Minimally Invasive Surgery Plus Recombinant Tissue-type Plasminogen Activator for Intracerebral Hemorrhage Evacuation Decreases Perihematomal Edema

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Background and Purpose—Perihematomal edema (PHE) can worsen outcomes after intracerebral hemorrhage (ICH). Reports suggest that blood degradation products lead to PHE. We hypothesized that hematoma evacuation will reduce PHE volume and that treatment with recombinant tissue-type plasminogen activator (rt-PA) will not exacerbate it.

Methods—Minimally invasive surgery and rt-PA in ICH evacuation (MISTIE) phase II tested safety and efficacy of hematoma evacuation after ICH. We conducted a semiautomated, computerized volumetric analysis on computed tomography to assess impact of hematoma removal on PHE and effects of rt-PA on PHE. Volumetric analyses were performed on baseline stability and end of treatment scans.

Results—Seventy-nine surgical and 39 medical patients from minimally invasive surgery and rt-PA in ICH evacuation phase II (MISTIE II) were analyzed. Mean hematoma volume at end of treatment was 19.6±14.5 cm³ for the surgical cohort and 40.7±13.9 cm³ for the medical cohort (P<0.001). Edema volume at end of treatment was lower for the surgical cohort: 27.7±13.3 cm³ than medical cohort: 41.7±14.6 cm³ (P<0.001). Graded effect of clot removal on PHE was observed when patients with >65%, 20% to 65%, and <20% ICH removed were analyzed (P<0.001). Positive correlation between PHE reduction and percent of ICH removed was identified (ρ=0.658; P<0.001). In the surgical cohort, 69 patients underwent surgical aspiration and rt-PA, whereas 10 underwent surgical aspiration only. Both cohorts achieved similar clot reduction: surgical aspiration and rt-PA, 18.9±14.5 cm³; and surgical aspiration only, 24.5±14.0 cm³ (P=0.41). Edema at end of treatment in surgical aspiration and rt-PA was 28.1±13.8 cm³ and 24.4±8.6 cm³ in surgical aspiration only (P=0.41).

Conclusions—Hematoma evacuation is associated with significant reduction in PHE. Furthermore, PHE does not seem to be exacerbated by rt-PA, making such neurotoxic effects unlikely when the drug is delivered to intracranial clot. (Stroke. 2013;44:627-634.)

Key Words: brain edema ■ clot aspiration ■ intracerebral hemorrhage ■ minimally invasive surgery ■ MISTIE ■ rt-PA ■ thrombolysis

Intracerebral hemorrhage (ICH) remains a devastating form of stroke. The initial injury induced by the mechanical effect of the hematoma on surrounding brain tissue as well as the subsequent cascade of processes, such as perihematomal edema (PHE), account for the high 30-day mortality and poor neurological outcome in the surviving victims. Attempts at clot removal via craniotomy and hematoma evacuation with operative hemostasis have failed to provide an effective treatment alternative for most ICH patients.1–3 The advent of minimally invasive surgery (MIS) in recent years has allowed testing of new modalities of clot evacuation. Concomitant use of direct aspiration, endoscopic removal, or ultrasound-enhanced thrombolysis of intraparenchymal clots have been reported, suggesting positive results regarding the safety and efficacy of such techniques.4,5 In particular, the administration of recombinant tissue-type plasminogen activator (rt-PA) using MIS has been reported by several groups in the last decade showing important results favoring...
accelerated clot thrombolysis with an acceptable safety profile.6–8 As a result of this, the minimally invasive surgery and rt-PA in ICH evacuation phase II (MISTIE II) was designed and conducted in 2 stages, dose finding and safety, from 2005 to 2012 to determine the safety and efficacy of using MIS combined with rt-PA administration.9

Interest in the physiopathology of PHE has gained significant momentum in recent years. The role of inflammation and blood–brain barrier breakdown in the genesis of this form of edema has been known for some time. Thrombin, iron, microglia, neutrophils, matrix metalloproteinases, and cytokines have been identified as playing key roles in the process of edema formation.10–12 Experimental studies have shown promise in ameliorating the cascade of secondary neuronal injury leading to PHE by modifying the process of inflammation involved in this response.13 In humans, knowledge of the natural history of this form of edema and its independent impact on neurological outcome is still incomplete. Early clinical studies seem to suggest delayed worsening of mass effect owing to cerebral edema.14 Wijman et al15,16 have better defined the natural history of PHE using magnetic resonance imaging techniques. Fainardi et al17 have also identified the longitudinal changes of apparent diffusion coefficient in the perihematoma regions that evolve from elevated apparent diffusion coefficient (vasogenic edema) to reduced apparent diffusion coefficient (cytotoxic edema). Staykov et al18 using computerized tomographic (CT) studies reported that PHE can double the original edema volume from 7 to 11 days after the ictus. Unlike cerebral edema after ischemic stroke, however, the relation of this form of edema to treatment, tissue injury, and neurological outcome after ICH remains poorly understood.19,20 Therefore, improved knowledge of PHE in patients with ICH is necessary.

MISTIE II enrollment was completed in 2012. We tested the hypothesis that hematoma removal in patients treated with MIS and rt-PA would lead to concomitant reduction of edema volume at the end of treatment (EOT) as compared with ICH patients treated with medical management. As part of this analysis, we also tested the hypothesis that MISTIE II patients treated with intraclot rt-PA do not develop PHE exacerbation in the process of thrombolysis as compared with patients treated with the clot aspiration only.

Subjects and Methods

Subjects

MISTIE II (R01NS046309) was a multicenter, randomized, prospective trial testing image-guided catheter-based removal of blood clot in subjects with hypertensive ICH. Patients were recruited by 27 sites. This 2-stage trial included a dose finding and a safety phase. Eighty-one patients were assigned to MIS and 42 patients to standard medical care (either as pilot or randomized subjects). Five patients were excluded, 3 medical, and 2 surgical, because of previous craniotomy or poor image quality. In the surgical arm, 69 patients received surgical aspiration and rt-PA (S + rt-PA) (Alereplase, Genentech, Inc, South San Francisco, CA), whereas 10 patients received surgical aspiration only (SO). A list of inclusion/exclusion criteria as well as an outline of the surgical technique is provided in the online-only Data Supplement.

Thrombolysis Protocol

After the postoperative CT scan, intraclot rt-PA administration followed by a sterile flush was initiated. After each assigned dose, the system was closed for 1 hour to allow drug clot interaction. After 1 hour, the system was opened for gravitational drainage. Subsequent doses of 0.3 mL (18 patients) or 1.0 mL (51 patients) were given every 8 hours, up to 9 doses, or until an end point was reached. Clinical endpoints included reduction of clot to 20% of original size, or clot size is reduced to ≤10 cm³. Additional end points include any clinically significant rebleeding event or any new hemorrhage (treatment failures). CT scans were obtained every 24 hours to evaluate drainage or as clinically indicated.

Medical Treatment Protocol

The medical management of these patients followed the MISTIE II protocol, which followed the American Heart Recommendations for the treatment of Spontaneous ICH.21

Volumetric Analysis of Hematoma and PHE

Independent and adjudicated volumetric measurements of all intraparenchymal clot and edema volumes were performed by W.A.M. and J.R.C. using an open source DICOM viewer software program for MAC (Osirix v. 4.1, Pixmeo; Geneva, Switzerland). Generous regions were drawn by hand to include areas of ICH and PHE susceptible to the computerized analysis, as determined by the reader. A semiautomated threshold-based approach using a Hounsfield unit range of 5 to 33 HU was then used to identify regions of PHE, as previously reported by Volbers et al.22 Using such range, a fixed lower value of 5 HU was set. The upper limit and absolute maximum of 33 HU was adjusted to obtain the best delineation of edema and avoid artifact introduced by leukoaraiosis. Once these HU limits were determined, Osirix created edema regions and produced a volume in cubic centimeters (cm³) by computing region of interest and slice thickness. Volumes were calculated using a similar threshold-based segmentation on well-definable boundaries of blood on CT (Figure 1).

For the purpose of this study, we identified the baseline stability (BLS) scan as the closest gradable scan before randomization. An EOT scan was defined as the scan performed 24 hours (±12) post last dose for S+rt-PA or post operative treatment for SO. A homologous time window was then ascribed to the medical cohort to perform the statistical analysis (closest scan to 3.9 days post onset).

Statistical Analysis

r Tests were done to test differences in means for continuous variables. ANOVA was used to determine differences across groups. Wilcoxon rank-sum tests and a Kruskal–Wallis test also determined that inferences were not different at a probability value of 0.05 using these nonparametric tests. Fisher exact tests were done to determine differences in the distributions of categorical variables across groups. Locally weighted scatterplot smoothing smoothing was used to determine the relationship between variables. Spearman ρ was used to determine the association between variables when the relationship seemed monotonic but not necessarily linear. We choose direct comparisons of pretreatment and posttreatment edema volume as the most specific primary analysis of data to support or reject our hypothesis. We performed multivariate linear models to assess factors with the possibility to affect edema reduction.

Results

MISTIE II was composed of 2 stages: (1) dose finding (2005–2009) and (2) safety (2009–2012). One hundred and twenty-three patients were prospectively enrolled into 1 of 2 treatment groups, MIS plus rt-PA (surgery) or best medical management (medical), as shown in Table 1. Eighty-one patients were randomized to receive MIS, whereas 42 were randomized to medical management. Imaging of 5 patients (3 medical, 2 surgical) was not graded owing to instance of prior craniotomy creating image artifact and therefore poor image quality. The data of 118 patients are reported in this communication.
Demographic and Clinical Data

The surgical and medical cohorts were similar in age, sex, race, hematoma location, and admission Glasgow Coma Scale (Table 1). It is important to note that instance of symptomatic hemorrhage and central nervous system infection, within the analysis window (BLS-EOT), was low. Three symptomatic hemorrhages occurred in the surgical cohort ($P=0.30$), and 2 instances of central nervous system infection compared with 1 in the medical cohort ($P=1.00$).

**Neuroradiologic Features**

Data on 118 patients were analyzed; time from ictus to BLS, ictus to EOT, and number of patients with intraventricular involvement were similar for the surgical and medical cohorts (Table 2).

ICH and edema volumes at BLS for surgical patients were similar compared with the medical cohort: surgical ICH, $43.8\pm17.2$ cm$^3$, PHE, $33.3\pm19.5$ cm$^3$; medical ICH $42.2\pm14.8$ cm$^3$, PHE, $30.3\pm12.0$ cm$^3$. Neither of these...
comparisons was statistically significant (Table 2). Surgical patients had lower EOT ICH volume, 19.6±14.5 cm³, as compared with their medical counterparts, 40.7±13.9 cm³ (P<0.001). EOT edema volume was lower in surgical patients, 27.7±13.3 cm³, when compared with medical patients, 41.7±14.6 cm³ (P<0.001) as shown in Figure 2.

When patients were subdivided into roughly equally sized tertiles respecting the trial goal of clot removal of >65% (n=32), 20% to 65% (n=39), and <20% (n=8) clot removal from BLS to EOT, surgical patients with >65% clot removal demonstrated PHE reduction of 10.7±13.9 cm³, whereas medical patients, all with <20% resolution by EOT, showed an increase in PHE of 11.4±9.6 cm³ (P<0.001) as depicted in Figure 3. A significant graded effect of clot removal on PHE was observed overall (ANOVA P<0.001). Furthermore, a positive correlation between PHE reduction and percent of ICH removed was identified (Spearman ρ=0.66; P<0.001) as represented in Figure 3. In multivariate analyses, this relation was unaltered by dose of rt-PA, osmotherapy, or intracranial pressure therapy.

In the surgical arm, 69 patients received S+rt-PA, whereas 10 patients received SO. Both treatment subgroups were comparable for enrollment Glasgow Coma Scale, intraventricular involvement, time from symptom onset to BLS or EOT, baseline ICH volume, and baseline PHE volume but differed for age: SO, 68.9±9.2 years old and S+rt-PA, 59.4±11.4 years old (P=0.01). Both treatment cohorts achieved similar blood clot reduction: S+rt-PA, 18.9±14.5 cm³ and SO, 24.5±14.0 cm³ (P=0.26). Mean edema at EOT in patients treated with S+rt-PA was 28.1±13.8 cm³, while in patients treated with SO was 24.4±8.6 cm³ (P=0.41). Edema levels for both arms of the surgical cohort, S+rt-PA and SO, at BLS and EOT are shown in Figure 4.

**Conclusions**

We report on the effect of hematoma removal using MIS and rt-PA on PHE formation in ICH patients. We identified a significant PHE reduction in patients who underwent successful clot evacuation after the MISTIE procedure. Furthermore, administration of rt-PA for clot lysis in addition to initial

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**Table 2. Radiological and Volumetric Data of the Study Patients**

<table>
<thead>
<tr>
<th></th>
<th>Surgical (n=79)</th>
<th>Medical (n=39)</th>
<th>P Value</th>
<th>SO (n=10)</th>
<th>S+rt-PA (n=69)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset to EOT scan, days</td>
<td>3.9 (1.1)</td>
<td>3.7 (0.5)</td>
<td>0.23</td>
<td>3.6 (0.7)</td>
<td>4.0 (1.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Patients w/ IVH extension</td>
<td>48 (60.8%)</td>
<td>25 (64.1%)</td>
<td>0.84</td>
<td>5 (50.0%)</td>
<td>43 (62.3%)</td>
<td>0.50</td>
</tr>
<tr>
<td>BLS ICH volume, mL</td>
<td>43.8 (17.2)</td>
<td>42.2 (14.8)</td>
<td>0.61</td>
<td>40.1 (15.7)</td>
<td>44.4 (17.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>EOT ICH volume, mL</td>
<td>19.6 (14.5)</td>
<td>40.7 (13.9)</td>
<td>&lt;0.001</td>
<td>24.5 (14.0)</td>
<td>18.9 (14.5)</td>
<td>0.26</td>
</tr>
<tr>
<td>BLS edema volume, mL</td>
<td>33.3 (19.5)</td>
<td>30.3 (12.0)</td>
<td>0.37</td>
<td>6.4 (12.9)</td>
<td>34.3 (20.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>EOT edema volume, mL</td>
<td>27.7 (13.3)</td>
<td>41.7 (14.6)</td>
<td>&lt;0.001</td>
<td>24.4 (8.6)</td>
<td>28.1 (13.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Reduction in edema (BLS-EOT)</td>
<td>5.6 (15.1)</td>
<td>−11.4 (9.6)</td>
<td>&lt;0.001</td>
<td>2.1 (10.6)</td>
<td>6.2 (15.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Relative PHE stability</td>
<td>0.8 (0.3)</td>
<td>0.7 (0.3)</td>
<td>0.66</td>
<td>0.7 (0.2)</td>
<td>0.8 (0.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>Reduction in edema/stability ICH*</td>
<td>0.1 (0.3)</td>
<td>−0.3 (0.3)</td>
<td>&lt;0.001</td>
<td>0.0 (0.3)</td>
<td>0.1 (0.3)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

BLS indicates baseline stability scan; EOT, end of treatment scan; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; PHE, perihematomal edema; SO, surgery only; and S + rt-PA, surgery + rt-PA.

*Relative PHE difference, edema reduction divided by BLS ICH.
aspiration did not enhance edema formation in relation to patients treated with clot aspiration only.

PHE is an almost universal occurrence after ICH. Early interpretations of perihematomal events included cerebral ischemia, which found some support in animal experiments. Subsequent human studies using surrogates of cerebral ischemia, such as single photon emission CT and perfusion weighted magnetic resonance imaging, corroborated the presence of hypoperfused tissue surrounding parenchymal clots. Only when studies measuring cerebral metabolism were performed did it become clear that hypoperfusion was likely the result of hypometabolism. This metabolic state of hibernation is hypothesized to be associated to vasogenic cerebral edema. Attempts to indirectly quantify blood–brain barrier disruption using diffusion weighted magnetic resonance imaging have suggested a cause-effect or dose-response association between the volume of ICH, intensity of apparent diffusion coefficient elevation PHE volume.

The clinical significance of PHE remains unclear. Volumetric analyses of PHE using CT and magnetic resonance imaging studies have repeatedly demonstrated edema volumes reaching 2- to 3-fold the original hematoma volume. Delayed neurological deterioration as late as 2 to 3 weeks after the ictus, likely the result of PHE, has also been described. However, the independent impact of these events on long-term neurological outcome remains unknown. Gebel et al reported on the paradoxical improved functional outcome predicted by relative PHE in the initial 24 hours. These studies and ours are limited by difficulty completely blinding the edema analysis of surgical subjects and our still limited knowledge of factors that provoke and mitigate edema.
Targeted therapies for this form of edema for ICH are lacking; thus the differential impact of PHE modification on neurological outcome is largely unknown. Therapeutic trials for ICH have concentrated primarily on clot evacuation.24 Several early clinical trials comparing best medical therapy alone versus best medical therapy and surgical evacuation of the hematoma have been completed. Minimally invasive neurosurgical procedures seem to minimize trauma to viable brain tissue. Studies using MIS and clot aspiration, thrombolysis, and endoscopic evacuation have reported on their safety and potential for efficacy when used in selected ICH patients. These studies not only suggest that hematoma evacuation is safe but that a parallel response between hematoma volume reduction and PHE volume exists.41–43 Our results confirm such observations in this prospectively recruited cohort of patients. The combined effect of this form of hematoma evacuation and edema volume attenuation on neurological recovery after ICH awaits testing in a properly powered prospective clinical trial.

rt-PA has been used in several paradigms of brain injury, more conspicuously as the thrombolytic agent for acute recanalization during acute ischemic stroke. The safety and efficacy profiles of rt-PA in this setting have been evaluated in several studies before its recommendation as thrombolytic agent for the treatment of acute cerebral ischemia using the intravenous administration route. The experimental use of rt-PA in the treatment of intraventricular and ICH, however, has opened 2 new modalities of drug delivery that have not been previously tested. After completing proof of concept and dose escalation studies, Clot Lysis: Evaluating Accelerated Resolution of Hemorrhage with rt-PA Intraventricular Hemorrhage (CLEAR IVH) and MISTIE Lysis: Evaluating Accelerated Resolution of Hemorrhage with administration route. The experimental use of rt-PA in the treatment of intraventricular and ICH, however, has opened 2 new modalities of drug delivery that have not been previously tested. After completing proof of concept and dose escalation studies, Clot Lysis: Evaluating Accelerated Resolution of Hemorrhage with rt-PA Intraventricular Hemorrhage (CLEAR IVH) and MISTIE Lysis: Evaluating Accelerated Resolution of Hemorrhage with clot evacuation from the intraventricular and intraparenchymal compartments using rt-PA. Concerns of toxicity produced from the direct exposure of the drug to neuronal tissue have, however, been raised by some investigators.44,45 Early reports of retinal toxicity when tissue plasminogen activator and L-arginine when used in the treatment of vitreal hemorrhage exist.46–48 Furthermore, first in a pig model and more recently in a clinical study, rt-PA has been postulated to worsen vasogenic edema when used in the treatment of intraventricular hemorrhage and ICH.49,50 Nonetheless, no evidence for this toxicity was noted when histological assessments in large animal intracranial and retinal hemorrhage models were performed.51–55 Additionally, recent mouse tissue plasminogen activator knockout studies suggest amelioration of blood-clot-related neuronal and glial tissue injury by rt-PA.56 Finally, no signs of human neuronal rt-PA toxicity have been noted in the current treatment of ischemic stroke, despite administration under conditions of blood–brain barrier disruption.57

Our study is the first a priori investigation that uses a semi-automated volumetric analysis for prospectively obtained group of patients treated with clot aspiration alone versus clot aspiration and thrombolytic therapy with rt-PA. Both groups achieved similar clot volume reduction without experiencing differences in PHE volumes, confirming the overall positive impact of hematoma removal using rt-PA on PHE volumes, reported by our group as well as others.

Our analysis of 118 patients enrolled in the MISTIE II trial is consistent with the hypothesis that successful hematoma evacuation leads to significant edema volume reduction. In 2008, we did report on such association after the retrospective analysis of a convenience cohort of ICH patients treated using a similar approach with MIS and thrombolysis. This is the first time such an observation is confirmed in a prospectively obtained cohort of ICH patients. Hematoma evacuation and its impact on vasogenic edema formation leading to improved neurological outcomes after ICH remains under investigation. MISTIE III offers to test for such association. In the meantime, our results demonstrate that efficient hematoma evacuation using a combined approach of MIS and aspiration with or without rt-PA leads to a significant reduction in PHE.

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Online Supplement

Inclusion criteria:
1. Age 18 - 80
2. GCS ≤ 14 or NIHSS ≥ 6
3. Spontaneous supratentorial ICH ≥ 20cc
4. Stable clot (increase no greater than 5cc) at second CT scan done six hours later
5. First dose given within 54 hrs. of the initial CT scan
6. Symptoms less than 12 hours prior to diagnostic CT scan
7. SBP < 200 mmHg or MAP <130 mmHg over 6 hours
8. Historical Rankin score of 0 or 1
9. Negative pregnancy test

Exclusion criteria:
1. Infratentorial hemorrhage
2. Platelet count < 100,000, INR > 1.3, or an elevated PT or APTT
3. Pre-existing irreversible coagulopathy
4. Any concurrent serious illnesses that would interfere with the safety assessments
5. Patients with a mechanical cardiac valve
6. Patients with unstable mass or evolving intracranial compartment syndrome
7. Ruptured aneurysm, AVM, vascular anomaly, Moyamoya disease
8. Irreversibly impaired brainstem function, GCS less than or equal to 4
9. Obstructive intraventricular hemorrhage requiring external ventricular drainage
10. Internal bleeding, involving retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts
11. Superficial or surface bleeding, observed mainly at vascular puncture and access sites or site of recent surgical intervention
12. Known risk for embolization, including history of left heart thrombus, mitral stenosis with atrial fibrillation, acute pericarditis, or subacute bacterial endocarditis
13. In the investigator’s opinion, the patient is unstable and would benefit from a specific intervention rather than supportive care or MIS + tPA removal of the ICH
14. Prior enrollment in the study
15. Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated
16. Participation in another simultaneous trial of ICH treatment

Operative technique

For enrolled patients randomized to surgery, a 14-French cannula was stereotactically placed into the center of the parenchymal clot two-thirds the length of the long axis, and within the middle one-third of the clot. Directly after cannula placement, an initial aspiration of clot was conducted using a 10 cc syringe until the surgeon notes resistance to free-hand suction. Following completion of hematoma aspiration, a soft ventriculostomy catheter was then passed through the rigid cannula and the rigid cannula was removed leaving the soft catheter in the center of the residual hematoma. A postoperative CT scan was taken to confirm accurate placement and check for any instance of new bleeding.