

Minimally invasive stereotactic puncture and thrombolysis therapy improves long-term outcome after acute intracerebral hemorrhage

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Abstract The purpose of this study was to judge the clinical value of minimally invasive stereotactic puncture and thrombolysis therapy (MISPTT) for acute intracerebral hemorrhage (ICH). A randomized control clinical trial was undertaken. According to the enrollment criteria, 122 acute ICH cases were analyzed, of which 64 cases received MISPTT (MISPTT group, MG) and 58 cases received conventional craniotomy (CC group, CG). The Glasgow coma scale (GCS) scores, postoperative complications (PC), and rebleeding incidences were compared. Moreover, 1 year postoperation, the long-term outcomes of patients with regard to hematoma volume (HV) <50 mL and HV ≥50 mL were judged, respectively, by the Glasgow

outcome scale (GOS), Barthel index (BI), modified Rankin Scale (mRS), and case fatality (CF). MG patients showed obvious amelioration in GCS score compared with that of CG patients. The total incidence of PC in MG decreased compared with that of CG. The incidences of rebleeding in MG and CG were 9.4 and 17.2%, respectively ($P = 0.243$). There were no obvious differences between the CFs of MG and CG (17.2 and 25.9%, respectively, $P = 0.199$). The GOS, BI, and mRS representing long-term outcome for both HV <50 mL and HV ≥50 mL in MG were ameliorated significantly greater than that in CG patients (all $P < 0.05$). These data suggest that there are advantages with MISPTT not only in trauma and safety, but the MISPTT group had fewer complications and a trend toward improved short-term and long-term outcomes.

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Introduction

Spontaneous intracerebral hemorrhage (ICH) comprises 8–30% of all stroke victims, depending on regional and ethnic differences, and is a devastating form of stroke with the high mortality twofold to sixfold higher than that for ischemic stroke [1] and a 1-year survival rate less than 50% [2]. Hitherto, morbidity and mortality following ICH remain the highest among all forms of cerebrovascular diseases, with a 30-day mortality rate of 35–52%, with 50% of the deaths occurring in the first 2 days [3–5]. After initial irreversible tissue injury is suffered near the hemorrhage nidus, a progressive cascade of elevated local pressure, edema, and excitotoxicity cause additional

secondary injury to surrounding areas [6–8]. Secondary brain injury by hematoma often occurs in the days following the initial hemorrhage and is intimately associated with significant neurological deterioration.

Despite being considerably frequent, the treatment of hematomas within the basal ganglia continues to be a matter of debate among neurologists and neurosurgeons. The present powerful evidence provided by the results of the International Study of the Treatment of Intracranial Hemorrhage (STICH) corroborates this statement which has been established previously: there was not significant benefit for conventional aggressive surgical treatment over conservative medical treatment for the acute care of ICH [9]. Nevertheless, more than 7,000 patients with ICH in the United States undergo traditional evacuation procedures each year [10].

However, various clinical studies testing the hypothesis that clot burden plays a significant role in several forms of intracranial hemorrhage have been published in recent years, suggesting that clot reduction plays an important role in limiting brain edema and additional neuronal injury, as well as in reducing the severity of neurological deficits following ICH [11–14]. Because of the lack of validated therapeutic options for this form of stroke, the role of minimally invasive surgery (MIS) in the treatment of ICH has gained importance and several different operational methods have emerged over the past decade. In this context, our treatment with a stereotactic technique, which we have termed minimally invasive stereotactic puncture and thrombolysis therapy (MISPTT), is herewith presented.

MISPTT is a novel operative technique for ICH, which was developed by Pro Jia in 1997. Although several clinical studies on MISPTT in the acute phase of ICH have been published during the past decade, the impact of MISPTT on the short-term and long-term neurological function of patients who survive the acute phase is less clear. The purpose of the present study was to investigate whether the long-term and short-term benefits of MISPTT are maintained and whether this method improves the ultimate outcome in these ICH patients. Therefore, we compared the long-term outcome 1 year after treatment in a consecutive series of ICH patients treated by MISPTT with the results achieved in a comparable group of patients who were treated by conventional craniotomy (CC).

Methods

A randomized control clinical trial was undertaken. All ICH patients were in-hospital patients from 2005–2008 diagnosed with ICH, according to the ICH criteria drafted by ASA [15]. All cases were monitored in a dedicated stroke unit. The volume of the ICH in milliliters (mL) was

estimated on the basis of approximate ellipsoid volume with the formula $A \times B \times C/2$, where A represents the largest diameter of the hematoma on axial CT slices in centimeters, B the diameter of hematoma perpendicular to A on the same slice, and C the number of CT slices in which the hematoma is visible multiplied by the slice thickness in centimeters [16, 17].

Inclusion and exclusion criteria for patients

Inclusion criteria were as follows: (1) diagnosed as having spontaneous hemorrhage in the basal ganglion or brain lobe of the brain by CT scan; (2) hemorrhage volume: 30–100 ml; (3) age range: 40–75 years; (4) muscle strength of the paralyzed limbs: grades 0–3 on the muscle strength scale; (5) hemorrhagic duration (from stroke onset to hospital) within 24 h; and (6) informed consent from patients and/or their legal representative.

Exclusion criteria were as follows: (1) disturbances of blood coagulation, e.g., thrombocytopenia, hepatitis; (2) traumatic intracranial hemorrhage; (3) intracranial or general infection; (4) complicated with serious heart, liver, renal, or lung disease or functional failure; (5) a previous stroke history with neurological deficits; (6) intracranial aneurysm or arteriovenous malformation complicated with hemorrhage; (7) consent form not obtained from the patient or their legal representative.

There were 122 patients analyzed, of which 64 cases were treated with MISPTT and 58 cases with CC. There were no statistically significant differences in sex, age, GCS score, localization of bleeding, hemorrhage volume, or blood pressure level during hospitalization, duration of hypertension and the accompanying diseases in the two groups. Although the accompanying diseases such as diabetes, hyperlipidemia, coronary heart disease and cerebral infarction in the two groups were similar (all $P > 0.05$), diabetes accounted for 62.5% and 60.3%, respectively, in MISPTT group and CC group, and was perhaps one important risk factor for ICH onset (Table 1).

Treatment methods

Minimally invasive stereotactic puncture and thrombolysis therapy

All operations were performed under local anesthesia and intravenous sedation unless the patient was already intubated for medical or neurological indications independent of the procedure. Stereotactic aspiration of the hematomas was performed in the acute phase between the 6th and the 24th hour after onset of stroke as required in the MISPTT protocol. First, the target points were defined according to the CT, and target points were generally chosen in the scan

Table 1 The baseline characteristics of patients

Group	MISPTT patients	CC patients	<i>P</i> value
Number of patients	64	58	
Gender (m:f)	41:23	38:20	0.866
Mean age (years)	58.7 ± 9.0	57.6 ± 8.6	0.483
GCS score (<i>n</i> /%)			0.998
4–5	7/10.9	6/10.3	
6–9	22/34.4	20/34.5	
10–12	23/35.9	19/32.8	
13–15	12/18.8	13/22.4	
Hematoma volume (<i>n</i> /%)			0.987
30–49 (mL)	27/42.2	22/37.9	
50–79 (mL)	23/35.9	21/36.2	
80–100 (mL)	14/21.9	15/25.9	
Direction of the hematoma (<i>n</i> /%)			0.468
Left-sided	34/53.3	27/51.3	
Right-sided	30/46.7	31/48.7	
Location of the hematoma (<i>n</i> /%)			0.344
Basal ganglia	48/53.3	39/50.0	
Thalamus	16/17.8	19/24.4	
Mean BP			
SBP	174.3 ± 14.1	172.2 ± 11.0	0.361
DBP	96.7 ± 9.7	98.8 ± 9.4	0.255
Duration of BP (years)	7.1 ± 1.9	7.4 ± 2.0	0.312
Accompanied disease (<i>n</i> /%)			
Diabetes	40/62.5	35/60.3	0.807
Hyperlipidemia	27/42.2	22/37.9	0.632
Coronary heart disease	20/31.3	21/36.2	0.563
Cerebral infarction	14/21.9	15/25.9	0.605

with the largest expansion of the hematoma and special attention was paid to stay away from important cortex function areas (Fig. 1). Puncture situs was measured and marked on the head, again avoiding main blood vessels, then a puncture needle of suitable length (type YL-1) was fixed to the operative electric drill. The puncture needle was entered to the predetermined depth, then the probe core was removed; the hematoma was withdrawn gently using a syringe (diluted with saline if blood thickened) until one-third of hematoma was removed, then a needle-like hematoma disintegrator was inserted. When no more blood could be withdrawn, the hematoma cavity was thoroughly rinsed with saline, until the saline fluid was clear.

To confirm gross hematoma evacuation, an immediate postoperative CT scan was taken to assess the puncture needle placement and residual hematoma volume. If the placement of puncture needle was at the center of hematoma and stable, without rebleeding, a drainage bag connected to the puncture needle was hung 10 cm upon the head and switched for drainage. Upon rebleeding, 1 ku

reptilase or 1 mg adrenalin should be injected into the hematoma, drained after 0.5 hour, and rinsed after 6–8 hours. All patients were treated in a dedicated intensive care unit, where subsequent thrombolysis and clot drainage were performed at the bedside using sterile techniques. The hematoma was continuously liquefied by liquefacient (containing 20,000–40,000 U urokinase/2–3 mL saline solution) for 2–4 days (3–5 times/day). On the 1st, 3rd, 5th, and 7th day of postoperation, patients were re-examined using CT. For hematomas that are difficult to liquefy, it should be liquefied as far as possible at first, followed by repeated, gentle aspiration using an agitation maneuver of the liquefacient to achieve vacuity. For hematomas affecting one lateral cerebral ventricle, then only that hematoma cavity should be perforated, but for patients with a hematoma affecting both lateral cerebral ventricles and the casting mould, the hematoma cavity and the contralateral cerebral ventricle should be perforated simultaneously.

In addition, for those patients with a hematoma breaking into the lateral cerebral ventricle, lumbar puncture could be

Table 2 Consciousness level after surgery, GCS score, and incidence of complications

Group	MISPTT patients	CC patients	<i>P</i> value
Number of patients	64	58	
GCS score			
Before operation	8.7 ± 1.9	8.4 ± 2.2	0.445
After operation	11.0 ± 1.2	8.1 ± 1.0	0.000
Incidence of complication (n/%)	20/31.3	46/79.3	0.000
Pulmonary infection	6/9.4	13/22.4	0.047
Digestive tract hemorrhage	10/15.6	20/34.5	0.016
Epilepsy	4/6.3	13/22.4	0.010
Bleeding recurrence (n/%)	6/9.4	10/17.2	0.199

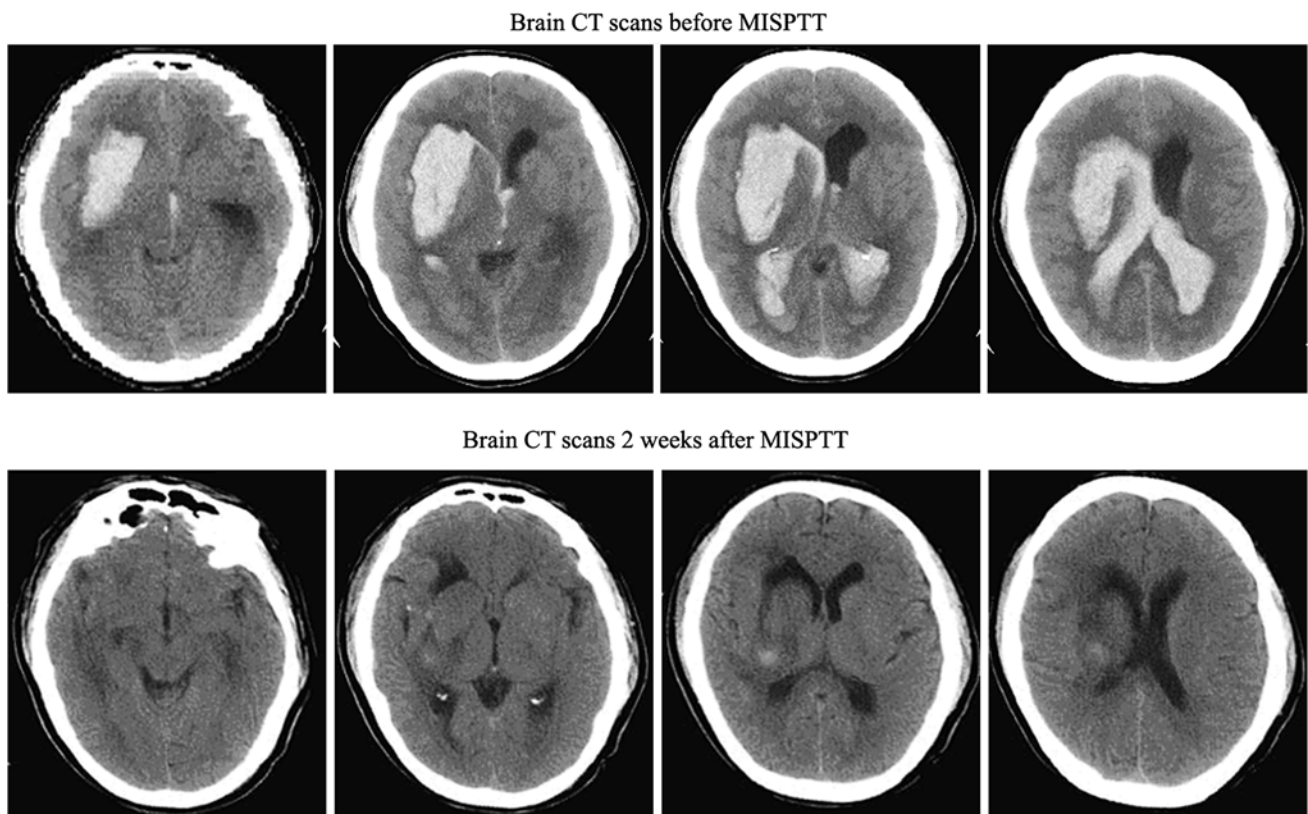


Fig. 2 CT scans of a patient in a coma (GCS score 5) with a large hematoma (>70 mL) before MISPTT (*top*), and CT scans of the same patient during consciousness (GCS score 14) 2 weeks after MISPTT (*bottom*). These scans demonstrate the size of the hematoma on serial

axial CT images. CT scans 2 weeks after MISPTT showed obvious amelioration in hematoma volume and edema in the surrounding brain compared with that prior to MISPTT. The patient was able to completely return to a normal lie 1 year after on-set

(17.2 and 25.9%, respectively, *P* = 0.243); however, on the whole, the results showed that the survival in the MISPTT group was significantly better than that of the CC group. There were 27 cases with a HV <50 mL in the MISPTT group and there were no deaths 1 year postoperation, and 22 cases with a HV <50 mL in the CC group, of whom 2 had died within 1 year postoperation. Three parameters representing long-term outcome, the GOS (4.4 ± 0.6), BI (82.6 ± 9.5), and mRS (1.8 ± 1.0) in the MISPTT group with a HV <50 mL had significantly

ameliorated compared to those in the CG group (GOS 3.4 ± 1.1, BI 73.0 ± 14.6, and mRS 2.7 ± 1.3, respectively) (*P* = 0.000, *P* = 0.009, and *P* = 0.009, respectively). There were 37 cases with a HV ≥50 mL in the MISPTT group, of whom 11 patients had died 1 year postoperation, while there were 36 cases with a HV ≥50 mL in the CC group and 13 patients had died 1 year postoperation. The GOS (3.3 ± 1.6), BI (73.3 ± 15.6), and mRS (2.2 ± 1.2) in the MISPTT group with a HV ≥50 mL had significantly ameliorated compared to those in the CG

Table 3 Outcome 1 year after stroke

Group	MISPTT patients	CC patients	<i>P</i> value
Number of patients	64	58	
Case fatality (<i>n</i> %)	11/17.2	15/25.9	0.243
GOS			
HV < 50 mL	4.4 ± 0.6 (27 cases)	3.4 ± 1.1 (22 cases)	0.000
HV ≥ 50 mL	3.3 ± 1.6 (37 cases)	2.5 ± 1.5 (36 cases)	0.040
BI			
HV < 50 mL	82.6 ± 9.5 (27 cases)	73.0 ± 14.6 (20 cases)	0.009
HV ≥ 50 mL	73.3 ± 15.6 (26 cases)	62.2 ± 21.5 (23 cases)	0.042
mRS			
HV < 50 mL	1.8 ± 1.0 (27 cases)	2.7 ± 1.3 (20 cases)	0.009
HV ≥ 50 mL	2.2 ± 1.2 (26 cases)	3.0 ± 1.6 (23 cases)	0.033

GOS Glasgow outcome scale, *mRS* modified Rankin Scale, *BI* Barthel index, *HV* Hematoma volume

group (GOS 2.5 ± 1.5 , BI 62.2 ± 21.5 , and mRS 3.0 ± 1.6 , respectively) ($P = 0.040$, $P = 0.042$, and $P = 0.033$, respectively). The results are shown in Table 3.

Discussion

The mass effect of a hematoma can lead to the brain damage, including intracranial hypertension or cerebral hernia [18]. There is, however, some evidence that the mass effect caused by a HV (<60 mL) was not the dominant injury mechanism, whereas the toxic substances released from the hematoma were the most important factor in the pathological mechanism of the cerebral hemorrhage [19–21]. It was reported that elevated levels of glutamate were found in the perihematoma region after ICH and these levels decreased after hematoma drainage. Conversely, ischemic LPRs were not found in perihematoma regions and were unchanged after hematoma drainage. These data suggest that excitotoxicity related to glutamate may have an important impact on secondary injury. The data failed to support the role of ischemia in secondary perihematoma damage [6].

Thus, effective removal of the hematoma during the acute phase is a crucial principle in the treatment of ICH in order to save lives and improve long-term quality of life. CC by removing a bone flap is a classical technique for the treatment of ICH, which is characterized by good visualization, complete clearance of the hematoma, easy hemostasis, and complete reduction of pressure, but also has some shortcomings such as length of operation, severe brain damage due to manipulation of the brain during the operation, damage of brain tissue around the hematoma by electrocoagulation, re-bleeding readily, pathophysiological changes postoperation (e.g., disturbance of water and electrolyte balances, fluctuation of blood sugar, instability of life signs), which result in severe impairment of neurological function, multiple complications, higher invalidism

rates and fatality rates. With regard to basal ganglia hemorrhages, comparing the outcome of patients treated surgically with that of patients managed conservatively, many earlier and current publications showed no benefit from conventional surgery [9, 10, 22–25]. Only a few reports have demonstrated a trend towards better outcomes with conventional surgery [26–28]. While analyzing the given data, it becomes obvious that the major drawback in all these studies is the heterogeneity of the ICH patient groups with regard to their preoperative neurological status due to the very different degrees of neurological impairment and no uniform consciousness levels, applying different surgical approaches, and different intervals with regard to the onset of the hemorrhagic stroke. Thus, it is an essential issue to select appropriate patients and a homogenous group to determine whether patients truly benefit from the neurosurgical stereotactic evacuation of the hematomas in the acute phase. In many recent studies, the minimally invasive methods have shown to be highly efficient with little risk of re-bleeding and better short-term outcomes [29–31]. Presently, some clinicians are exploring new methods to elevate curative effect of minimally invasive operation techniques. A study by Marquardt and coworkers [32] focused on the use of a novel multiple target aspiration technique in 64 patients to aspirate a “sufficient proportion” of the hematoma with minimal risk for the patient. More than 80% of the hematoma volume was successfully aspirated in 73.4% of the patients with only one episode of re-bleeding. Montes et al. [33] showed that CT-guided thrombolysis and aspiration was safe and effective in the reduction of ICH volume. In the meantime, they proposed further studies were needed to assess optimal thrombolytic dosage, including controlled comparisons of mortality, disability outcome, time until convalescence, and cost of care in treated and untreated patients.

MISPTT is a new and novel operative technique that is obviously different from other types of minimally invasive operations in design principle, which was developed by Pro

Jia in 1997 with a distinctive thrombolysis installation, and highly safe and efficient function for dissolving and draining coagulated blood. This treatment had been widely applied in China. According to some studies in the past, it was presented that MISPTT in acute ICH efficiently cleared the hematoma, relieved hydrocephalus, reduced intracranial hypertension, and relieved the cytotoxicity of blood thrombin. Furthermore, the washing liquor decreased the levels of cytotoxic substances. In subacute hemorrhage, MISPTT reduced the neurotoxicity of the hemoglobin and its decomposition products. This technique is characterized by its simplicity and is not limited by equipment. Puncturing the brain in MISPTT does little harm to the brain and accelerates recovery of cerebral function, while the liquefaction technique contributes to liquefying the blood coagulum—all helping to shorten the course of disease. In the operations performed, patients were only treated with a 3 mm needle (diameter). Because there is no gap between the needle and skull, the incidence of infection is reduced. Furthermore, it is not necessary to open the skull and use general anesthesia; thus, this procedure is more economical than other operations. The Chinese National Research and Extension Community of the Minimally Invasive Operation suggested that MISPTT is suitable for cases having a hemorrhage volume >30 mL in the basal ganglia and further standardized the operation indication, operation procedure, and the methods to apply the hematoma liquefiant, according to the random sampling of The Ministry of Public Health.

Although there are many studies investigating the minimally invasive operation indication for ICH, few specially concerned the indication for the MISPTT. Furthermore, most of these investigations lacked control groups with uniform baseline characteristics prior to operation, did not analyze the correlation factors (e.g., GCS score, hematoma volume, hematoma location, duration of BP and accompanied diseases), and did not observe the long-term outcome for survival. In our study, the above shortcomings were overcome by the inclusion of many factors, e.g., preoperative neurological status, surgical approach, patient selection, GCS score, incidence of complications, rebleeding after surgery, and long-term outcome 1 year after onset. In addition, accompanying diseases in the two groups of ICH patients were observed, such as diabetes, hyperlipidemia, coronary heart disease and cerebral infarction. There were no statistically significant differences between the two groups (all $P > 0.05$), but it was noticed that diabetes accounted for 62.5% and 60.3%, respectively, in MG and CG, which indicated that diabetes was perhaps one important risk factor for ICH onset (Table 1). The results showed that the level of consciousness and GCS in MISPTT were better than that of the CC group. Of the 13 patients with GCS scores of 4–5 in the two groups,

11 patients died (84.6%); the two survivors were treated with MISPTT (Table 1, one case referring to Fig. 2). The incidence of complications (e.g., pulmonary infection, hemorrhage of the digestive tract, and epilepsy) in MISPTT was obviously reduced compare to the CC group. There were no cases of intracranial infection in either the MISPTT or the craniotomy group. The statistical analysis did not show a significant difference on the rebleeding incidence in the two groups (9.4 and 17.2%, respectively, $P = 0.199$). There were no obvious differences between the case fatalities in the MISPTT group and the CC group (17.2 and 25.9%, respectively, $P = 0.243$). The long-term outcome in the MISPTT group surpassed that of the CC group, with respect to GOS, mRS, and BI (all $P = 0.000$).

Currently, the thrombolysis methods have only been partly explored. We used UK as thrombolysis method in our MISPTT study. In another cohort of ICH patients treated using FAST, volumetric analysis of ICH and perihematomal edema seemed to suggest that local use of rtPA for thrombolysis, which differed from the UK used in our MISPTT study, does not exacerbate brain edema formation. Furthermore, there seems to be a strong association between reduction of the ICH volume and reduction of edema volume, as would be expected following the concept of “hemotoxicity” postulated by some investigators [34].

These above results indicate that for the ICH patient meeting MISPTT operation requirements, it is unsuitable to choose CC. However, if the patient has a huge hemorrhage volume, is rapidly deteriorating, or is in the early state of cerebral hernia, then a craniotomy should be selected to reduce cerebral pressure. In addition, another study [33] pointed out that although MIS on patients with cerebral hernia may not result in a good curative effect, the hematoma volume can be partially decrease and the intracranial pressure can be rapidly reduce, thus, gaining time for craniotomy. Of course, CC is occasionally superior in the treatment of ICH with bulk volume. Murthy et al. [35] combined decompressive craniectomy and hematoma clearance to cure 12 patients with hemorrhage volumes >60 mL in the right hemisphere. As a result, 11 survivors were able to leave the hospital (92% survival rate), while in 6 cases, the survivors recovered well.

Conclusion

Larger randomized trials proving the increased benefits of MISPTT treatment over traditional craniotomy or purely medical management are currently in process. However, our study and some other treatment trials regarding this treatment modality have reported optimistic results, showing superiority of MMISPTT over CC or PMT. Several methodological issues surrounding this form of

treatment remain to be resolved, including comparison of the relative efficacies of various mechanisms of clot thrombolysis and drainage. If successful, MISPTT for ICH may perhaps become an important tool in the growing treatment armamentarium for ICH and the potential for a disease modifying impact in these ICH patients. It is our hope that this ongoing study will bring us closer to other randomized tests regarding more relevant factors with MISPTT as an alternative treatment for ICH. Objectively, MISPTT is currently limited in its ability to achieve hemostasis and completely evacuate the hematoma. Proper selection of the ICH patient group to receive this type of therapy may hold the key to these advances.

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Conflicts of interest None.

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