two treatment modalities *(50)*. Alternative methods of hematoma evacuation have become the subject of research in an attempt to minimize the morbidity and mortality induced by the mass effect of the hematoma and the toxicity induced by blood degradation products *(10,14–18)*.

Minimally invasive surgery has been successfully used for some time in Japan as an alternative method to craniotomy and hematoma evacuation in this group of stroke patients *(31,39–41)*. However, its implementation in the United States has been delayed until recently. Several open label trials with urokinase *(34)* or rtPA *(51)* in the treatment of ICH patients have repeatedly suggested the safety and efficacy of ICH aspiration and thrombolysis. Based on recent experience with rtPA in the treatment of IVH *(52)*, the use of 2 mg rtPA every 12 hours administered via a flexible catheter embedded in the clot was deemed safe and likely to induce effective clot lysis. We observed two instances of hematoma enlargement (13.3%) that developed within the first 24 hours from treatment onset. Although the natural history of ICH growth within the initial 24 hours reaches 33%, as demonstrated by Brott and coworkers *(53)*, the delayed occurrence of this complication in our patient cohort could relate to the lytic therapy. Therefore dose-escalation studies should follow to identify the best safety and efficacy profile of this form of treatment *(54)*. Dosing studies also become especially important when assessing the safety of this novel form of treatment, because amplification of blood-induced neurotoxicity triggered by rtPA has been reported *(10)*.

External ventricular drainage introduces a risk of cerebrospinal fluid (CSF) colonization and infection of approximately 5 to 6% *(55)*. In the present cohort of ICH patients, 1 of 15 patients (6%), all of whom required conventional EVD for ICP monitoring and CSF drainage in addition to the intraclot catheter, did develop ventriculitis. Two instances of de novo, peri-intraventricular drain contusion/hematoma were observed, raising the possibility that passage to the ventricles and tracking of rtPA through the ventriculostomy tract could increase the risk of such a complication. Further studies in larger groups of patients should give more insight into the etiology of periventriculostomy contusions/hematoma.

Conclusions

The current report suggests that minimally invasive clot aspiration and thrombolysis in patients with supratentorial spontaneous ICH is feasible. Safety concerns of delayed hematoma enlargement when using this form of therapy need to be further addressed in larger patient groups. The observed trend toward an increased chance of surviving at 30 days after the ictus compared with the predicted mortality in the same group of patients seems to suggest a treatment effect. Our results should be incorporated with recent reports suggesting a beneficial impact of this form of treatment on the outcome of ICH patients *(46,51)*. We, however, acknowledge the limitations of the small number of patients. Furthermore, we recognize that critical care alone could have played a different role during the study period than in 1998, when the validation of the formula used in this study to calculate the predicted mortality of our patients was first reported. Nevertheless, we put forth the hypothesis that MIS and clot aspiration-thrombolysis by using rtPA are feasible and also could have the potential to favorably modify survival and perhaps neurological function after ICH. Future randomized studies are needed to test the clinical efficacy of this alternative form of treatment. Also, the dose escalation aspects of this novel form of therapy need to be investigated in larger groups of ICH patients to clarify the seemingly increased risk of delayed hematoma enlargement we report here.

Acknowledgments

W.M.C. is partially supported by National Institutes of Health/National Institute of Neurological Disorders and Stroke R01-38905. D.F.H. is partially supported by FD-R-001693 and FD-R-002018-01.

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