Major Clinical Trial

Low-Dose Recombinant Tissue-Type Plasminogen Activator Enhances Clot Resolution in Brain Hemorrhage
The Intraventricular Hemorrhage Thrombolysis Trial

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Background and Purpose—Patients with intracerebral hemorrhage and intraventricular hemorrhage have a reported mortality of 50% to 80%. We evaluated a clot lytic treatment strategy for these patients in terms of mortality, ventricular infection, and bleeding safety events, and for its effect on the rate of intraventricular clot lysis.

Methods—Forty-eight patients were enrolled at 14 centers and randomized to treatment with 3 mg recombinant tissue-type plasminogen activator (rtPA) or placebo. Demographic characteristics, severity factors, safety outcomes (mortality, infection, bleeding), and clot resolution rates were compared in the 2 groups.

Results—Severity factors, including admission Glasgow Coma Scale, intracerebral hemorrhage volume, intraventricular hemorrhage volume, and blood pressure were evenly distributed, as were adverse events, except for an increased frequency of respiratory system events in the placebo-treated group. Neither intracranial pressure nor cerebral perfusion pressure differed substantially between treatment groups on presentation, with external ventricular device closure, or during the active treatment phase. Frequency of death and ventriculitis was substantially lower than expected and bleeding events remained below the prespecified threshold for mortality (18% rtPA; 23% placebo), ventriculitis (8% rtPA; 9% placebo), symptomatic bleeding (23% rtPA; 5% placebo, which approached statistical significance; $P=0.1$). The median duration of dosing was 7.5 days for rtPA and 12 days for placebo. There was a significant beneficial effect of rtPA on rate of clot resolution.

Conclusions—Low-dose rtPA for the treatment of intracerebral hemorrhage with intraventricular hemorrhage has an acceptable safety profile compared to placebo and historical controls. Data from a well-designed phase III clinical trial, such as CLEAR III, will be needed to fully evaluate this treatment.

Clinical Trial Registration—Participant enrollment began before July 1, 2005.

(*Stroke*. 2011;42:3009-3016.)

Key Words: intracerebral hemorrhage ■ intraventricular hemorrhage ■ tissue-type plasminogen activator ■ thrombolysis

Among the different stroke subtypes, brain hemorrhage has a disproportionately high mortality rate. Mortality rates for patients with intracerebral hemorrhage (ICH) with an associated intraventricular hemorrhage (IVH) range from 50% to 80%.[1,2] Animal models demonstrate substantial physiological and functional benefits associated with the early removal of blood clots from either the ventricle or the intraparenchymal spaces.[3–5] Small trials have demonstrated the feasibility of a minimally invasive technique using intraventricular catheters and low-dose thrombolytics, and suggest clinically significant benefits in terms of reduced mortality.[6–9] However, little attention has been given to measuring the efficacy of clot removal.[10–12]
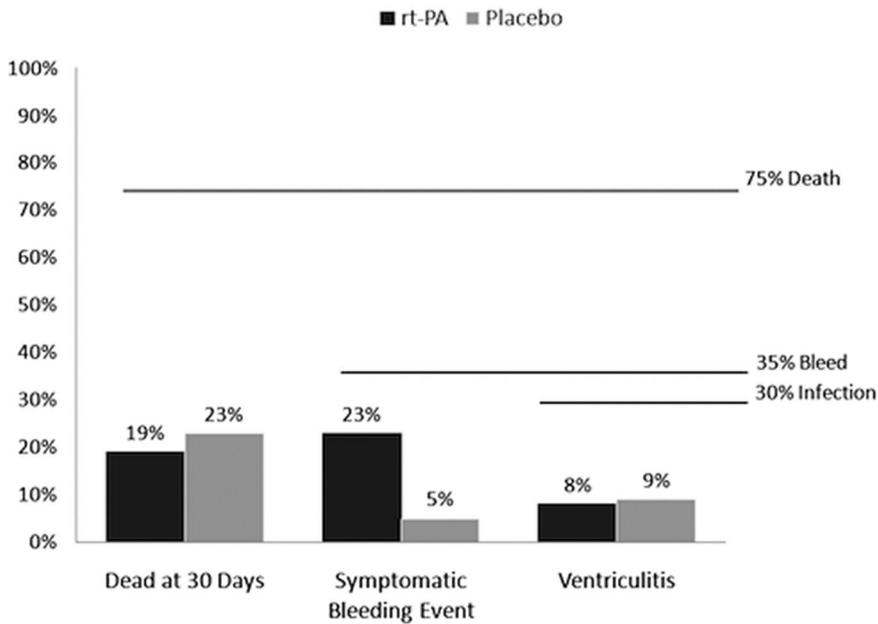
■ rt-PA ■ Placebo

Figure 1. Prespecified safety triggers and events. None was significant (death at 30 days, $P=1.00$; symptomatic bleeding event, $P=0.106$; ventriculitis, $P=1.00$).

This study was designed primarily to assess the safety of low-dose recombinant tissue-type plasminogen activator (rtPA) administered via extraventricular drainage catheter in the treatment of ICH with massive IVH, in terms of mortality, ventricular infection, and bleeding events. In addition, we tested the secondary hypothesis that administration of 3 mg of rtPA via external ventricular device (EVD) every 12 hours increases the rate of intraventricular clot lysis compared to placebo-irrigated (normal saline) catheters.

Patients and Methods

Patient Selection

The study was conducted at 14 neurocritical care centers using a uniform protocol approved by the Institutional Review Boards at each participating center (FDA IND 8523). Inclusion criteria were patients 18 to 75 years of age who experienced a small supratentorial ICH ($\leq$30 mL) with massive IVH with an EVD already placed for treatment of obstructive hydrocephalus, per standard of care, and could be randomized within 24 hours of diagnostic CT showing IVH. Thus, no patients were exposed to the risk of an EVD insertion if they would not otherwise have one. A CT scan performed after EVD placement to demonstrate clot stability and proper EVD placement. Exclusion criteria included presence of infratentorial or subtentorial parenchymal bleeding, pregnancy, radiological evidence of arteriovenous malformation, aneurysm, or tumor as a source for the ICH and evidence of coagulopathy (international normalized ratio >1.7; platelet count <100 000).

Clinical Protocol

Subjects were randomized to receive either 3 mg/3 mL of rtPA or 3 mL of normal saline injected via the EVD into the ventricular spaces. CT scans were performed daily to monitor for asymptomatic bleeding and measure clot resolution while the subject received rtPA/placebo administrations and once between days 28 and 32 after enrollment. The rtPA/placebo administration was continued every 12 hours until CT evidence of clot resolution was sufficient to remove the catheter (at a minimum the opening of the third and fourth ventricles) or until a safety end point (symptomatic bleeding, infection, or death) occurred, whichever came first. Data on well-established ICH severity factors were collected at time of presentation.[2] Daily monitoring for serum coagulation factors and infection markers in the cerebrospinal fluid was undertaken. Subjects were monitored for blood pressure, temperature, and cerebral perfusion pressure fluctuations every 8 hours, and for ICP elevation every 4 hours while receiving rtPA/placebo. Functional outcome assessment was performed by a blinded observer.

Test Article Administration

Activase (Alteplase; rtPA) is a sterile lyophilized preparation intended for intravascular infusion. Genentech provided the Activase for the trial in the form of 50-mg vials labeled for investigational use. Drug was reconstituted with sterile water to yield a solution that contained 1 mg of Activase per mL. The Activase and a 4-mL normal saline flush were prepared in sterile syringes and delivered to the intensive care unit. At each site, pharmacists used a strict sterile reconstitution and preparation protocol. An isovolumetric administration technique was used with cerebrospinal fluid aspirated before dosing. Compliance with dosing and administration mechanics was high for the entire cohort, with 553 of 575 planned doses (96%) administered. Those administering study medication and nursing personnel were blinded to whether the patient received rtPA or placebo.

Adverse Event Monitoring

All adverse and end point events were determined by the site investigator and validated by site visit. Adverse events were then reviewed by the coordinating center and the Principal Investigator using standard Good Clinical Practice definitions (21 Code of Federal Regulations, Part 312, Investigational New Drug Application). End point events were reviewed by the PI and then reviewed in a blinded manner by an end point committee consisting of the study quality assurance monitor, an intensivist-neurologist, a neurosurgeon, and a coordinator.

Safety Monitoring

All adverse events and end points were reviewed in an unblinded manner by an independent Data Safety and Monitoring Board (DSMB) consisting of 2 neurologists, a neurosurgeon not associated with the study, and the study statistical consultant. The following were prespecified to trigger early Data Safety and Monitoring Board analysis and possible study suspension: 30-day survival <25%, a symptomatic rebleeding (clot enlargement with concurrent decline in Glasgow Coma Scale [GCS] of >2) rate >35%,[13] and an infection (fever and positive cerebrospinal fluid culture) rate >30% (Figure 1).[14]

CT Hemorrhage Volume Analysis

On completion of the study, CT scan copies were sent to a central location for analysis by a neuroradiologist blinded to treatment

assignment. The CT reader demarcated all areas of ICH and IVH clot on each slice. IVH and ICH volumes were determined using a modification of the axial CT volume analysis method of Steiner et al.[15] Within each CT slice, custom software was used to determine the pixel count within the marked areas while outlined against a back-lit digitizing tablet (model A56BL with Macintosh Accessory Kit; Numonics). This pixel count was multiplied by area per pixel to obtain the cross-sectional area within the marked portion of that slice. Volume was calculated as the product of this area and the collimation width of the slice. The total volume of interest was calculated as the sum of volumes within all slices. The intraobserver variability in volume determinations with this method has been <1.5%.[16]

Clot Resolution Rate
Random-effects linear regression was performed to examine whether receiving rtPA resulted in a different rate of clot resolution than placebo. IVH volumes from all head CT scans performed during the 4 days immediately after the stability CT were used, with clot volumes standardized as a percent of the stability CT IVH volume. Interaction terms between receiving active drug and time since stability scan were created.

GCS Score and Clot Resolution Rate
Random-effects linear regression was also performed to examine whether a patient's rate of clot resolution was associated with short-term (96 hours) change in level of consciousness, based on change in GCS from the GCS recorded closest in time to the start of treatment. Preference was given to scores from before the start of treatment if measured within 2 hours of treatment. Individual rates of clot resolution were estimated for each patient using CT scans performed during the first 5 days after the stability CT scan. For this analysis, we used CT scans from the first 5 days rather than the shorter time periods used in the analyses described to enable us to better-capture the considerable variation in individual rates of clot resolution. All patients, both rtPA–treated and placebo-treated, who survived without symptomatic rebleed were included. Factors independently associated with change in level of consciousness, such as initial GCS score, were also considered. Because change in GCS over time was not expected to be uniform, higher-order terms for time were examined and included when significant.

Deaths and symptomatic rebleeding events, which typically result in cessation of treatment, might have biased the result because of "informative" rather than "at random" censoring of both GCS and clot resolution data. To avoid this problem, the analysis was limited to patients who were successfully treated, defined as those surviving and not experiencing a symptomatic rebleed event (n=36). One additional patient who did not have GCS readings recorded after admission was excluded from this analysis. On average, 11.6 GCS readings (range, 1–14) were available for each patient.

Statistical Methods
Categorical baseline characteristics and frequencies of adverse events were compared by treatment using Fisher exact test. Ordinal variables and non-normally distributed continuous variables were compared using the Wilcoxon rank-sum test and normally distributed continuous baseline characteristics were compared using Student t test. The outcome measure, percent clot resolution rate, was estimated and compared by treatment assignment using random-effects generalized least-squares regression with the consistency of the estimates evaluated using the Hausman specification test.

All statistical analyses were performed using STATA statistical software (STATA), with tests being 2-tailed. $P \leq 0.05$ was considered to indicate statistical significance.

Results

Patient Characteristics
Forty-eight patients were randomized to twice daily (every 12 hours) isovolumetric injections of either 3 mg intraventricular

Table 1. Patient Characteristics

Characteristic	Placebo (N=22)	rtPA (N=26)	Total (N=48)	P*
Mean age (SD)	56.5 (1.6)	54.1 (2.4)	55.2 (1.5)	0.45†
Male (%)	31.8%	73.1%	54.2%	0.008
Black, not Hispanic	45.5%	65.4%	56.2%	
Asian/Pacific Islander	4.6%	11.6%	8.3%	
White, not Hispanic	31.8%	11.6%	20.8%	
Hispanic	18.2%	11.6%	14.6%	0.26
History of hypertension	86.4%	76.9%	81.2%	0.48
History of diabetes mellitus	13.6%	26.9%	20.8%	0.31
History of seizures	0.0%	0.0%	0.0%	…
History of migraine	0.0%	3.8%	2.1%	1.00
History ETOH	18.2%	15.4%	16.7%	1.00
History of tobacco use	18.2%	11.6%	14.6%	0.69
History of illicit drug use (cocaine)	9.1%	11.6%	10.4%	1.00

ETOH indicates ethanol; rtPA, recombinant tissue-type plasminogen activator; SD, standard deviation.

*Fisher exact test for all variables except age.

†t test.

rtPA (n=26) or vehicle (n=22). Demographic characteristics of study subjects are presented in Table 1. Only gender was not distributed evenly across treatment groups, (rtPA group 73% versus placebo 32%, male subjects). Presenting clinical and disease severity characteristics are displayed in Table 2. Severe hypertension and decreased levels of consciousness characterized the entire population. Severity factors, including admission GCS, ICH volume, IVH volume, and admission blood pressure, were evenly distributed across the 2 groups. The location of primary ICH favored deep paramedian regions such as caudate, globus pallidus, putamen, and thalamus. The treatment goal of early initiation, ie, no sooner than 12 hours and no later than 24 hours from the CT scan diagnosing the IVH, was achieved in 47 of 48 subjects.

Initial Emergency Care
Emergency care did not differ between treatment groups. On average, time from symptom onset to emergency department arrival was 4 hours, and initial diagnostic CT was performed within 50 minutes of arrival. Time from diagnostic CT to complete a ventricular catheter insertion was 6.1±5.8 hours; time from EVD insertion to postinsertion stability CT scan was 6.8±7.0 hours; and time from stability CT scan to first dose of rtPA/placebo was 7.8±6.8 hours. ICP was generally well-controlled throughout the entire treatment period. Neither ICP nor cerebral perfusion pressure differed substantially between treatment groups on presentation, with EVD closure, or during the active treatment phase.

Test Article Administration
The average duration of dosing did not differ significantly: 10.2±8 days for rtPA and 12.7±8.4 days for placebo. However, a trend toward a shorter dosing period can be seen, with the median duration of dosing being 7.5 days for rtPA and 12 days for placebo. Dosing with test article required

Table 2. Initial Patient Severity

	Placebo (N=22)	rtPA (N=26)	Total (N=48)	P*
SBP	189.0 (7.3)	191.0 (7.4)	190.1 (5.2)	0.85
DBP	101.2 (5.7)	105.6 (5.6)	103.6 (4.0)	0.58
MAP	130.5 (5.9)	134.1 (5.9)	132.4 (4.2)	0.67
PP calculated (SBP−DBP)	87.9 (4.5)	85.4 (4.6)	86.5 (3.2)	0.71
ICP	9.0 (1.6)	11.8 (1.0)	10.5 (0.9)	0.14
CPP	86.7 (3.4)	90.7 (4.3)	88.8 (2.7)	0.47
GCS, median (IQR)	7 (4.8–9.0)	8 (5.0–10.3)	7 (5–9.8)	0.44†
Admit NIH Stroke Scale, median (IQR)	25 (13.0–32.0)	24 (17.0–37.0)	24.5 (15.3–32.8)	0.46†
ICH volume, median (IQR)	7.9 (0–21.4)	7.2 (0.7–12.7)	7.5 (0–16.7)	0.54†
IVH volume	50.1 (6.7)	54.8 (5.8)	52.7 (4.4)	0.60
IVH grade, median	15.5 (12.5–17.3)	15 (12.0–17.0)	15 (12.3–17.0)	0.69†
Subarachnoid hemorrhage	0%	0%	0%	…
Location of ICH				0.34
No ICH	6 (27.3%)	4 (15.4%)	10 (20.8%)	
Caudate	2 (9.1%)	7 (26.9%)	9 (18.8%)	
Globus pallidus	0 (0.0%)	2 (7.7%)	2 (4.2%)	
Putamen	3 (13.6%)	3 (11.5%)	6 (12.5%)	
Thalamus	11 (50.0%)	10 (38.5%)	21 (43.8%)	
Mean predicted mortality‡ (actual mortality)	74.52% (23%)	74.49% (19%)	74.5% (21%)	<0.00001§

Data shown are mean (SD) or median (IQR).

CPP indicates cerebral perfusion pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; ICP, intracranial pressure; IQR, interquartile range; IVH, intraventricular hemorrhage; MAP, mean arterial pressure; NIH, National Institutes of Health; PP, pulse pressure; rtPA, recombinant tissue-type plasminogen activator; SBP, systolic blood pressure; SD, standard deviation.

*t test for normally distributed continuous variables, Wilcoxon rank-sum test for ordinal and all non-normally distributed continuous variables, and Fisher exact test for categorical variables.

†Wilcoxon rank-sum test.

‡Tuhrim S, Dambrosia JM, Price TR. Intracerebral hemorrhage: external validation and extension of a model for prediction of 30-d survival. *Ann Neurol.* 1991;29:658–663.

§Represents the binomial probability of actual death rate occurring given the predicted injury severity.

closure of the catheter for 1 hour to test the clot lysing abilities of rtPA. Catheter closure was well-tolerated with ICP increasing from 12.8 to 17.8 mm Hg for rtPA patients and 11.5 to 16.7 mm Hg for placebo patients. The median number of test article injections was 11 injections, and the mean was 12.0. On 15 of 575 occasions, the catheter was opened before 1 hour to control ICP. Elevated ICP with IVC closure occurred rarely, and compromise of cerebral perfusion pressure was even less frequent with IVC closure. The percentage of closure-related elevations >30 mm Hg was 8% (46/575), 10.3% (28/272) in the rtPA group, and 5.9% (18/303) in the placebo group. Decreases of cerebral perfusion pressure <60 mm Hg showed a similar pattern of 3% (18/575), 1.8% (5/272) in the rtPA group, and 4.3% (13/303) in the placebo group.

Four patients underwent craniotomy for uncontrolled intracranial hypertension not responding to drainage and medical management; each case was associated with an episode of intracranial bleeding, as determined by central analysis of serial CT scans (3 rtPA, 1 placebo). In 3 cases, surgery was successful providing long-term control of ICP.

Safety Hypothesis

Mortality, bleeding events during the treatment period, and ventriculitis represented the prespecified safety outcomes against which treatment was judged as our primary goal. Frequency of events was substantially lower than expected for death and ventriculitis and remained below the prespecified threshold for bleeding (Figure 1). Predicted (30-day) mortality using a well-validated severity algorithm[17,18] was 75% for both treatment groups (Table 2). Actual mortality was 19% in the rtPA–treated group and 23% in the placebo group. Ventriculitis occurred among 8% and 9%, respectively, of those groups and symptomatic bleeding was reported for 23% of the rtPA–treated group and 5% of the placebo group. Asymptomatic bleeding demonstrated a similar trend, with 5 events in the rtPA and 2 in the placebo group. Adverse events were frequent in both study groups (Table 3). They were generally similar between groups except for an increased frequency of respiratory system events in the placebo-treated group. None of these differences reached statistical significance. However, differences in the symptomatic bleeding event rate approached statistical significance (P=0.1).

Death was attributed directly to initial hemorrhage in 9 of the 10 reported deaths. The remaining death was attributed to a delayed mass effect and herniation event. Primary and secondary causes of death include delayed mass effect (5), withdrawal of care attributed directly to initial hemorrhage

Table 3.   Adverse Events

No. of Patients With	rtPA	Placebo	P
Any adverse event	18 (69.2)	20 (90.9)	0.084
Any serious adverse event	16 (61.54)	8 (36.36)	0.147
No. of patients with events by body system			
Nervous system	14 (53.9)	9 (40.9)	0.401
Nervous system hemorrhage	10 (38.5)	3 (13.6)	0.101
General body system/ miscellaneous	10 (38.5)	12 (54.6)	0.384
Digestive system	1 (3.9)	1 (4.6)	1.000
Cardiovascular system	6 (23.1)	6 (27.3)	0.751
Respiratory system	10 (38.5)	15 (68.2)	0.049
Endocrine/metabolic system	1 (3.9)	4 (18.2)	0.165
Heme/lymphatic system	0 (0.0)	1 (4.6)	0.458
Urogenital	2 (7.7)	3 (13.6)	0.649

rtPA indicates recombinant tissue-type plasminogen activator.

(5), rebleeding (2), renal failure (1), ventriculitis (1), hypertension (1), increased ICP (1), ischemia (1), vasospasm (1), and brain death (1).

Clot Size Reduction Hypothesis

The rate of blood clot resolution was significantly greater in the rtPA–treated patient group (18% per day versus 8% per day for placebo-treated patients; $P<0.001$; Figure 2). This was associated with a higher rate of successful removal of catheter at the end of rtPA/placebo administration (50% versus 20%), less reliance on ≥ 3 EVD (4% versus 32%), and a shorter length of treatment.

Improved 30-day outcomes for rtPA–treated patients were observed for all prespecified functional outcome measures,

Figure 2. Rates of clot reduction tissue-type plasminogen activator (tPA) vs control, shown with 95% confidence intervals. Note the rate for reduction with tPA diverges from placebo within 2 days ($P<0.001$).

such as Glasgow Outcome Scale ≤ 2 (57% rtPA versus 64% placebo), modified Rankin Scale score ≤ 4 (52% rtPA versus 27% placebo), National Institutes of Health Stroke Scale ≤ 10 (54% rtPA versus 29% placebo), and Barthel Index score ≥ 80 (19% rtPA versus 18% placebo). None of these differences reached statistical significance.

Effect of rtPA and Time on Clot Resolution

Estimates of the rate of clot resolution over the 4 days after the stability CT were based on 147 CT scans. The estimated IVH volume as a percentage of IVH volume on stability CT was as follows:

$$IVH \% \ volume = 96.97 - (7.93*t) + (21.42*rtPA)$$

$$- (34.10*rtPA*t) + (5.57*rtPA*t^2)$$

where t indicates time in days since stability CT, up to 4 days, and rtPA equals 1 if treated with rtPA and equals 0 if treated with placebo. The terms are all statistically significant, and composite testing of the 3 rtPA terms with a Wald test had a χ^2 (3 degrees of freedom) of 29.39 ($P<0.001$). Estimated volumes for each group over time based on this analysis are shown in Figure 2 with 95% confidence intervals. As seen in Figure 2, much of the lysing activity in the rtPA group occurs during the first 3 days. Since time to remove blood clot may be an important treatment variable; furthermore, because the rtPA effect on clot resolution is nearly constant over time for the first 3 days, we performed a further analysis limited to the first 3 days. Estimated resolution for rtPA–treated patients over this period was 22.3% per day (95% confidence interval, 16.7%–28.0%) and for placebo-treated patients was 9.9% per day (95% confidence interval, 3.5%–16.2%).

The rate of IVH resolution for placebo-treated patients was estimated to be a constant 7.93% per day, whereas the rate of IVH resolution for rtPA–treated patients was not constant, being more rapid during the first 2.5 days and then leveling off. Forty-eight, 72, and 96 hours after the stability scan, the estimated percent IVH volume remaining for rtPA–treated versus placebo-treated patients was 56.6% versus 81.1%, 42.4% versus 73.2%, and 39.4% versus 65.3%.

Model of Relation Between Clot Resolution and Change in Consciousness

Initial GCS and a patient's rate of clot resolution were independently associated with change in GCS during the 96 hours after the start of treatment. Baseline ICH volume was not independently associated with change in GCS once initial GCS was taken into account. The composite testing of all terms in the model with a Wald test had a χ^2 (5 degrees of freedom=50.68; $P<0.001$). There was a family of curves for the predicted short-term GCS over time depending on initial GCS, but the relationship of rate of clot resolution to change in GCS remained the same in each. Figure 3 shows the predicted short-term GCS for patients with a GCS of 8 at the start of treatment, the median for these patients, for 4 rates of clot resolution: 0% per day, 10% per day, 20% per day, and 30% per day. In this example, as well as for other initial GCS values, each 10% per day increase in the rate of clot resolution was associated with a 1.1-point improvement in
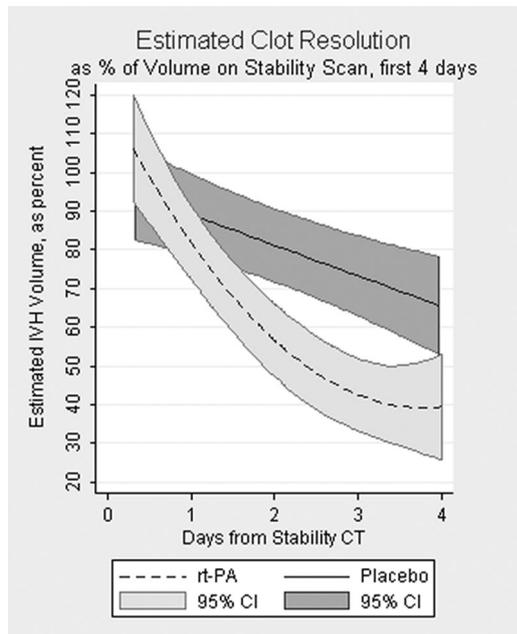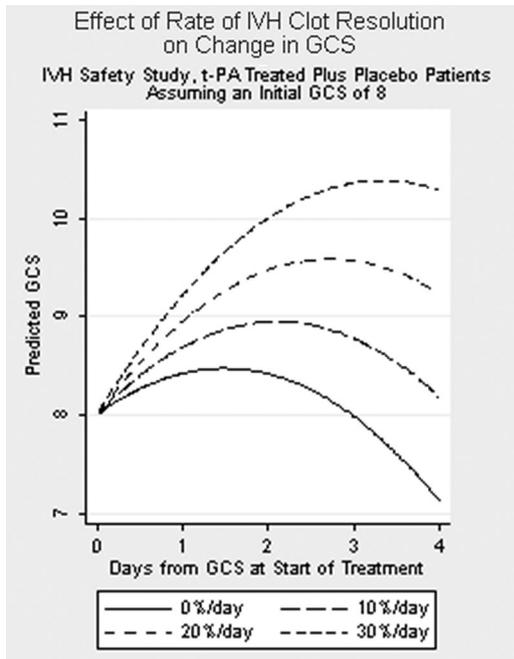
Figure 3. Relation of rate of intraventricual hemorrhage (IVH) clot resolution to change in Glasgow Coma Scale (GCS). *P* value for rate of IVH clot resolution as a continuous variable is <0.001. Included are patients who survived without symptomatic rebleed (N=35).

GCS 96 hours after the initial GCS (95% confidence interval, 0.49–1.63 point improvement; *P*<0.001). For patients with an initial GCS of 8 and a 0% per day short-term rate of clot resolution, predicted GCS by 96 hours was ≈7. At the other extreme, patients with an initial GCS of 8 and 30% per day short-term rate of clot resolution had a predicted GCS by 96 hours of >10.

Discussion

The volumes of blood in both the intraparenchymal and intraventricular spaces are potent factors in determining mortality.[2,19] This relationship has been consistent in multiple cohorts of patients.[6,12,20] The safety data presented here represent the first prospective effort to define the safety of a minimally invasive approach to removing clot using intraventricular low-dose thrombolytics. This trial provides additional data regarding the amount and timing of blood clot removal produced by low-dose rtPA or EVD alone.

The mortality rate in both treatment groups was substantially lower than that of previous reports,[1,21,22] despite the selection of a severely impaired group of patients with a high likelihood of mortality based on their presenting GCS, ICH size, IVH size, and blood pressure.[2] These severity factors were equally distributed across treatment groups and a mortality difference between the groups was not demonstrated. Case series data have suggested that extraventricular drainage controls ICP elevation but does not alter mortality.[21] This study confirms prospectively the finding of Adams[21] that extraventricular drainage can produce controlled ICP.

Several factors could account for the substantial difference between our mortality and that of earlier reports.[1,21] Possible factors include good intensive care unit care and regular patient monitoring (the Hawthorne effect). Furthermore, all patients selected for the study had an EVD in place, and a goal of the study was to maintain catheter patency and to continue extraventricular drainage until acute obstructive hydrocephalus was relieved and normal cerebrospinal fluid circulation was reestablished. Possibly, this practice alone is associated with improved mortality. Specifically, these clinical goals were achieved in all study survivors. Both groups also achieved marked reduction of clot size over the initial treatment phase and initial 30 days, with rtPA–treated group achieving a radiological reduction of ≈60% over 4 days and the placebo group achieving the same reduction over 8 days, as demonstrated by the clot reduction model. An association of improved mortality with clot reduction is consistent with that of animal models,[23–25] as well as previous observations in which attempts at blood clot removal were either not made[21] or ineffective.[8] Differences in patient severity between the Adams[21] and Coplin[1] series and ours do not appear to explain the enhanced survival we demonstrated. However, withdrawal of life sustaining therapies was more frequent in the those cohorts.[26] Other cohorts have larger ICH and smaller IVH, and thus they represent different subgroups of the overall ICH population.[12,27]

Lower absolute mortality and the absence of any unfavorable comparison to either the concurrent placebo group or the historical controls suggest that low-dose thrombolytic therapy can be performed safely in a severely impaired group of deep ICH patients with massive intraventricular hemorrhage. Careful attention to ICP control and IVC catheter antisepsis was associated with a low frequency of ICP elevation and catheter-related infections. However, a consistent trend toward increased frequency of bleeding events was noted in the rtPA–treated group. Secondary bleeding events over the 30-day study period included rebleeding at the primary site, rebleeding at secondary sites (predominantly in the catheter tract), and several instances of IVH extension. Because clinical clot stability was required before administration of the thrombolytic, these findings could represent evidence of ongoing drug-related susceptibility to bleeding.

Given the finding of significantly enhanced clot lysis and a strong trend toward increased secondary bleeding events, caution with respect to the overall safety of low-dose rtPA in the treatment of ICH needs to be expressed. Multiple factors, including blood pressure, coagulation state, ethnicity, diabetes mellitus, and concurrent medications such as aspirin, blood pressure-elevating drugs, and illicit drugs, have all been implicated as risk factors for bleeding. Data on the management of these factors and their interactions with low-dose rtPA are absent; our study is not informative because the bleeding event rate is too low to draw conclusions about these factors. Additionally, data demonstrating a dose-response relationship between rtPA and bleeding events or clot lysis rate are absent. A dose-finding study is necessary to investigate whether lower doses of rtPA may be associated with a high degree of clot lysis but provide a substantially better safety margin with respect to rebleeding.

Two methodologically robust studies of clot removal have demonstrated baseline clot lysis rates from 6% to 12% per day.[6,16] The 8%±2% per day intraventricular clot lysis rate in

our placebo group is consistent with these previous observations and the latest estimate from this study is strengthened by the greater frequency of clot volume measurements used. Thus, we conclude that the enhanced clot lysis rate observed for the rtPA–treated patients is a robust effect; however, it is not as great or as effective as the effects demonstrated in animal models in which clot removal produced decreased edema and prevented subependymal inflammation.[4,5,28] Despite this, several other findings from the animal models were demonstrated in this human study, such as decreased mortality from herniation and ICP events[24] and an enhanced or more rapid recovery of impaired consciousness.[3] More rapid removal of clot could be translated into a shorter intensive care unit stay if the EVD is removed earlier.

This study was neither designed nor powered to assess functional outcome. Others have suggested that ICH patient functional outcome is best assessed at longer time intervals after the initial event.[29,30] This suggestion is consistent with our data that demonstrated high degrees of impaired consciousness at presentation and initial therapeutic periods, with recovery of consciousness occurring slowly over the 30-day study period. The ability of patients to return to previous independent lifestyles could not be properly assessed over this timeframe. However, the study demonstrates that some individuals (3 subjects) were capable of returning to their premorbid functional status within 30 days after severe IVH. Therefore, it seems likely that future studies, including the current CLEAR III (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III) Trial, will need to assess functional performance in the 90- to 180-day timeframe or as far out as 365 days. The location of ICH as well as extent of ICH should significantly influence functional outcome. The selection criteria for this study controlled for lesion location and ICH volume. Therefore, these factors will require further study and evaluation if patient selection is to be optimized. The presence of increased brain tissue injury with prolonged blood clot exposure in animal models and humans[31,32] suggests a strong logical rationale for improving the timing and efficiency of blood clot removal in these patient groups. To date, a treatment modality to perform this does not exist in the clinical arena. Multiple daily doses of rtPA could provide the desired intervention capable of rapidly removing blood from tissue contact.

This study demonstrates that low-dose rtPA has an acceptable safety profile compared to placebo and historical controls of the natural history of ICH with IVH. Although 3 mg of rtPA irrigation every 12 hours clearly accelerates clot removal from the ventricular system, neither dose safety nor dose efficacy was fully explored for this approach. Data from a well-designed phase III clinical trial, such as CLEAR III, will be needed if this treatment is to be fully evaluated.

Acknowledgments

Sources of Funding

Disclosures

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Low-Dose Recombinant Tissue-Type Plasminogen Activator Enhances Clot Resolution in Brain Hemorrhage: The Intraventricular Hemorrhage Thrombolysis Trial

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