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Minimally Invasive Surgery plus rt-PA for Intracerebral Hemorrhage Evacuation (MISTIE) Decreases Perihematomal Edema

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Abstract

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

Methods—MISTIE II tested safety and efficacy of hematoma evacuation after ICH. We conducted a semi-automated, computerized volumetric analysis on CT to assess impact of hematoma removal on PHE and 2) effects of rt-PA on PHE. Volumetric analyses were performed on Baseline Stability (BLS) and End of Treatment (EOT) scans.

Results—Seventy-nine surgical and 39 medical patients from MISTIE II were analyzed. Mean hematoma volume at EOT was 19.6±14.5 cc for the surgical cohort and 40.7±13.9 cc for the medical cohort ($p<0.001$). Edema volume at EOT was lower for the surgical cohort: 27.7±13.3 cc than medical cohort: 41.7±14.6 cc ($p<0.001$). Graded effect of clot removal on PHE was observed when patients with >65%, 20-65%, and <20% ICH removed were analyzed ($p<0.001$). Positive correlation between PHE reduction and percent of ICH removed was identified ($\rho=0.658$; $p<0.001$). In the surgical cohort, 69 patients underwent surgical aspiration and rt-PA (S+rt-PA)

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while 10 underwent surgical aspiration only (SO). Both cohorts achieved similar clot reduction: S+rt-PA, 18.9±14.5 cc; and SO, 24.5±14.0 cc (p=0.26). Edema at EOT in S+rt-PA was 28.1±13.8 cc and 24.4±8.6 cc in SO (p=0.41).

Conclusions—Hematoma evacuation is associated with significant reduction in PHE. Furthermore, PHE does not appear to be exacerbated by rt-PA, making such neurotoxic effects unlikely when the drug is delivered to intracranial clot.

Clinical Trial Registration Information—URL: http://clinicaltrials.gov/ct2/show/NCT00224770?term=MISTIE&rank=1

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Keywords

Intracerebral hemorrhage; Thrombolysis; rt-PA; Clot aspiration; Minimally Invasive Surgery; Brain edema; MISTIE

Introduction

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 and refinement 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 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 Intracerebral hemorrhage 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 (BBB) 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 due to cerebral edema.(14) Wijman and coworkers have better defined the natural history of PHE using MRI techniques.(15,16) Fainardi and coworkers have also identified the longitudinal

changes of ADC in the perihematoma regions that evolve from elevated ADC (vasogenic edema) to reduced ADC (cytotoxic edema).(17) Staykov and coworkers using computerized tomographic (CT) studies reported that PHE can double the original hematoma volume from 7 to 11 days after the ictus.(18) Unlike cerebral edema following ischemic stroke, however, the relation of this form of edema to treatment, tissue injury and or 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 as compared to 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 to 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, due to prior craniotomy or poor image quality. In the surgical arm, 69 patients received surgical aspiration and rt-PA (Alteplase, Genentech, Inc, South San Francisco, CA), S + rt-PA, while 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 supplemental data, please see http://stroke.ahajournals.org.

Thrombolysis Protocol

Following the postoperative CT scan, intra-clot rt-PA administration followed by a sterile flush was initiated. After each assigned dose, the system was closed for 1 hr to allow drug clot interaction. After 1 hr, 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 h, up to 9 doses, or until an endpoint was reached. Clinical endpoints included: 1) reduction of clot to 20 % of original size, or 2) clot size is reduced to 10 cc or less. Additional endpoints include any clinically significant rebleeding event or any new hemorrhage (treatment failures). CT scans were obtained every 24 h 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 Perihematomal Edema (Figure 1)

Independent and adjudicated volumetric measurements of all intraparenchymal clot and edema volumes were performed by WAM and JRC 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 semi-automated 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 and coworkers.(22) Using such range, a fixed lower value of 5 HU was set. The upper limit and absolute maximum of 33 HU was adjusted in order 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 (cc) by computing ROI and slice thickness. Volumes were calculated using a similar threshold-based segmentation on well-definable boundaries of blood on CT.

For the purpose of this study, we identified the “Baseline Stability” (BLS) scan as the closest gradable scan prior to randomization. An “End of Treatment” (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 in order to perform the statistical analysis (closest scan to 3.9 days post onset).

Statistical Analysis

T-tests were done to test differences in means for continuous variables. ANOVA was employed to determine differences across groups. Wilcoxon rank-sum tests and a Kruskal-Wallis test also determined that inferences were not different at a p-value of 0.05 using these nonparametric tests. Fisher’s exact tests were done to determine differences in the distributions of categorical variables across groups. LOWESS smoothing was used to determine the relationship between variables.(23) Spearman ρ was used to determine the association between variables when the relationship appeared monotonic but not necessarily linear.We choose direct comparisons of pre and post treatment 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 comprised of 2 stages: 1) Dose finding (2005 to 2009) and 2) Safety (2009 to 2012). One hundred and twenty three patients were prospectively enrolled into one of two 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 while 42 were randomized to medical management. Imaging of 5 patients (3 medical, 2 surgical) was not graded due 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 (GCS) (Table 1). It is important to note that instance of

symptomatic hemorrhage and CNS infection, within the analysis window (BLS-EOT), was low. Three symptomatic hemorrhages occurred in the surgical cohort (p=0.30), and two instances of CNS infection compared to one in the medical cohort (p=1.00).

Neuroradiologic Features (Table 2)

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).

Intracerebral hemorrhage and edema volumes at BLS for surgical patients were similar compared to the medical cohort: surgical ICH, 43.8±17.2 cc, PHE, 33.3±19.5 cc; medical ICH 42.2±14.8 cc, PHE, 30.3±12.0 cc. Neither of these comparisons was statistically significant (Table 2). Surgical patients had lower EOT ICH volume, 19.6±14.5 cc as compared to their medical counterparts, 40.7±13.9 cc (p<0.001). End of treatment edema volume was lower in surgical patients, 27.7±13.3 cc when compared to medical patients, 41.7±14.6 cc (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), 20-65% (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 cc, while medical patients, all with < 20% resolution by EOT, showed an increase in PHE of 11.4±9.6 cc (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 ICP therapy.

In the surgical arm, 69 patients received surgical aspiration and rt-PA (S+rt-PA) while 10 patients received surgical aspiration only (SO). Both treatment subgroups were comparable for enrollment GCS, 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 cc and SO, 24.5±14.0 cc (p=0.26). Mean edema at EOT in patients treated with S+rt-PA was 28.1±13.8 cc while in patients treated with SO was 24.4±8.6 cc (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 aspiration did not enhance edema formation in relation to patients treated with clot aspiration only.

Perihematomal edema is an almost universal occurrence following ICH. Early interpretations of perihematomal events included cerebral ischemia, which found some support in animal experiments.(24-31) Subsequent human studies using surrogates of cerebral ischemia such as single photon emission computerized tomography and perfusion weighted MRI corroborated the presence of hypoperfused tissue surrounding parenchymal clots.(32-34) Only when studies measuring cerebral metabolism were performed did it become clear that hypoperfusion was likely the result of hypometabolism.(35) This metabolic state of “hibernation” is hypothesized to be associated to vasogenic cerebral edema. Attempts to indirectly quantify BBB disruption using diffusion weighted MRI have suggested a cause-effect or dose-response association between the volume of ICH, intensity of ADC elevation PHE volume.(36-38)

The clinical significance of PHE remains unclear. Volumetric analyses of PHE using CT and MRI studies have repeatedly demonstrated edema volumes reaching 2 to 3 fold the original hematoma volume.(38) 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 and coworkers reported on the paradoxical improved functional outcome predicted by relative PHE in the initial 24 hours.(39,40) Using data from the INTERACT trial, Arima and coworkers reported differently. These investigators found PHE to be significantly associated to the underlying hematoma volume but lacking independent effect on the outcome of ICH patients.(20) 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.(2,3) 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 appear 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 following ICH awaits testing in a properly powered prospective clinical trial. Recombinant tissue-type plasminogen activator (rt-PA) has been utilized 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 prior to 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 intracerebral hemorrhage, however, has opened two new modalities of drug delivery that have not been previously tested. After completing proof of concept and dose escalation studies, CLEAR IVH and MISTIE II have reported on the efficient and safe 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 tPA 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 IVH 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 t-PA knockout studies suggest amelioration of blood-clot-related neuronal and glial tissue injury by rt-PA.(56) Lastly, 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 following 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 following 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 perihematomal edema.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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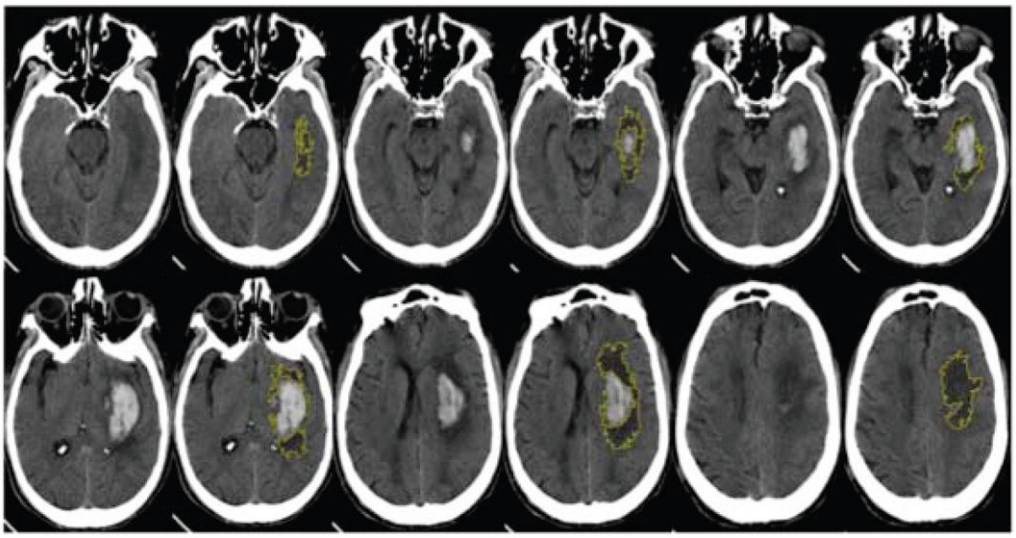

Figure 1.
CT scan at EOT for a medical patient with (right) and without (left) the semi-automated threshold based segmentation of perihematomal edema. EOT, end of treatment scan.

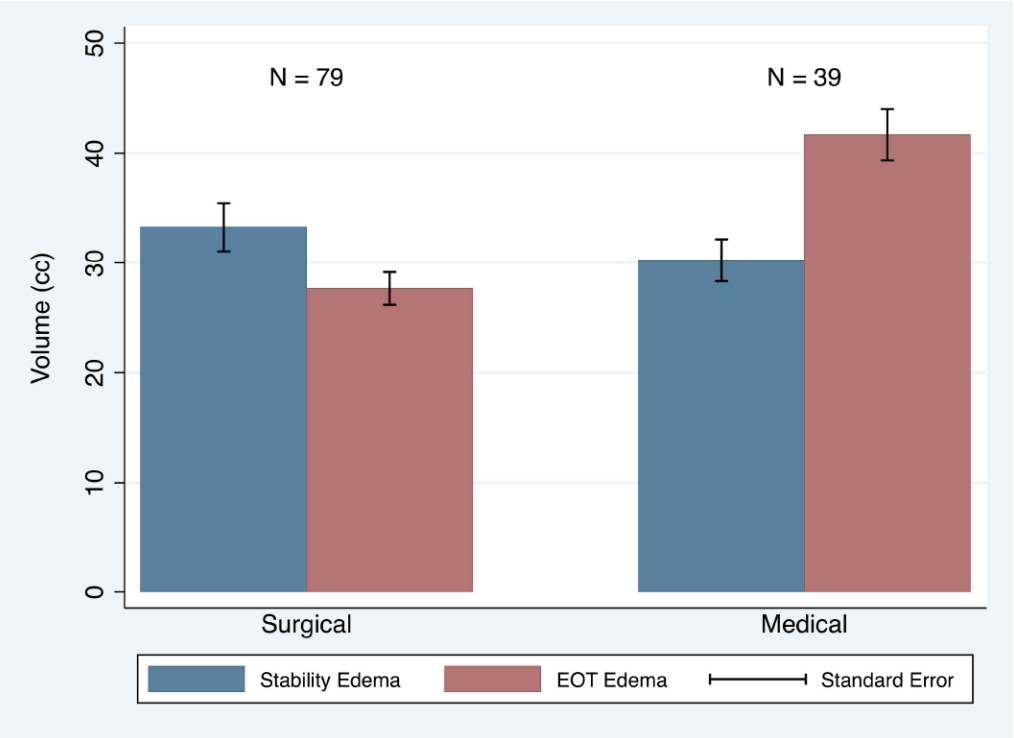

Figure 2.
BLS and EOT edema volumes for the surgical (S+rt-PA and SO) and medical cohorts. BLS, baseline stability scan, EOT, end of treatment scan.

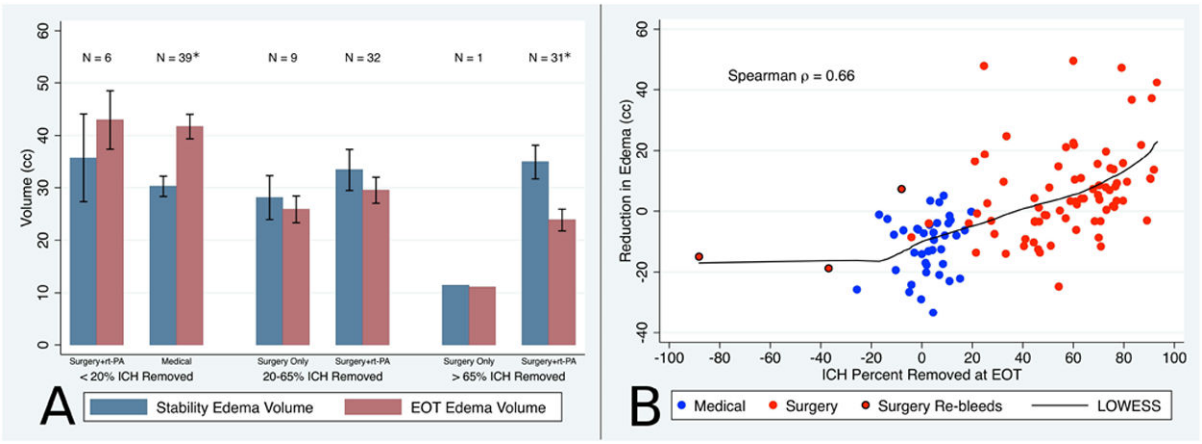

Figure 3.

A.) BLS and EOT edema volumes for patients separated by treatment group (medical, surgical aspiration only, and surgery plus rt-PA) and trichotimized by order of % ICH removed. BLS, baseline stability scan, EOT, end of treatment scan. **B.)** Percent of ICH removed as calculated by [(BLS ICH volume - EOT ICH volume)/ BLS volume] in a continuous fashion versus reduction in edema (BLS edema volume - EOT edema volume) for patients receiving medical management (blue) and MIS (red). BLS, baseline stability scan, EOT, end of treatment scan, S + rt-PA, surgery plus rt-PA, SO, surgical aspiration only. *- denotes statistical significance

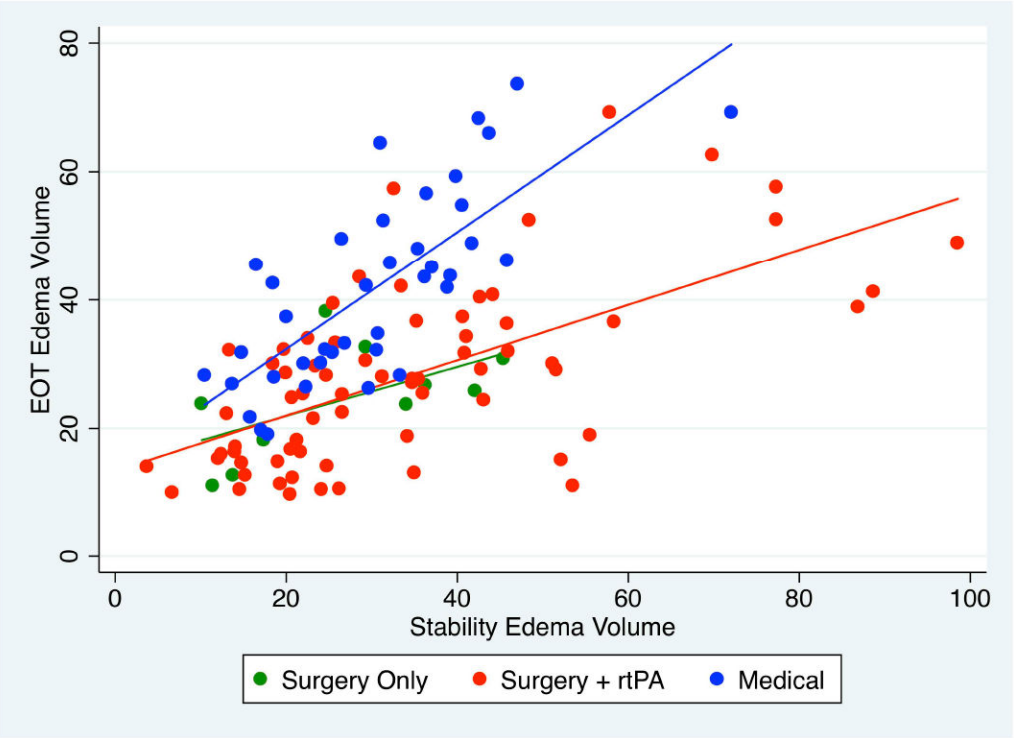

Figure 4.

Correlation between percent of ICH removed as calculated by [(BLS ICH volume - EOT ICH volume)/ BLS volume] and reduction in edema (BLS edema volume - EOT edema volume). BLS, baseline stability scan, EOT, end of treatment scan, S + rt-PA, Surgery plus rt-PA, SO, Surgical aspiration only.

Table 1

Demographic and Clinical characteristics of the study patients

	Surgical (n=79)	Medical (n=39)	p	SO (n=10)	S+rt-PA (n=69)	p
Symptom Onset Age (years)	60.6 (11.5)	61.0 (12.4)	0.87	68.9 (9.2)	59.4 (11.4)	0.01
Enrollment GCS	10.1 (2.9)	10.4 (3.8)	0.67	11.5 (2.8)	9.8 (2.9)	0.09
% Male	53 (67.1%)	26 (66.7%)	1.00	6 (60.0%)	47 (68.1%)	0.72
Race			0.60			0.81
Caucasian	44 (55.7%)	21 (53.8%)		7 (70.0%)	37 (53.6%)	
African American	25 (31.6%)	10 (25.6%)		2 (20.0%)	23 (33.3%)	
Hispanic	9 (11.4%)	5 (12.8%)		1 (10.0%)	8 (11.6%)	
Asian or Pacific Islander	1 (1.3%)	2 (5.1%)		0 (0.0%)	1 (1.4%)	
Unknown	0 (0.0%)	1 (2.6%)		0 (0.0%)	0 (0.0%)	
Clot Location			0.22			0.10
Thalamus	4 (5.1%)	1 (2.6%)		0 (0.0%)	4 (5.8%)	
Putamen	46 (58.2%)	24 (61.5%)		3 (30.0%)	43 (62.3%)	
Lobar	22 (27.8%)	14 (35.9%)		6 (60.0%)	16 (23.2%)	
Globus Pallidus	7 (8.9%)	0 (0.0%)		1 (10.0%)	6 (8.7%)	
CNS Infection*	2 (2.5%)	1 (2.6%)	1.00	0 (0.0%)	2 (2.9%)	1.00
Symptomatic Bleed*	3 (3.8%)	0 (0.0%)	0.55	0 (0.0%)	3 (4.3%)	1.00
Emergent ICP Therapy†	14 (17.7%)	10 (25.6%)	0.34	1 (10.0%)	13 (18.8%)	0.68
Emergent Osmotherapy	10 (12.7%)	9 (23.1%)	0.18	1 (10.0%)	9 (13.0%)	1

SO, Surgery only; S+tPA, Surgery + rt-PA; CNS, central nervous system,

*within analysis window of BLS to EOT;

†ICP Therapy included Osmotherapy, Aggressive Hyperventilation, and Surgical Decompression

Table 2

Radiological and volumetric data of the study patients

	Surgical (n=79)	Medical (n=39)	p	SO (n=10)	S+rt-PA (n=69)	p
Symptom Onset to EOT Scan (days)	3.9 (1.1)	3.7 (0.5)	0.23	3.6 (0.7)	4.0 (1.1)	0.27
Patients w/IVH extension	48 (60.8%)	25 (64.1%)	0.84	5 (50.0%)	43 (62.3%)	0.50
BLS ICH Vol (mL)	43.8 (17.2)	42.2 (14.8)	0.61	40.1 (15.7)	44.4 (17.4)	0.46
EOT ICH Vol (mL)	19.6 (14.5)	40.7 (13.9)	< 0.001	24.5 (14.0)	18.9 (14.5)	0.26
BLS Edema Vol (mL)	33.3 (19.5)	30.3 (12.0)	0.37	26.4 (12.9)	34.3 (20.1)	0.24
EOT Edema Vol (mL)	27.7 (13.3)	41.7 (14.6)	< 0.001	24.4 (8.6)	28.1 (13.8)	0.41
Reduction in Edema (BLS-EOT)	5.6 (15.1)	-11.4 (9.6)	< 0.001	2.1 (10.6)	6.2 (15.7)	0.43
Relative PHE Stability	0.8 (0.3)	0.7 (0.3)	0.66	0.7 (0.2)	0.8 (0.4)	0.24
Reduction in Edema / Stability ICH*	0.1 (0.3)	-0.3 (0.3)	< 0.001	-0.0 (0.3)	0.1 (0.3)	0.31

SO, Surgery only, S + rt-PA, Surgery + rt-PA; EOT, End of treatment scan; BLS, Baseline stability scan; Vol, Volume;

*Relative PHE Difference, edema reduction divided by BLS ICH.