



Stereotactic Aspiration-Thrombolysis of Intracerebral Hemorrhage and its Impact on Perihematoma Brain Edema

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Abstract

Background Recent reports suggest that when thrombolytic agents are administered within the clot, lysis rate accelerates at the expense of increased risk of worsening edema. To test this hypothesis, we report on the volumetric analysis of (1) the intraparenchymal hematoma and, (2) perihematoma edema in a cohort of ICH patients treated with intraclot rtPA.

Methods A convenience sample of highly selected ICH patients underwent frameless stereotactic aspiration and thrombolysis (FAST) of the clot. Two milligrams of rtPA were administered every 12 h until ICH volume ≤ 10 cc, or catheter fenestrations were no longer in continuity with the clot. ICH and perihematoma edema volumes were calculated from CT scans. Using random effects linear regression we estimated the rate of hematoma and edema

volume resolution as well as their relationship during the first 8 days of lytic therapy.

Results Fifteen patients were treated, mean age: 60.7 years, median time from ictus to FAST: 1 (range 0–3) day. Using a random effects model that considered volume resolution over the first 8 days following lytic therapy we found that the both percentage hematoma and percentage perihematoma edema resolution per day were quadratic with respect to time. Percentage residual hematoma volume on day $K = 97.7\% - [24.36\%*K] + [1.89\%*K^2]$; $P < 0.001$ for both terms. Percentage residual edema on day $K = 97.4\% - [13.94\%*K] + [1.30\%*K^2]$; $P < 0.001$ for K and $P = 0.01$ for K^2 . Examination of each patient's volume data suggests that there exists a strong direct relationship between perihematoma edema volume and same day hematoma volume.

Conclusions In this cohort of ICH patients treated using FAST, volumetric analysis of ICH and perihematoma edema seems to suggest that local use of rtPA does not exacerbate brain edema formation. Furthermore, there seems to be a strong association between reduction in ICH volume and reduction in edema volume, as would be expected following the concept of "hemotoxicity" postulated by some investigators.

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Introduction

Morbidity and mortality following ICH remain the highest among all forms of cerebrovascular diseases. Although several outcome-modifying clinical variables are well recognized, the impact of perihematoma brain edema on neurological function of patients who survive the acute phase of the disease is less clear.

Plausible mechanisms of neurological deterioration following development of perihematomal edema are: (1) Mass effect introduced by perihematomal edema on an already challenged intracranial compliance, and (2) Secondary neuronal injury triggered by blood/degradation products (“hemotoxicity”) with potential to alter brain function [1, 2]. Unfortunately, directed therapies for ICH-induced brain edema are lacking. It has been only recently (when thrombolytic agents were used to locally lyse intraparenchymal hematomas in animal models of ICH) that efficient reduction in the volume of perihematomal edema has been reported [3]. Okuda and coworkers have also suggested a positive effect of early hematoma removal on perihematomal edema formation in a heterogeneously treated cohort of ICH patients [4]. Similarly, Mayer and coworkers demonstrated an association between hematoma size and volume of perihematomal edema [5]. Although the relative safety of using local thrombolysis in different clinical paradigms of acute brain injury (subarachnoid hemorrhage, ICH, ischemic stroke) is well documented, experimental data suggesting that parenchymal clot lysis using thrombolytic agents potentiate brain edema formation as well as induce direct neurotoxicity have raised concern [6–9]. To better define the impact of recombinant tissue plasminogen activator (rtPA) on clot volume resolution as well as to clarify conflicting results of studies testing the effects of thrombolytic agents on perihematomal edema formation after human ICH, we report on our experience using frameless clot aspiration and thrombolysis (FAST) using rtPA in the treatment of a selected cohort of ICH patients. Specifically, we report on (1) rate of hematoma volume and perihematomal edema volume resolution; and (2) the association between perihematomal edema volume and hematoma volume during the 8 days following the onset of treatment with thrombolysis.

Subjects and Methods

The study cohort consisted of selected ICH patients treated with a FAST protocol using rtPA. This therapy was considered an acceptable alternative to open craniotomy with hematoma evacuation in selected cases at Sinai Grace Hospital rather than a clinical trial designed to test its safety or efficacy. It was applied in a clinically uniform manner to sequentially eligible patients [10, 11]. The decision to perform clot aspiration and thrombolysis was made by a single senior neurosurgeon (RRJ) after patient/family discussions were held. Inclusion criteria when identified within 72 h from the ictus were:

1. Computed tomographic (CT) diagnosis of spontaneous supratentorial ICH of ≥ 35 cc of volume, following Tuhim and Broderick estimations that mortality

following ICH increases significantly when hematoma volume reaches 30 cc and larger [12–14].

2. Reduced level of consciousness leading to incapacity to follow commands (Score of 2 in the NIH Stroke scale item 1a).
3. Absence of signs of herniation for at least 8 h from ICH onset (To ensure neurological stability prior to the procedure).
4. Patient’s age ≥ 18 years (as children are not part of the center’s usual patient population).
5. No clinical or radiological evidence of vascular abnormality (e.g. aneurysm, arterio-venous malformation) as cause of ICH.
6. No clinical/laboratory evidence of a bleeding diathesis.

Although no pre-defined time window was specified for the time between patients were first seen in the Emergency Department and the time aspiration/lysis therapy was started, the treating team allocated every effort in expediting this complex process.

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

Operative Technique

Following initial resuscitation and radiographic evaluation, potentially eligible patients underwent repeat CT scan with fiducials using a stereotactic protocol that utilized 1- or 2-mm slices that were then loaded onto a Stealth Station (Medtronic, Inc; Minneapolis, MN). Under general anesthesia, the patient’s head was fixed in a Mayfield clamp and a reference arc was attached to the apparatus. Fiducials were identified as landmarks on the CT scan using the Stealth planning software. The goal of placement was to center the catheter along the long axis of the clot with the tip of the catheter near the posterior end of the hematoma to allow maximum exposure of the clot to instilled rtPA. Virtual elongation of the pointer was used to determine burr hole placement and optimal trajectory and depth to the target. Following burr hole placement, the virtual pointer was placed on the dura to reconfirm trajectory and depth. The dura was then opened and a rigid brain cannula (Medtronic Inc, Minneapolis, MN) was placed along the predetermined trajectory to the desired depth. Following placement of the rigid catheter, manual hematoma aspiration was performed. No other methods to mechanically disrupt the clot were attempted. After measuring the aspirate volume, no more than 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

long and 1- to 2-mm internal diameter—(Codman, Raynham, MA) was placed along the same trajectory. The intraclot catheter was tunneled under the scalp and sutured in place.

Thrombolysis Protocol

In the operating room, 14/15 patients received 2 mg of 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 h. If ICP increased to 20-mm Hg or more for longer than 10 min, the catheter 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. Subsequent drug administration was performed using identical and sterile technique at the bedside in the ICU.

Information in regards to the ideal dose of rtPA in this clinical paradigm was extrapolated from available safety information [15–17], such that we administered 2 mg of rtPA into the clot cavity every 12 h 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 catheter fenestrations were no longer in continuity with the clot. Throughout the treatment protocol all patients underwent close neurological and ICP monitoring using standard external ventricular drainage (EVD) placed in the lateral ventricular system. The medical management of these patients followed the current recommendations formulated by the American Heart Association [18]. As is our usual practice, patients received daily coagulation parameter testing (e.g. prothrombin and partial thromboplastin times, platelet count). Following our usual practice, patients did not receive routine antibiotic prophylaxis.

Measurement of Intraparenchymal and Intraventricular Hematoma Volumes

Using the software “ImageJ” for Macintosh (v 1.32e, Wayne Rasband, NIH, Bethesda, MD), volume measurements of blood clots and their perihematomal edema were performed according to their specific signal density on head CT slices (Hyperdensity for hematoma regions and hypodensity within white matter and in perihematomal distribution for brain edema). The distinct boundaries of the hematoma and perihematomal edema areas (Fig. 1) were traced by hand on each slice by one of the investigators (JRC). The cross-sectional area of each slice (square

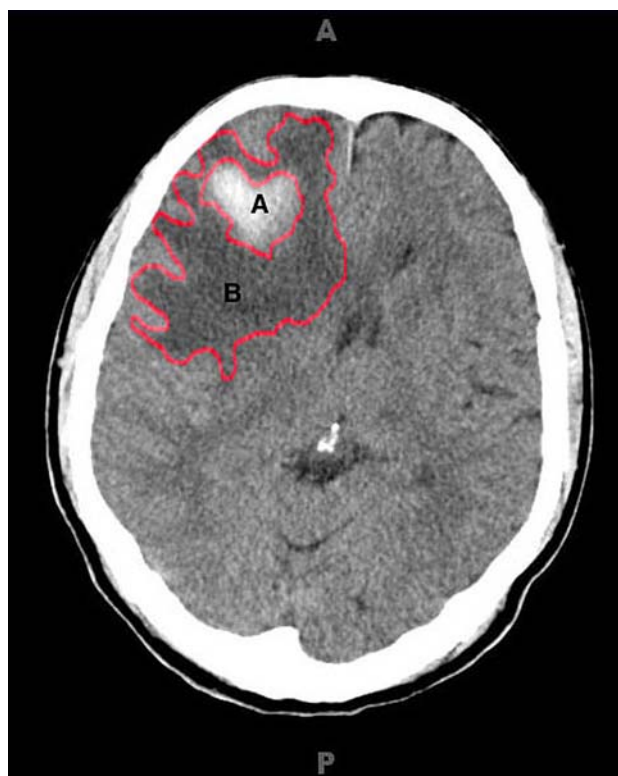


Fig. 1 Boundaries' definition for blood clots and perihematomal edema using predefined radiological criteria: (a) Hyperdensity for hematoma regions, and (b) hypodensity within white matter and in perihematomal distribution for brain edema

millimeters) was then multiplied by the slice thickness and added up to give the total hematoma and perihematomal edema volumes (cubic millimeters). We and other investigators have previously validated such an approach, with high inter- and intraobserver reliability in the measurements of ICH and perihematomal edema volumes using CT imaging [19, 20]. Single observer variability of less than 1.5% was previously reported by our group [19] when using this methodology in the study of IVH resolution.

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

Estimating Rate of Resolution and Association of Perihematomal Edema Volume and Hematoma Volume

Daily percent hematoma and edema resolution rate, and association between perihematomal edema volume and hematoma volume were estimated using random effects generalized least squares regression. The time of each CT from the start of lytic therapy was calculated in days. Rates of resolution for the hematoma and perihematomal edema were carried out taking into account the volume at the start of lytic therapy. Before carrying out regressions

to estimate the rate of hemorrhage (or edema) resolution over time, each patient’s data were first standardized into volume expressed as a percent of the patient’s hemorrhage (or edema) volume at the start of lytic therapy (time = 0). As the data are very sparse after the first 8 days (see Fig. 2) we estimated resolution using only data from the first 8 days following the start of therapy. Furthermore we excluded the two patients with hematoma enlargement. The data point for edema for patient 9 on day 5 violated the model’s assumptions about normally distributed residuals and was excluded. All statistical analyses were performed using STATA statistical software (STATA Corporation, College Station, TX) with tests being two-tailed. A *P*-value of less than 0.05 was considered to indicate statistical significance.

Results

Relevant demographic, clinical, and neuroradiologic 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, 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 the 15 patients had premorbid hypertension. Hematoma location was thalamic (1 patient), lobar (1 patient), and basal ganglia (13 patients). 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. Mean admission systolic blood pressure was 229.3 (range: 160–300; SD: 44.7) mmHg; mean diastolic blood pressure was 125.5 (range: 90–170; SD: 24) mmHg. One patient developed bacterial ventriculitis. The ICH drain remained in place 7.9 (range: 4–15;

Fig. 2 Relationship of perihematoma edema and intraparenchymal hematoma volumes during lytic therapy, by patient and by day

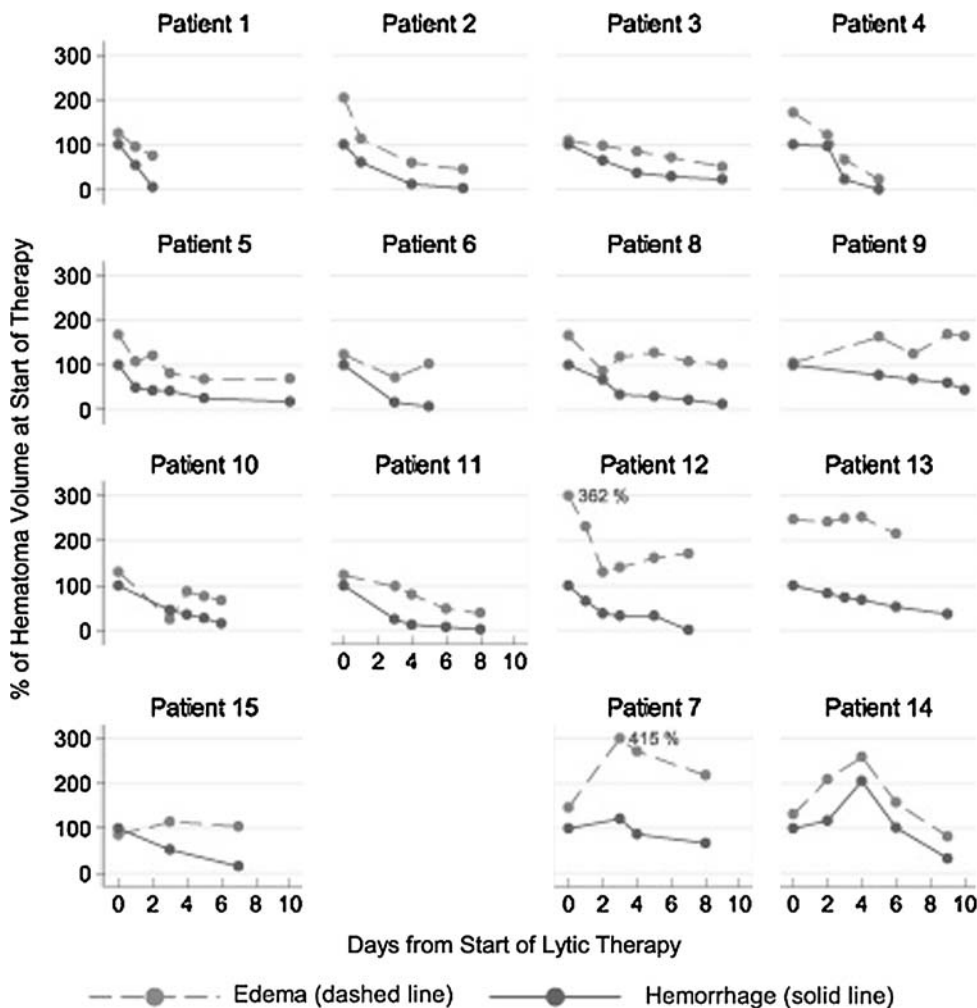


Table 1 Clinical characteristics of treatment cohort

Patient	Age/Sex	ICH onset to FAST (days)	Admission PP	Admission GCS	ICH location	IVH volume (cc)	ICH volume at onset of FAST (cc)	ICH volume at the end of FAST (cc)	Edema volume at onset of FAST (cc)	Edema volume at the end of FAST (cc)
1	73/M	1	1	9	BG	0	62.1	3.72	78.1	46.54
2	40/M	0	1	6	BG	0	53.9	1.7	110.4	24.36
3	50/M	1	1	10	BG	18.6	109.04	11.02	119.34	37.94
4	58/F	1	1	12	BG	0	28.79	0.30	49.3	6.62
5	53/F	0	1	14	BG	0	56.4	4.77	94.43	25.48
6	62/M	3	0	15	BG	0	40.08	3.26	50.33	41.77
7	79/M	N/A	N/A	N/A	BG	0	81.44	54.10	118.92	177.34
8	59/M	3	1	5	BG	53.8	72.05	8.99	119.48	73.30
9	80/M	1	0	13	Lobar	37.8	107.7	47.40	112.81	177.46
10	86/F	1	1	11	BG	0	77.06	21.01	100.26	50.82
11	64/F	2	0	6	BG	5.05	43.8	1.05	53.84	16.73
12	28/M	1	1	14	BG	0	54.1	17.28	195.83	87.21
13	54/F	2	1	4	Thalamic	14.91	36.55	2.83	90.02	35.36
14	64/M	2	0	9	BG	0	39.75	12.61	51.84	32.44
15	60/M	1	1	11	BG	0	23.5	3.64	19.85	24.39

PP, pulse pressure; 0, ≤ 85 mm Hg; 1, >85 mm Hg

M, male; F, female; BG, Basal ganglia; IVH, Intraventricular hemorrhage volume; ICH, Intracerebral hemorrhage volumes; GCS, Admission Glasgow Coma Score

N/A Not available

FAST: Frameless clot aspiration and thrombolysis

SD: 3.6) days. Patient 3 required repositioning of the ICH drain. There were two deaths (Patients 7 and 13). Care was not withdrawn or withheld in any of the 15 patients. Median GCS at the time of discharge was 11.0 ($n = 14$; range: 3–15; SD: 3.5). Besides two patients with enlargement of the ICH (Patients 7 and 14), no other clinical or laboratory-based evidence of CNS or systemic bleeding was reported. In patient 7, 20.15% hematoma enlargement was identified at day 3. No clinical information of this patient was available for further analysis. Patient 14 developed 16.97% hematoma enlargement on day 2 of the treatment with an associated GCS decline from 9 to 8. This hematoma enlargement peaked at 105.2% on day 4. Thrombolytic treatment was discontinued after day 2 in this patient.

Treatment

All 15 patients received rtPA for a mean of 4.8 (range: 2–10; SD: 2.3) days. Median time from ictus to clot aspiration and thrombolysis treatment was 1 (range: 0–3; SD: 0.92) day.

Neuroradiologic Features

Mean ICH volume at the start of rtPA lysis was 59.1 (range: 23.5–109; SD: 26.8) cc. Intraventricular hemorrhage was

present in five patients, with mean IVH volume of 8.7 (range: 0–53.8; SD: 16.4) cc. No intraventricular thrombolysis was administered in this patient cohort. Radiological evidence of ICH enlargement occurred in patients 7 and 14 (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 h from the onset of lytic therapy and 17% (range: 1–57.5; SD: 16.2) at the end of the treatment. Two patients demonstrated radiological evidence of non-enlarging, periventricular catheter tract contusion/hematoma; no such instances were recorded near the intraclot drain. Using a random effects model that considered volume resolution over the first 8 days following lytic therapy we found that the both percentage hematoma and percentage perihematoma edema resolution per day were quadratic with respect to time. Percentage residual hematoma volume on day $K = 97.7\% - [24.36\%*K] + [1.89\%*K^2]$; $P < 0.001$ for both terms. Percentage residual edema on day $K = 97.4\% - [13.94\%*K] + [1.30\%*K^2]$; $P < 0.001$ for K and $P = 0.01$ for K^2 . The relationship of hematoma and perihematoma edema volumes over the 10 days following the start of treatment is shown in Fig. 2 (by patient). To facilitate a comparison of the relative size of hematoma and perihematoma edema volumes for each patient over time all volumes are represented as percent of the patient's hematoma volume at the start of lytic therapy. Figure 2 not only

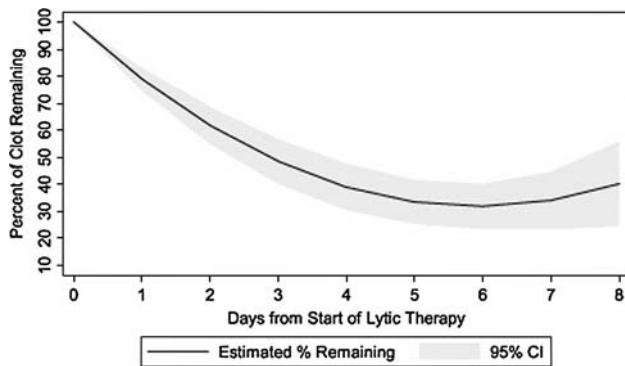


Fig. 3 Estimated ICH clot resolution by time from start of lytic therapy, excluding two patients with hematoma enlargement

depicts the overall downward trend in both hematoma and perihematomal edema volumes that was expressed by the regression equations presented above, but suggests that there exists a strong direct relationship between perihematomal edema volume and same day hematoma volume, occurring even as hematoma volume increased and then decreased in the two patients with hematoma enlargement. Figure 3 shows the estimated hematoma clot resolution over time from the start of lytic therapy and its 95% confidence interval. These are estimated from the regression models described above.

Discussion

We report on the evolution of perihematomal brain edema in the 15 patients treated using FAST. We identified significant rate of hematoma (9.65% per day) and perihematomal edema resolution (4.1% per day) as well as direct association between daily perihematomal edema and hematoma volumes ($P < 0.001$) within the first 8 days following institution of FAST. The precise mechanism for such association is unclear, although “hemotoxicity” inhibition via removal of blood/blood degradation products remains a plausible hypothesis that needs to be further tested.

Intense investigative effort is currently invested in better understanding mechanisms of secondary neuronal injury following ICH. Perihematomal edema has emerged as an important surrogate of pathological processes within brain tissue surrounding the blood clot that are triggered by the initial insult. It also has the distinct potential to negatively modify the overall outcome of ICH victims, as suggested by Zazulia and coworkers [1]. These investigators reported on a “second wave” of neurological injury that threatens ICH patients within the second and third weeks after the initial ictus. In this report, perihematomal edema was identified as directly or indirectly linked to neurological deterioration in a significant number of ICH patients, likely

due to elevated intracranial pressure and tissue shifts. In addition to the mechanical stress that edema inflicts on already challenged cranial vault dynamics, presence of vasogenic edema seems to also represent neuronal stress of different nature. Postulated processes triggered by blood and its degradation products vary from apoptosis to neuronal inflammation [2]. The long-term consequences of such processes on neurological function and recovery are poorly understood.

In view of the apparent lack of additional efficacy of surgical hematoma evacuation over best medical treatment in ICH patients, significant interest has developed in testing alternative therapies such as minimally invasive surgery to remove intracerebral hematomas [21, 22]. Different techniques include simple clot aspiration to more recently the application of fibrinolytic agents into the hematoma following the stereotactic placement of a soft catheter [15, 23–30]. Several small case series in the US 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 [10, 27, 31]. It is this lack of clinical experience in the use of this modality of treatment and the lack of randomized trial testing this high-risk therapy versus other more conventional/standard forms of therapy in ICH patients that makes FAST largely restricted to centers specialized in the advanced treatment of stroke patients. Although the natural history of intraparenchymal clot resolution is not yet reported, a daily clot resolution rate of 9.12% in our cohort of patients treated using FAST contrasts sharply against the observed spontaneous resolution seen in daily clinical practice. If such accelerated clot lysis modifies favorably survival, then functional neurological outcome and quality of life in these patients become important variables to be prospectively evaluated.

Reports on the effects of rtPA on neuronal tissue have shown conflicting results. In an experimental ischemic stroke paradigm, Wang and coworkers raised the concern that rtPA could promote neurotoxicity [32]. Using an ICH porcine model, Wagner and coworkers reported on the impact of clot removal using rtPA and on the associated reduction in perihematomal edema formation [3]. This positive interaction between clot removal and reduced edema formation seems to conform to the growing evidence assigning thrombin a neurotoxic role in hemorrhagic models of brain injury. Nevertheless, more recently, Thiex and coworkers have reported findings, also in a porcine model of experimental ICH, suggesting the lack of efficacy of clot removal in decreasing inflammation and perihematomal edema [33, 34]. Furthermore, Yepes and coworkers have recently suggested that rtPA opens the blood brain barrier in an experimental model of cerebral ischemia [9]. Although the exact nature of these conflicting

results of the effect of parenchymal clot lysis on perihematoma edema is unclear, translational limitations from experimental paradigms of brain injury to the living human model remain a testable hypothesis. Similar to what Wagner and coworkers reported, in our cohort of 15 patients treated with FAST, we identified both, hematoma volume reduction (achieved by the administration of rtPA) and edema volume reduction, as well as a significant association between these volumes each day. If reproduced, these results could be indicative of the beneficial effects of early clot removal, not only on the physical stress that such a mass causes on the cranial compliance of ICH patients, but also on mitigating the secondary neuronal injury mediated by the exposure of viable brain tissue to thrombin and other blood degradation products. Also, prospective confirmation of our results will strengthen the available literature addressing the safety of thrombolytic therapy in paradigms of acute brain injury.

The limitations of the current study are several, however:

First, the retrospective and selected nature of the study, as well as small sample size hamper generalizations of these results. Future prospective studies in an open, unbiased population testing the impact of clot aspiration-lysis on neurological outcome of ICH patients should confirm this preliminary association between hematoma resolution and perihematoma edema formation.

Second, the methodology used to quantify volumes of interest relies on visual identification and free-hand definition of the boundaries of the intraparenchymal clot (hyperdensity) and perihematoma edema (hypodensity) following standard diagnostic CT criteria. Although the visual identification and discrimination of such structures is less prone to subjectivity in T2 weighted- and FLAIR MR imaging, such an approach using CT imaging has been previously tested and validated by Zimmerman and coworkers [20]. These investigators found good inter- and intraobserver correlation for the measurements of edema volume (intra- and interclass correlation coefficient of 0.73 and 0.72, respectively), when using visually defined, free-hand methodology, as we did. Nevertheless, prospective studies aiming to validate our findings should incorporate MR imaging to their methodology to better define the accuracy of the more globally available CT measures. Furthermore, our patient cohort underwent CT imaging daily or every-other-day, thus minimizing errors in the accurate sequential description of the volumes of interest in this study. Future clinical trial testing thrombolytic therapy in ICH patients should be incorporated in their design daily CT imaging to address this issue.

Third, other clinical variables with reported potential to modify edema formation, such as serum glucose and blood pressure elevation, were not prospectively recorded during the treatment phase of these patients. Thus, the analysis of such data and their association to evolution of perihematoma edema was not incorporated in this study. Such variables should carefully be evaluated in prospective studies using clot aspiration and lysis in the treatment of ICH, to properly account for the actual response of perihematoma edema to clot removal.

In summary, our investigation allows us to postulate that parenchymal clot treatment using FAST protocol for ICH patients can lead to clot volume resolution with an associated amelioration of perihematoma edema formation. If confirmed in a prospective manner, these observed effects of rtPA on perihematoma edema formation provide an added benefit to clot lysis acceleration induced by this novel form of therapy in ICH. Furthermore, our observations serve as clinical evidence favoring the concept of blood/blood product induced neurotoxicity suggesting that the evacuation of intraparenchymal blood could become mandatory using minimally invasive procedures, once prospectively reproduced.

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