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Intraclot Recombinant Tissue-type Plasminogen Activator Reduces Perihematomal Edema and Mortality in Patients with Spontaneous Intracerebral Hemorrhage*

Li-fei LIAN (连立飞), Feng XU (许 峰), Zhou-ping TANG (唐洲平), Zheng XUE (薛 峥), Qi-ming LIANG (梁奇明), Qi HU (胡 琦), Wen-hao ZHU (朱文浩), Hui-cong KANG (康慧聪), Xiao-yan LIU (刘晓艳), Fu-rong WANG (王芙蓉), Sui-qiang ZHU (朱遂强)#

Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Summary: The study aimed to investigate the impact of intraclot recombinant tissue-type plasminogen activator (rt-PA) on perihematomal edema (PHE) development in patients with intracerebral hemorrhage (ICH) treated with minimally invasive surgery (MIS) and the effects of intraclot rt-PA on the 30-day survival. We reviewed the medical records of ICH patients undergoing MIS between October 2011 and July 2013. A volumetric analysis was done to assess the change in PHE and ICH volumes at pre-MIS (T_1), post-MIS (T_2) and day 10–16 (T_3) following diagnostic computed tomographic scans (T_0). Forty-three patients aged 52.8±11.1 years with (n=30) or without rt-PA (n=13) were enrolled from our institutional ICH database. The median rt-PA dose was 1.5 (1) mg, with a maximum dose of 4.0 mg. The ratio of clot evacuation was significantly increased by intraclot rt-PA as compared with controls (77.9%±20.4% *vs.* 64%±15%; P=0.046). From T_1 to T_2, reduction in PHE volume was strongly associated with the percentage of clot evacuation (ρ=0.34; P=0.027). In addition, PHE volume was positively correlated with residual ICH volume at the same day (ρ ranging from 0.39–0.56, P<0.01). There was no correlation between the cumulative dose of rt-PA and early (T_2) PHE volume (ρ=0.24; P=0.12) or delayed (T_3) PHE volume (ρ=0.19; P=0.16). The 30-day mortality was zero in this cohort. In the selected cohort of ICH patients treated with MIS, intraclot rt-PA accelerated clot removal and had no effects on PHE formation. MIS aspiration and low dose of rt-PA seemed to be feasible to reduce the 30-day mortality in patients with severe ICH. A large, randomized study addressing dose titration and long-term outcome is needed.

Key words: intracerebral hemorrhage; minimally invasive surgery; clot aspiration; perihematomal edema; recombinant tissue-type plasminogen activator

Spontaneous intracerebral hemorrhage (ICH) is a serious and often fatal stroke subtype. It has an annual incidence of 20 per 100 000, accounting for 10%–15% of all strokes in the United States and up to 30%–50% in China[1]. The primary damage, caused by the mechanical effect of the hematoma on surrounding brain tissue, as well as the secondary cascade of processes, such as perihematomal edema (PHE), is responsible for the high 30-day mortality and poor clinical outcome in survivors[2–5]. Hematoma volume is the strongest predictor of poor outcome in patients with ICH[3]. In theory, hematoma evacuation is beneficial because it reduces clot size and lowers the chance of PHE formation. However, no proven medical or surgical treatment for ICH or PHE currently exists.

Fibrinolytic therapy for spontaneous ICH using recombinant tissue plasminogen activator (rt-PA) has been considered to be a promising treatment strategy over the last 20 years. Studies show minimally invasive surgery (MIS) combined with intraclot rt-PA can help to reduce clot size and early PHE volume[6–8], with a trend towards decreased short-term mortality[9, 10]. However, preclinical data suggest local administration of rt-PA for clot lysis and aspiration may exert dose-dependent pro-edematous effects and aggravate PHE formation[11–15]. Therefore, it seems likely that the benefits of fibrinolytic therapy with rt-PA for ICH may be counteracted by PHE exacerbation. As evidenced in a recently retrospective study, intraventricular rt-PA administration exacerbated PHE and the presence of sterile meningitis in patients with intraventricular hemorrhage (IVH)[16]. Thus, the safety and feasibility of local rt-PA administration is a major topic of concern in this context. Thus, we addressed the effect of low dose rt-PA on PHE formation in ICH patients treated with MIS and its effects on their 30-day survival in the current study.

We hypothesized that clot evacuation leads to re-

Li-fei LIAN, E-mail: lianlifei@gmail.com
#Correspponding author, E-mail: zhusuiqiang@163.com
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duction in PHE and that intraclot rt-PA does not exacerbate early or late PHE after ICH in a series of ICH patients treated with MIS and rt-PA (rt-PA group) or MIS aspiration alone (control).

1 MATERIALS AND METHODS

1.1 Patient Selection

The study was approved by the Institutional Review Board at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China. We initially identified patients with a diagnosis of spontaneous ICH, who were hospitalized and treated with MIS at our neurological intensive care unit (NICU) from October 2011 to July 2013. We obtained demographic, clinical, and radiological data from our prospectively organized institutional ICH database where admissions are recorded.

Inclusion criteria for MIS were as follows: age >18 years; Glasgow coma scale (GCS) score between 4 and 14 on admission; no severe concurrent illness with life expectancy <6 months; diagnostic computed tomographic (CT) scan (T_0) with evidence of supratentorial ICH ≥20 mL shown to be stable for >6 h following a second CT scan; MIS was performed between 6 and 72 h after onset; CT angiography was obtained prior to MIS to rule out vascular anomaly; written informed consent must be obtained from the patient or legal surrogate before MIS.

Exclusion criteria for MIS were as follows: infratentorial hemorrhage; ICH caused by trauma, intracerebral tumor, or vascular malformation; severe IVH requiring external ventricular drainage (EVD); clinical and radiological signs of brain herniation on admission; patients with "do not resuscitate" orders, surgical hematoma evacuation, pregnancy, or lack of informed consent; severe neurological deficit (modified Rankin Scale ≥2) prior to ICH.

1.2 Volumetric Assessment of ICH and PHE

CT scans were performed on a fourth-generation scanner (Lightspeed VCT, GE, USA). The majority of CT scans consisted of 5.0–7.5 mm thick slices through both skull base and cerebrum. Because time points of CT acquisition were not identical among patients, the following time clusters were defined to analyze the change in PHE and ICH volumes during the course of treatment: diagnostic CT (T_0), pre-MIS (T_1), post-MIS (T_2) and day 10–16 after the attack (T_3). The distinct boundaries of ICH and PHE areas were independently traced by hand on each slice by 2 trained investigators who were blind to clinical data using a computerized image analysis software (Image J; NIH, Bethesda, USA). Briefly, the volumes of ICH and PHE were measured according to their specific signal density on CT slices, with hyperdensity representing hematoma and hypodensity surrounding hematoma considered PHE (fig. 1). The ICH volume was calculated for each slice from the traced area and corresponding slice thickness, results were summed. Total lesion volume was determined similarly. PHE volume was determined by subtracting the ICH volume from the total lesion volume. Relative PHE (rPHE) was defined as a ratio of PHE volume to T_1 ICH volume.

1.3 MIS and Thrombolysis Protocol

Patients were treated in a dedicated NICU with staff experienced in the acute care of patients with ICH and MIS. MIS was performed under local anesthesia according to previously described protocol[17–19]. In brief, the target and puncture track were defined according to the pre-MIS CT scan (T_1) and the puncture point was measured and marked on the head surface. The YL-1 type of hematoma puncture needle (Beijing WanTeFu Medical Apparatus Co., Ltd, Beijing, China) of suitable length was then fixed to the operative electric drill and entered to the predetermined depth. Then the probe core was removed, and hematoma was manually and gently aspirated using a 5 mL syringe until the clot could not be aspirated easily. If clot aspiration alone did not reach a clinical endpoint, intraclot rt-PA was injected under sterile conditions. The hematoma evacuation was performed by two trained neurologists.

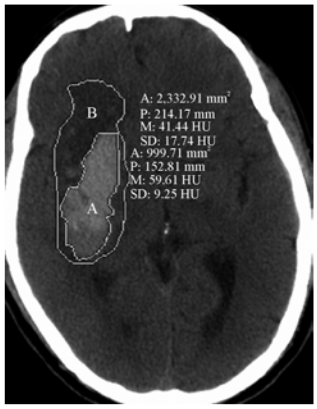

Fig. 1 CT scan showing region of interest for ICH and PHE
A: hyperdensity for ICH; B: hypodensity surrounding hematoma for PHE

After the postoperative CT scan, patients received a first dose rt-PA (Alteplase, Boehringer Ingelheim, Germany) dissolved in 1.0 mL of normal saline no sooner than 1 h and no later than 24 h after MIS. The catheter was slowly flushed with 2.0 mL of normal saline. After each injection, the catheter was clamped for 2 h to allow adequate time for interaction of rt-PA and clot. The catheter was then unclamped to drain hematomas at the gradient set by the treating physician. The regimen of rt-PA injection was either 0.5 mg or 1.0 mg every 24 h, up to 4.0 mg, until a clinical endpoint. Clinical endpoints included reduction of clot to 80% of T_1 ICH volume, T_2 ICH volume ≤10 mL or the clot around the tip of the needle nearly invisible. Safety endpoints included any clinically significant rebleeding events, any new ICH, central nervous system (CNS) infection, or death. CT scans were obtained before each dose of rt-PA to evaluate drainage. The daily volume of liquid drainage was recorded throughout the treatment period. All patients received close neurological surveillance with daily GCS assessment during the study period.

1.4 Medical Treatment Protocol

The medical management of these patients followed standard NICU care procedures according to our institutional protocol, which followed the guidelines from the American Heart Association[20]. Following our institu-

tional practice, patients received routine antibiotic prophylaxis and daily coagulation parameter testing.

1.5 Outcome Assessment

The following clinical outcomes were assessed: 30-day mortality, ICU length of stay, CNS infection, MIS-associated hemorrhage, and symptomatic rebleeding. The predicted 30-day mortality using the ICH score[21] was 48.6% in this series of ICH patients.

1.6 Statistical Analysis

Continuous data were given as $\bar{x}\pm s$, and ordinal variables were expressed as median and interquartile range. Shapiro-Wilk test was used for normality of distribution. Student's *t*-test or ANOVA test was used for normally distributed data. Other data were compared using nonparametric Mann-Whitney *U* test. Frequency distributions were analyzed using the Chi-square and Fisher's exact tests. Correlation analysis was performed using the Spearman correlation test. Inter- and intra-rater reliability for volume measurements was determined using intraclass correlation coefficient. All statistical analyses were performed with SPSS 11.5 statistical software, with 2-tailed tests. A value of $P<0.05$ was considered statistically significant.

2 RESULTS

2.1 Patient Characteristics

Sixty-three patients treated with MIS (n=45 for rt-PA group, and n=18 for control group) between October 2011 and July 2013 were initially identified. Twenty patients (n=15 for rt-PA group, and n=5 for control group) were excluded because of hospital stay <10 days. The enrolled included 30 cases in rt-PA group, and 13 cases in control group. The demographic, clinical, and radiological characteristics of the patients are shown in table 1.

Table 1 Demographic, clinical, and radiological characteristics

	rt-PA (n=30)	Control (n=13)	P value
Age (years)	53.3±11.9	51.9±9.3	0.71
Male (n, %)	20, 66.7%	9, 69.2%	1.00
HP (n, %)	39, 65.0%	13, 65.0%	1.00
Admission SBP (mmHg)	166.7±22.2	166.2±15.3	0.92
Admission DBP (mmHg)	97.8±15.0	95.0±10.3	0.44
Admission GCS	10 (3)	10 (5.75)	0.68
Admission NIHSS	23 (6)	19 (8.5)	0.16
Time from onset to T_0 (h)	2.9±1.0	3.1±1.7	0.09
Time from onset to T_1 (h)	37.4±17.6	43.9±20.6	0.17
Time from T_1 to T_2 (days)	5.0±1.4	4.4±2.6	0.32
Time from onset to T_3 (days)	11 (5)	12 (4)	0.96
Side of ICH (left/right)	23/7	7/6	0.14
Clot location (lobar/deep)	5/25	3/10	0.68
IVH present (n, %)	13, 43.3%	5, 38.5%	0.77
Hematoma expansion (n, %)	8, 26.7%	3, 23.1%	0.80
T_0 ICH volume (mL)	44.1±23.1	41.7±23.8	0.86
T_0 PHE volume (mL)	33.1±17.6	25.7±8.9	0.17
T_0 rPHE	0.83±0.36	0.77±0.42	0.61

DBP: diastolic blood pressure; GCS: Glasgow Coma Scale; HP: hypertension; ICH: intracerebral hemorrhage; IVH: intraventricular hemorrhage; NIHSS: National Institutes of Health Stroke Scale; PHE: perihematomal edema; rPHE: relative perihematomal edema; rt-PA: recombinant tissue-type plasminogen activator; SBP: systolic blood pressure

No significant differences were found between rt-PA and control groups in any admission variables, including age, sex, time from onset to T_0, T_1, T_2 and T_3, ICH volume (44.1±23.1 mL *vs.* 41.7±24.6 mL; P=0.86), PHE volume (33.1±17.6 mL *vs.* 25.7±8.9 mL; P=0.17), and rPHE (0.83±0.36 *vs.* 0.77±0.42; P=0.61). The average age of the 43 patients was 52.8±11.1 years, with a median GCS score of 8 (5) and a median NIHSS score of 22 (7). The patients treated with intraclot rt-PA received a median of 2 (1) rt-PA doses (varied from 1 to 4 doses) with a median total dose of 1.5 (1) mg (varied from 0.5 mg to 4.0 mg). There was no relationship between cumulative rt-PA dose and rebleeding occurrence (ρ=0.26; P=0.17). In addition, there was no significant difference in the total volume of liquid drainage between T_1 and T_2 in both two groups [150 (360) mL *vs.* 150 (157.5) mL; P=0.07].

2.2 ICH Volume Reduced over Time

The mean volume of ICH at T_1 in rt-PA group and control group was similar (46.4±22.8 mL *vs.* 43.0±24.6 mL; P=0.86). We found no significant difference in residual hematoma at T_2 between the two groups (10.7±7.8 mL *vs.* 15.6±11.7 mL; P=0.12). Mean residual T_3ICH volume was comparable in both two groups (5.8±6.5 mL *vs.* 7.3±8.4 mL; P=0.54) (table 2 and fig. 2A).

Our data showed the hematoma volume was significantly smaller in both two groups at T_2 and T_3 than at T_1 (table 2 and fig. 3; within-group comparison, ANOVA; P<0.001). As demonstrated in table 2, there was significant difference in the ratio of clot removal between two groups (77.9%±20.4% *vs.* 64%±15%; P=0.046).

2.3 PHE Volume Reduced over Time

We also measured the change in PHE volume and rPHE in rt-PA group and control group over time. As can be seen in table 2 and fig. 2B–2C), the initial PHE volumes at T_1 between the two groups were similar (35.7±18.3 mL *vs.* 29.1±9.9 mL; P=0.13). We found no significant difference in rPHE at T_1 in rt-PA group and control group (0.84±0.41 *vs.* 0.84±0.39; P=0.99). Our data showed no significant changes in PHE and rPHE at

T_2 in both two groups (27.2±14.6 mL *vs.* 29.8±19.7 mL in PHE, P=0.64; 0.65±0.39 *vs.* 0.79±0.43 in rPHE, P=0.31). There were also non-significant differences in PHE and rPHE at T_3 in rt-PA group and control group (34.4±17.5 mL *vs.* 38.8±25.7 mL in PHE; P=0.52; 0.84±0.48 *vs.* 1.0±0.64 in rPHE; P=0.26).

As shown in table 2 and fig. 3, PHE volume remained unchanged in both two groups during the whole 10–16 day period after ICH (within-group comparison, ANOVA, P>0.05). rPHE was also stable over the same time course (within-group comparison, ANOVA, P>0.05). The treatment effect on PHE and ICH is depicted in fig. 4. These data suggest that the clot evacuation leads to reduction in PHE and intraclot rt-PA enhances clot removal without pro-edematous effects.

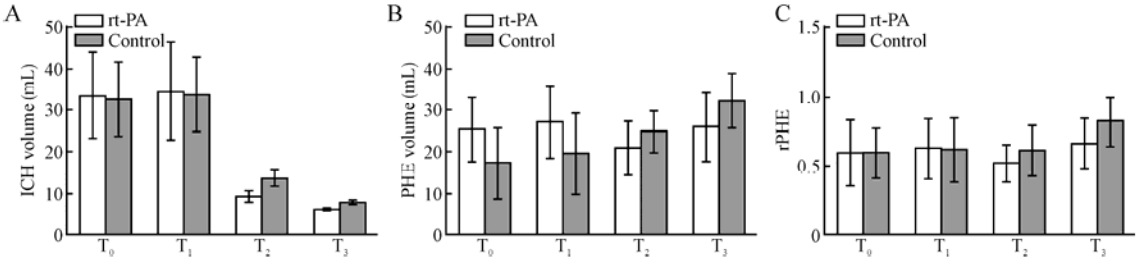

Fig. 2 Histogram for the rt-PA and control groups at different time points

No significant differences in ICH volume (A), PHE volume (B) and rPHE (C) could be shown between the two groups at T_0, T_1, T_2 and T_3 respectively. T_0: the time at which diagnostic computed tomographic scans were performed; T_1: pre-MIS; T_2: post-MIS; T_3: day 10–16 after onset. These abbreviations were applied to all figures and tables.

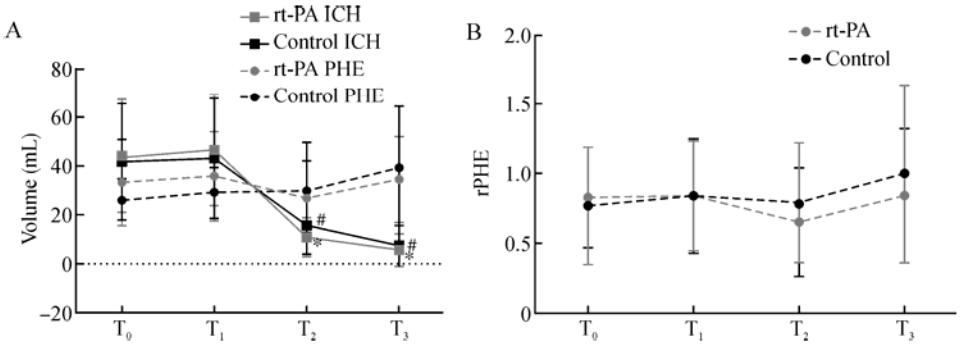

Fig. 3 Chronological change of ICH, PHE and rPHE from T_0 to T_3 between the rt-PA group and the control group

$^*P$<0.05 *vs.* rt-PA ICH group, $^\#P$<0.01 *vs.* control ICH group

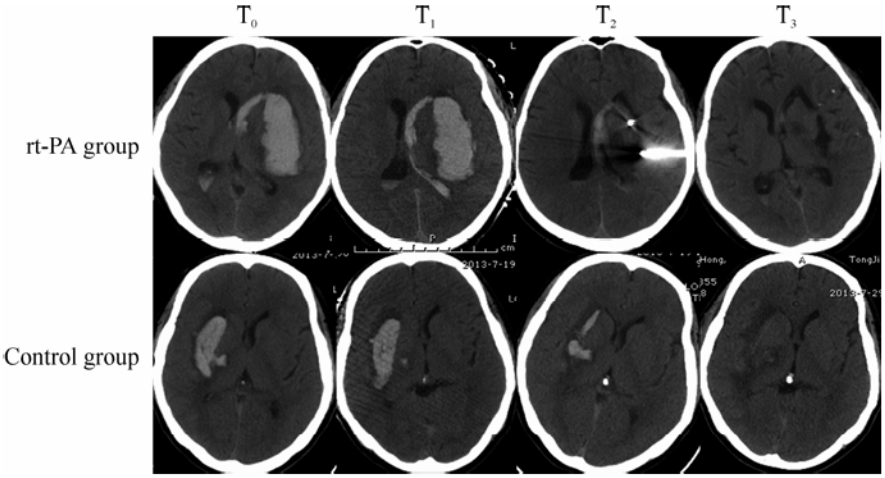

Fig. 4 Representative CT scans in rt-PA group and control group

2.4 Correlation between PHE and ICH

We found that PHE volumes were strongly correlated with ICH volumes at the same day in both two groups (ρ ranging from 0.39–0.56, P<0.01). Data indicated a larger residual hematoma was associated with larger PHE. There was no correlation between the cumulative dose of rt-PA and early (T_2) (ρ=0.24; P=0.12) or late (T_3) PHE volume (ρ=0.19; P=0.16). Furthermore, the percentage of clot evacuation was significantly associated with reduction in PHE volume (ρ=0.34; P=0.027).

2.5 Clinical Outcome

In this series of MIS-treated patients, median GCS scores were 8 (4.5) at admission and 12 (3.5) at hospital discharge (P=0.000<0.01). There were no deaths and no

CNS infection or seizures during the course of treatment. In addition, there were no significant differences in symptomatic rebleeding (6.7% *vs.* 7.7%; P=1.0), MIS-associated hemorrhage (6.7% *vs.* 7.7%; P=1.0), or length of ICU stay [12 (7.5) *vs.* 15 (8.5) days; P=0.89] between the two groups.

2.6 Excluded Patients with Hospital Stay <10 Days

Thirty-day mortality was zero in the excluded 20 patients who did not receive CT scans at T_3. Ten cases (n=7 for rt-PA group, and n=3 for control group) were transferred to local hospital because of economic reasons, and 10 cases (n=8 for rt-PA group, and n=2 for control group) went to rehabilitation center after hospital discharge when the hematomas were almost completely removed. There was a significant difference in the ratio of clot removal in rt-PA group and control group (81.7%±10% *vs.* 59.1%±17.8%; P=0.001). The mean volume of ICH at T_1 in both two groups was similar (49.2±19.9 mL *vs.* 37.3±7.2 mL; P=0.14). Mean T_1 PHE volume was comparable in both two groups (46.2±13.3 mL *vs.* 35.5±11.6 mL, P=0.43). There was a significant difference in residual hematoma at T_2 between the two groups (8.8±5.2 mL *vs.* 15.9±9.4 mL; P=0.048). T_2 PHE volume was similar in rt-PA group and control group (38.4±14.9 mL *vs.* 53.0±19.2 mL; P=0.065).

3 DISCUSSION

We report preliminary feasibility and safety data based on our experience with MIS and thrombolysis of ICH in a cohort of patients treated at a university-affiliated hospital. Our findings confirm that clot removal is associated with significant reduction in PHE. Furthermore, low dose rt-PA enhances hematoma evacuation and does not increase early or late PHE. Importantly, there seems to be a trend towards improved 30-day survival.

PHE commonly occurs after ICH. There are several underlying mechanisms responsible for PHE formation[22]. In the early phase (especially in the first few hours), hydrostatic pressure increases and clot retracts, allowing the remaining serum proteins to move from the hematoma into the surrounding tissues. The second phase, beginning from 24 h after attack, is characterized by a coagulation cascade and thrombin formation. The third phase, beginning from 72 h after attack, is primarily related to the toxicity of clot degradation products. In our study, MIS led to a significant reduction in hematoma and a relatively stable PHE during the first 10–16 days after ICH. In addition, the ratio of clot removal was significantly associated with reduction in PHE. Thus, these data support the concept that removal of clot/clot degradation products prevents PHE formation.

The clinical significance of PHE remains to be answered as yet. PHE develops early and reaches 2- to 3-fold the original ICH volume in the next 10–20 days after ICH[4]. Several studies reported that the additional mass effect caused by PHE growth contributed to delayed neurological deterioration as late as 2 to 3 weeks and poor outcomes after ICH[4, 5, 23]. Experimental data indicated intraclot rt-PA may exert dose-dependent pro-edematous effects and exacerbate PHE formation in the treatment of ICH[11–15]. Ducruet *et al* recently found a significant increase in PHE as well as rates of sterile meningitis and a trend toward shunt dependence in patients treated with intraventricular rt-PA[16]. Thus, taking into account the benefits of fibrinolytic therapy with rt-PA for ICH may be counteracted by PHE growth, such neurotoxic effects of intraclot rt-PA has been a source of concern. In this study, there was a significant correlation between PHE volume and residual ICH volume of the same day. In addition, the injection of rt-PA led to a larger ratio of ICH removal and a smaller residual ICH volume. Importantly, we did not find any correlation between the cumulative rt-PA dose and either early or late PHE volume. Thus, the rt-PA dose in this study seemed to be safe for PHE.

The optimal regimen of intraclot rt-PA for the treatment of ICH remains unknown. Literature on locally administered rt-PA varied greatly in dose, ranging from single dose of 0.3 mg–8.0 mg with a cumulative daily doses up to 32.0 mg, and in dose interval, ranging from 6 to 24 h[6, 9, 10, 12–15]. Some of the best evidence available for intraclot rt-PA administration came from multicenter prospective trials assessing safety, optimum dose, and frequency for ICH[7] and IVH[24, 25]. These studies recommended a dose of 1.0 mg rt-PA every 8 h with maximum of 9.0 or 12.0 mg. To date, little was known regarding the integrity of the brain tissue exposed to rt-PA. Figueroa *et al* reported that PHE caused by thrombin was significantly aggravated by intraclot rt-PA[11]. Perhaps the exogenous rt-PA mediated up-regulation of excitotoxicity or it competed with endogenous thrombin inhibitors[11, 13, 15]. Our findings supported low-dose of intraclot rt-PA could enhance the hematoma removal in MIS-treated ICH patients. In addition, we did not find any increased risk in rt-PA-related rebleeding, CNS infection or seizures. The neurotoxicity of clot degradation products may be more harmful to the perihematomal tissue than rt-PA itself. Thus, faster and more effective removal of hematoma after lysis using rt-PA may bring more clinical benefit for ICH patients. Clinical protocols addressed to remove clot and reduce PHE after ICH needs to be further investigated.

The ICH score is a commonly used clinical grading scale, and its validity is confirmed in predicting 30-day mortality in different socioeconomic populations[21, 26, 27]. In brief, this score predicted a 30-day mortality probability based on the following variables: GCS score, ICH volume, presence of IVH, infratentorial location of ICH, and the age of the patient. Thirty-day mortality rates for patients with ICH scores of 0, 1, 2, 3, 4 and 5 were 0, 13%, 26%, 72%, 97% and 100%, respectively[21]. After comparing the calculated 30-day mortality and the observed mortality of this cohort, MIS seemed to lead to significantly low 30-day mortality. In addition, the safety of rt-PA has been an issue of concern from its first use in ICH and IVH. Although the regimen of rt-PA had little effect on overall coagulation status, the Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage trial (CLEAR-IVH) found the ratio of symptomatic rebleeding in the rt-PA group was higher than that in controls[28]. In this study, the rebleeding risk was very low, and we did not find any correlation between cumulative dose of rt-PA and the occurrence of rebleeding. Thus, the regimen of low-dose rt-PA, 0.5 mg

or 1.0 mg every 24 h with a maximum of 4.0 mg, may be feasible for ICH patients treated with MIS. Future randomized studies are warranted to test dose titration of this treatment.

It is important to admit that our study has several unavoidable limitations, which are mainly derived from its retrospective design and small sample size. Firstly, PHE is difficult to delineate and assess on CT scans. However, the volumetric algorithm of this study was previously tested and validated with high inter- and intra-observer reliability in the measurements of ICH and PHE[29]. Secondly, other clinical factors, which may have contributed to PHE evolution, such as temperature, glucose, and serum osmolality, were not assessed in this study. However, the patients were treated with the same strategies, including management of temperature, glucose and intracranial pressure. Thirdly, we merged several days into single time points to analyze the change in PHE and ICH volumes during the first 10–16 days after ICH. Therefore, our conclusions are limited to that time period. Fourthly, we compared the observed cohort mortality with its predicted 30-day ICH mortality. Thus, no firm conclusions related to mortality can be made. Hopefully, these questions can be answered after completion of the ongoing clinical trial Minimally Invasive Surgery and rt-PA for ICH Evacuation phase Ⅲ (MISTIE Ⅲ).

In summary, MIS and rt-PA led to a significant reduction in ICH without relevant increase in either early or delayed PHE. rt-PA doses used in this study seemed to be safe for PHE. MIS aspiration and low dose rt-PA seemed to be feasible and to have a trend towards decreased 30-day mortality. Future prospective, randomized studies are needed to test the dose titration and the clinical efficacy of this treatment.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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