Original research

Does stereotactic thrombolysis with alteplase for intracerebral haemorrhage alter intraventricular haematoma volume? A secondary analysis of the MISTIE-III trial

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ABSTRACT

Background Stereotactic thrombolysis reduces intracerebral haemorrhage (ICH) volume in patients with spontaneous ICH. Whether intrahaematomal alteplase administration is associated with a change in intraventricular haemorrhage volume (deltaIVH) and functional outcomes is unknown.

Methods Post hoc secondary analysis of the Minimally Invasive Surgery plus Alteplase for Intracerebral Hemorrhage Evacuation Phase III (MISTIE-III) trial in patients with IVH on the stability CT scan. Exposure was minimally invasive surgery plus alteplase (MIS+alteplase). Primary outcome was deltaIVH defined as IVH volume on end-of-treatment CT minus IVH volume on stability CT scan. Secondary outcomes were favourable functional outcome (modified Rankin Scale 0–3) and mortality at 365 days. We assessed the relationship between MIS+alteplase and deltaIVH in the primary analysis using multivariable linear regression, and between deltaIVH and functional outcomes in secondary analyses using multiple logistic regression.

Results Of 499 patients in MISTIE-III, 310 (62.1%) had IVH on stability scans; mean age (SD) was 61.2±12.3 years. A total of 146 (47.1%) received the MISTIE procedure and 164 (52.9%) standard medical care (SMC) only. The MIS+alteplase group had a greater mean reduction in IVH volume compared with the SMC group (deltaIVH: −2.35 (5.30) mL vs −1.15 (2.96) mL, p=0.02). While IVH volume decreased significantly in both treatment groups, in the primary analysis, MIS+alteplase was associated with greater deltaIVH in multivariable linear regression analysis adjusted for potential confounders (β −0.80; 95% CI −1.37 to −0.22, p=0.007). Secondary analysis demonstrated no associations between IVH reduction and functional outcomes (adjusted OR (aOR) for poor outcome 1.02; 95% CI 0.96 to 1.08, p=0.61; aOR for mortality 0.99; 95% CI 0.92 to 1.06, p=0.77).

Conclusions Alteplase delivered into the ICH in MISTIE-III subjects with IVH was associated with a small reduction in IVH volume. This reduction did not translate into a significant benefit in mortality or functional outcomes at 365 days.

Trial registration number NCT01827046.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Minimally Invasive Surgery plus Alteplase for Intracerebral Hemorrhage Evacuation Phase III (MISTIE-III) treatment with intraparenchymal haematoma alteplase injection achieved improved functional outcome when associated with predefined intracerebral haemorrhage (ICH) volume reduction to below 15 mL.

WHAT THIS STUDY ADDS

⇒ In this cohort study of 310 patients with large ICH and intraventricular haemorrhage (IVH) who were enrolled in a randomised clinical trial, the MISTIE-III treatment (minimally invasive surgery plus alteplase) resulted in a small reduction in IVH volume compared with controls. However, no association was found between a reduction in IVH volume and death or major disability.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings of this study suggest that further investigation of the role of stereotactic thrombolysis in reducing IVH volumes and potentially improving outcomes is warranted in patients with a moderate to large ICH with IVH. Complete removal of IVH may require drug delivery directly into the ventricle as delivery into the ICH led to incomplete removal.

INTRODUCTION

Spontaneous intracerebral haemorrhage (ICH), the second most common type of stroke, has an incidence of 24.2 in 100 000 person-years and 1-month case fatality of 40.4% since the 1980s, with the majority of survivors remaining functionally dependent.[1–3] Currently established outcome prediction models of ICH include initial and interval volumes of blood in the brain tissue and the ventricles as determinants of poor outcomes.[4 5] Removal of intracerebral clots with minimally invasive surgery (MIS) plus a thrombolytic has been tested in large randomised clinical trials, such as the Minimally Invasive Surgery plus Alteplase for Intracerebral

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Hemorrhage Evacuation Phase III (MISTIE-III) trial; however, although the MISTIE-III procedure successfully reduced targeted clot volume and decreased mortality, it did not result in a significant improvement in functional outcomes, except for the subgroup of subjects achieving the predefined ICH volume reduction goal.[6–8]

A recently published post hoc exploratory analysis of the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR-III) trial demonstrated that intraventricular alteplase use in patients with ICH with obstructive intraventricular haemorrhage (IVH) was associated with a greater reduction of parenchymal ICH volume compared with intraventricular saline (control).[9] A suggested mechanism was that communication between intraparenchymal and intraventricular compartments enhanced ICH drainage. In this study, we sought to evaluate whether catheter-based thrombolysis with intrahaematomal alteplase in MISTIE-III is associated with a change in intraventricular clot volume during the treatment period in subjects presenting with IVH, and to assess whether catheter-assisted early change in IVH volume is associated with 365-day mortality and functional outcomes. We tested these hypotheses using data from a cohort of patients with large ICH who underwent protocolised serial neuroimaging and blinded follow-up as part of a large randomised clinical trial.

METHODS

Study design

We conducted a post hoc secondary analysis of prospectively collected participant data from the MISTIE-III trial,[7] a randomised, open-label trial conducted between December 2013 and September 2018 that examined whether image-guided MIS followed by gentle thrombolytic irrigation of the catheterised ICH clot with alteplase improved outcomes by removing ICH compared with standard medical care (SMC).

Participants and data collection

In the MISTIE-III trial, main inclusion criteria were: (1) age 18 years or older; (2) spontaneous, large (≥30 mL), supratentorial lobar or deep ICH; (3) presentation within 24 hours of symptom onset; (4) baseline modified Rankin Scale (mRS) score lower than 2; and (5) ICH that remained stable in size (interval growth <5 mL) for at least 6 hours after a prior CT scan within the 72-hour eligibility window. Main exclusion criteria included patients with expressed care limitations or those deemed to have life-threatening mass effect requiring neurosurgery as well as IVH with casting of all ventricles or causing midline shift due to a trapped ventricle. External ventricular drainage (EVD) was permitted at the discretion of the treating neurosurgeon as were normal saline flushes for EVD obstruction. Intraventricular fibrinolytics were prohibited. No patient received a lumbar drain. Details of the MISTIE-III trial methods and results have been published elsewhere.[6]

Written informed consent was obtained prior to enrolment for the original study. The need for informed consent was waived for this post hoc study due to its retrospective nature with no more than minimal risk to the patient. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.[10] This trial is registered with ClinicalTrials.gov (NCT01827046).

Neuroimaging

A non-contrast CT head scan was obtained on admission for ICH diagnosis ('diagnostic CT'), and subsequent imaging was taken as frequently as every 6 hours to confirm stable ICH and IVH size with an interval growth of no more than 5 mL for both ('stability CT'). ICH and IVH volumes were measured using semiautomated planimetry and were read centrally by radiologists and neurologists who were blinded to treatments and outcomes. We used OsiriX software which uses a semiautomated threshold-based approach with a range of 40–80 hounsfeld units (HU) to identify the boundaries of blood clots which were then manually adjusted to obtain the best delineation and avoid artefacts introduced by higher attenuation cerebrospinal fluid (CSF). A 3-dimensional volume is calculated. The software adjusts for changes in CT section thickness and thereby corrects for different CT techniques across centres. ICH and IVH volumes were measured at diagnosis, stability and 24 hours after the last MIS-alteplase treatment or similar time period in controls (end of treatment (EOT)). Lobar ICH was defined as selective involvement of cerebral cortex and/or underlying white matter, whereas deep ICH was defined as involvement of basal ganglia and/or thalami.[11]

Data collection and outcome measures

For the current cohort study, we included only patients with IVH presence on the stability CT scan. We extracted baseline characteristics, including age, sex, race/ethnicity, comorbidities and admission severity variables, such as Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale score and requirement for EVD. We collected MISTIE catheter drainage volume between alteplase doses when reported. The exposure in the study was MIS with alteplase injections (MIS+alteplase). 11 of the included 146 (7.5%) MIS patients did not require any alteplase injections or a drainage catheter to achieve a successful clot aspiration and were removed from the primary and secondary analyses.

The primary outcome was deltaIVH, defined as the change in IVH volume between the stability CT scan and EOT CT scan (IVH (EOTCT) minus IVH (StabCT)). Therefore, deltaIVH is always negative, if there is a reduction between stability and EOT IVH volume, and 'smaller' amounts in terms of 'more' negative amounts mean a larger reduction. DeltaIVH is meant everywhere, where 'change in IVH volume' is used. Change in ICH volume from stability to EOT CT was defined similarly. A representative image before and after the MISTIE procedure is presented (figure 1). Secondary outcomes were major disability or death (mRS of greater than 3) and mortality (mRS of 6) at 365 days.

Statistical analysis

We performed descriptive statistical comparisons between the MISTIE and SMC groups using Mann-Whitney U test and Student's t-test for continuous variables, depending on the normality of distributions, and Pearson χ^2 test for categorical variables. Data are reported as mean values with SD for normally distributed data; otherwise, median values with IQR. We conducted two analyses. First, we evaluated the association between MIS+alteplase (excluding 11 surgical patients who did not require alteplase) and deltaIVH using multivariable linear regression. Assumptions for linearity, homoscedasticity and multicollinearity were tested, the latter defined by a variance inflation factor value greater than 4. The following covariates were identified by a p value threshold of <0.2 in the bivariate analysis: Hispanic ethnicity, diabetes, baseline serum white cell count, stability IVH volume, EVD use, GCS at screening and time from ictus to EOT CT . We adjusted the model additionally

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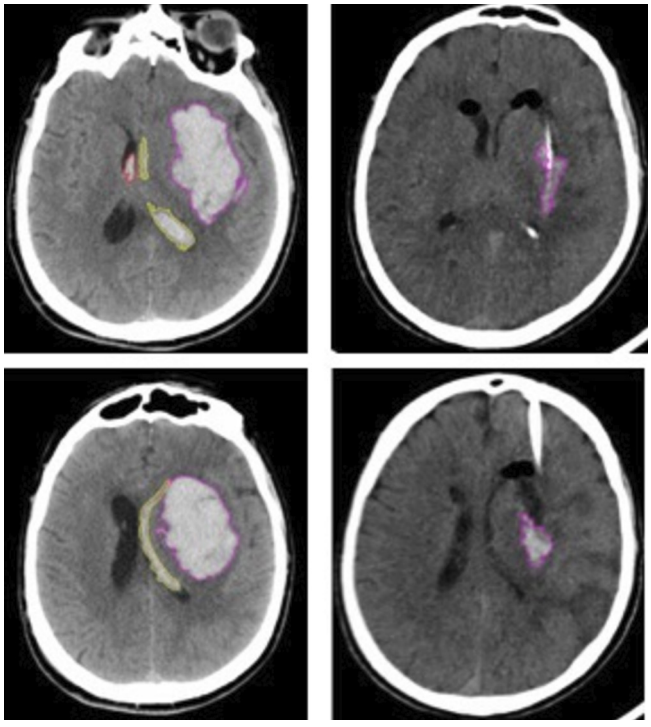

Figure 1 Representative CT imaging of a MISTIE-III subject with concurrent intraparenchymal and intraventricular haemorrhages, taken before (left) and after (right) the MISTIE procedure. MISTIE-III, Minimally Invasive Surgery plus Alteplase for Intracerebral Hemorrhage Evacuation Phase III.

for universal confounders (age, male sex, black race and stability ICH volume) regardless of their significance in the bivariate analysis. Model diagnostics assessed that the relationship between the independent variables and the dependent variable was linear, and there was no multicollinearity or heteroscedasticity; therefore, the assumptions of the linear regression model were met. We repeated the model with only covariates identified by a p value <0.2 (online supplemental eTable 2).

In the second analysis, we evaluated associations between deltaIVH and 365-day poor functional outcome, defined as mRS greater than 3, as well as between deltaIVH and mortality using multivariable logistic regression, adjusted for known factors of poor outcome in ICH such as age, GCS score at screening, admission ICH volume and ICH location (deep, lobar). In addition, we performed prespecified analyses with stratification by baseline ICH volume (<45 mL, ≥45 mL), and ICH location (deep, lobar) to evaluate for effect modification by baseline ICH severity indicators using the same threshold from the severity index developed for predicting the primary outcome in the MISTIE-III trial.[7]

We assessed IVH volumes on CT scans performed up to 1 week after randomisation in all 499 MISTIE-III patients to assess for IVH expansion events (defined as >5 mL increase in volume) which may have affected the change in IVH volume between stability and EOT CT.

We also assessed the association between deltaIVH and change in ICH volume from stability to EOT in the MIS group using linear regression. Finally, we assessed the association between intrahaematoma catheter drainage volume (per dose of alteplase) with change in IVH and ICH volume using Spearman correlation tests in the subset with these data (n=31) (reported in online supplemental data).

STATA V.17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, Texas: StataCorp) was used for all statistical analyses. Statistical testing was performed at an α level of 0.05.

RESULTS

Of the 499 patients enrolled in MISTIE-III, 310 (62.1%) had a concurrent IVH on the haematoma-stability scan, with mean (SD) age of 61.2 (12.3) years, 193 (62.3%) were male. 146 (47.1%) received the MISTIE procedure, and 164 (52.9%) received SMC only (control group). Table 1 summarises baseline demographic and clinical characteristics in the two groups. There were similar occurrences of cardiovascular comorbidities and EVD placement. Compared with patients in the SMC-only group, those in the MIS group had a higher proportion of deep haemorrhages (69.2% (n=101) vs 57.3% (n=94), p=0.03).

No significant differences in ICH characteristics were found, except for median (IQR) EOT ICH volume, which was lower in the MIS group than in the SMC group (15.3 (8.9–21.8) mL vs 46.9 (37.1–60.6) mL, p<0.0001). The median (IQR) EOT IVH volume was not significantly different between groups (MIS: 0.9 (0.3–2.7) mL vs SMC: 1.3 (0.3–3.0) mL, p=0.29). The MIS group had a greater mean (SD) reduction in IVH volume compared with the SMC group (2.31 (5.11) mL vs 1.15 (2.96) mL, p=0.02) (figure 2). A sensitivity analysis including only MIS patients who received alteplase (MIS+alteplase) (n=135) showed a similar result (2.35 (5.30) mL vs 1.15 (2.96) mL, p=0.02).

Primary analysis findings

In the unadjusted linear regression analysis (online supplemental eTable 1) including all SMC patients and only patients who received alteplase in the MIS group (n=135), MIS+alteplase use was associated with a change in IVH volume (β −1.20; 95% CI −2.16 to −0.25, p=0.01).

The multivariable linear regression model adjusted for age, sex, race and ethnicity, diabetes, baseline serum white cell count, stability ICH and IVH volumes, EVD use, GCS at screening and time from ictus to EOT CT (table 2) showed an association between MIS+alteplase and change in IVH volume (β −0.80; 95% CI −1.37 to −0.22, p=0.007). The association with MIS+alteplase remained similar when only covariates with p<0.2 in the univariate analysis were included (β −0.79; 95% CI −1.37 to −0.21, p=0.008) (online supplemental eTable 2). A total of 58/310 participants with IVH received an EVD (18.7%). EVD use, however, was not associated with change in IVH volume. Including 11 MIS patients who did not receive alteplase or a drainage catheter, the association between all MIS (n=146) and change in IVH volume in the adjusted analysis was no longer significant (β −0.53; 95% CI −1.12 to 0.06, p=0.08).

We assessed the association between deltaIVH and change in ICH volume from stability to EOT in the MIS group using linear regression (β −0.03; 95% CI −0.09 to 0.22, p=0.24). We also assessed whether the change in parenchymal haematoma volume from stability to EOT differed by the presence of IVH on stability CT in each treatment group in the full MISTIE-III cohort (n=499). In the MIS group (but not in the SMC group), those who had a concurrent IVH on stability CT (n=135) had a significantly greater decrease in mean ICH volume compared with those without IVH (n=96) (−37.61 (13.39) mL vs −30.19 (15.46) mL, p<0.001) (figure 3).

Secondary and subgroup analyses findings

Day 365 mRS was missing in two patients. In the unadjusted logistic regression analysis (table 3), no associations were

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Table 1 Baseline characteristics of MISTIE-III patients with intraventricular haemorrhage, stratified by treatment group

Characteristics	n (%)		P value*
	MISTIE group (n=146)	SMC group (n=164)	
Age, mean (SD), years	60.7 (11.6)	61.6 (13.0)	0.50
Sex			
Female	48 (32.9)	69 (42.1)	0.10
Male	98 (67.1)	95 (57.9)	
Race and ethnicity†			
Black	26 (17.8)	27 (16.5)	0.43
Hispanic/Latino	25 (17.1)	26 (15.9)	
White	88 (60.3)	96 (58.5)	
Other‡	7 (4.8)	16 (10.4)	
Hypertension	140 (95.9)	157 (95.7)	0.94
Diabetes	44 (30.1)	49 (29.9)	0.96
Hyperlipidaemia	52 (35.6)	66 (40.2)	0.40
Tobacco use	25 (17.1)	26 (15.9)	0.76
Cocaine use	4 (2.7)	7 (4.3)	0.47
Previous anticoagulant use	10 (6.8)	8 (4.9)	0.46
Previous antiplatelet use	45 (30.8)	54 (32.9)	0.69
Clinical severity factor			
GCS score at randomisation§	10 (8, 12)	10 (8, 13)	0.67
ICH location			
Lobar	45 (30.8)	70 (42.7)	0.03
Deep	101 (69.2)	94 (57.3)	
Parenchymal ICH volume on admission, mL§	46.8 (33.2–59.8)	45.8 (34–59.5)	0.87
IVH volume on admission, mL§	1.1 (0–5.2)	0.6 (0–3.8)	0.24
Parenchymal ICH volume at stability, mL§	51.6 (39.9–64.4)	50.3 (38.4–62.8)	0.38
IVH volume at stability, mL§	2.2 (0.7–5.9)	2.0 (0.5–4.9)	0.39
End-of-treatment parenchymal ICH volume, mL§	15.3 (8.9–21.8)	46.9 (37.1–60.6)	<0.0001
End-of-treatment IVH volume, mL§	0.9 (0.3–2.7)	1.3 (0.3–3.0)	0.29
EVD use	33 (22.6)	25 (15.2)	0.10
Time interval from ictus to end-of-treatment CT scan, hours§	125.5 (104–157.5)	116 (103–127)	0.0001
Number of doses of study agent§	4 (3, 7)	n/a	n/a
Time interval from ictus to first dose of study agent, hours§	71 (56–82)	n/a	n/a

*P<0.05 was considered statistically significant.
†Race and ethnicity were investigator reported in the MISTIE-III trial.
‡Other included Asian, Native American, Native Hawaiian or other Pacific Islander.
§Indicates values presented as median (IQR).
EVD, external ventricular drainage; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; MISTIE-III, Minimally Invasive Surgery plus Alteplase for Intracerebral Hemorrhage Evacuation Phase III; SMC, standard medical care.

found between change in IVH volume and either poor functional outcome (OR 0.99; 95% CI 0.95 to 1.05, p=0.87) or with mortality (OR 1.00; 95% CI 0.93 to 1.09, p=0.92). In the multivariable logistic regression models, no association was observed between a reduction in IVH volume and poor functional outcome (adjusted OR (aOR) 1.02; 95% CI 0.96 to 1.08, p=0.61) or with mortality (aOR 0.99; 95% CI 0.92 to 1.06, p=0.77). Prespecified subgroup analyses did not result in statistical significance between deltaIVH and 12-month outcomes (table 3).

Postrandomisation change in IVH volume

We assessed IVH volumes on CT scans performed up to 1 week after randomisation in all 499 MISTIE-III patients. There were six patients with IVH expansion >5 mL after stability CT scan. All had small IVH volumes on stability CT of <5 mL. Of these patients, they occurred each on days 1–5 after stability CT with one patient having two expansion events on days 2 and 4. Five of these patients were in the surgical group, including the patient with two postrandomisation expansion events. Three of the six patients with IVH expansion events had an EVD placed. Figure 4 shows line graphs trending IVH volumes among all MISTIE patients separated into four groups, depending on initial presence of IVH on stability CT scan, and the treatment group. None of the patients without IVH on stability CT had an IVH expansion >5 mL after randomisation. 31 patients (out of 189, 16.4%) had a new IVH after the stability CT scan; however, the IVH volume was small and ≤1 mL in most of these cases (24/31; 77%). All of seven patients with a new slightly larger IVH expansion (>1 and <5 mL) were in the surgical group.

DISCUSSION

Among patients with large ICH and concurrent IVH who were enrolled in the MISTIE-III trial, we found that MIS+alteplase was associated with a small reduction in IVH volume compared with SMC only. This change in IVH volume was not associated with improvement in functional outcome or mortality. However, stereotactic thrombolysis with alteplase may be a novel approach to drain both parenchymal and IVH volumes to improve outcomes in the presence of IVH. Our findings confirm

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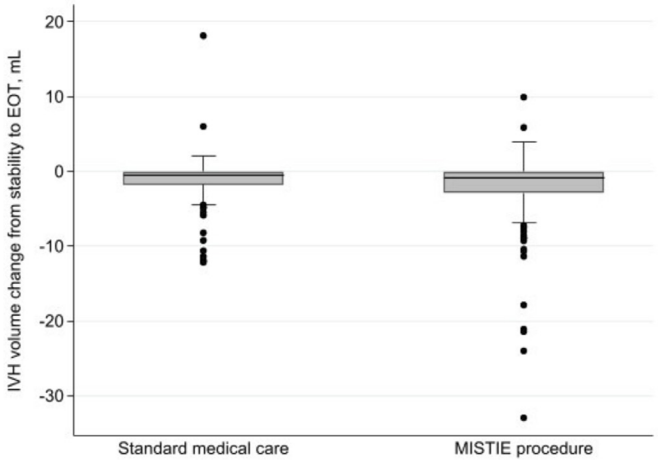

Figure 2 Change in the intraventricular haemorrhage (IVH) volume from stability to end of treatment (EOT) in 310 patients with IVH on stability CT scan, stratified by treatment group. MISTIE, Minimally Invasive Surgery plus Alteplase for Intracerebral Hemorrhage Evacuation.

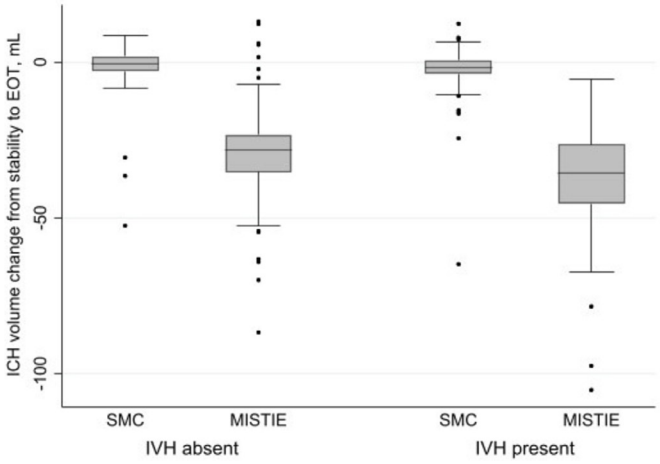

Figure 3 Change in intracerebral haemorrhage (ICH) volume from stability to end of treatment (EOT), by treatment group, in those without intraventricular haemorrhage (IVH) (n=189) and with IVH (n=310). MISTIE, Minimally Invasive Surgery plus Alteplase for Intracerebral Hemorrhage Evacuation; SMC, standard medical care.

the previously postulated mechanism that direct communication between the ventricular system and intraparenchymal clot facilitates clot drainage from both compartments with exposure to alteplase, while not increasing haemorrhage volume in the non-targeted compartment.[9]

We previously conducted a similar post hoc analysis of the CLEAR-III trial, which found that dissolving intraventricular clot with alteplase through an EVD also facilitated drainage of the associated intraparenchymal clot.[9] In this study, the MISTIE procedure with targeted thrombolysis of the intraparenchymal clot allowed alteplase access into the intraventricular space with resulting reduction in IVH volume. It is possible that alteplase lysed fibrin clot in the ventricle, converted it to liquid blood which then drained via normal CSF circulation or through an EVD if placed. When visible IVH was present on CT, MIS-alteplase irrigation of ICH clot also improved removal of parenchymal clot further by about 6 mL compared with cases without IVH. We may speculate that CSF provided an endogenous source of tissue plasminogen activator (t-PA) lysing ICH from the ventricular side.

IVH volume removal is influenced by multiple factors including rate of CSF production and flow, EVD mechanics and obstructive hydrocephalus. Our multivariable linear regression model revealed several additional significant factors associated with change in IVH volume besides exposure to alteplase. Smaller ICH volume was associated with greater IVH removal, which may imply easier access of alteplase to the ventricle, while larger IVH volume is plausibly associated with greater IVH removal in the range of small to moderate IVH volumes in MISTIE-III. EVD placement was associated with greater IVH volume change (reduction) in the univariate, but not in the fully adjusted model, perhaps reflecting that less than a fifth of our cohort with IVH required EVD placement. The inverse association between baseline white cell count and change in IVH volume may be secondary to larger ICH volume. There was a trend towards an association of longer time from ictus to EOT CT with greater IVH volume reduction which would be expected. Surgical patients had longer time to EOT CT compared with standard care patients by a median of 9.6 hours which may have biased our results.

The MIS+alteplase intervention improved both IVH and ICH volume reduction in those with IVH, but this did not translate into a significant improvement in mortality or functional outcome at 1 year. The parent MISTIE-III trial was neutral on its primary outcome of mRS 0–3 at 1 year, although strict protocol adherence with the prespecified ICH volume reduction goal to less than 15 mL was associated with improved functional outcome.[12] Given that EOT ICH volume in the MIS+alteplase group with IVH had a median of 15.3 mL, which was greater than that for the full MISTIE-III surgical cohort, 12.5 mL,[7] fewer surgical patients with IVH met the prespecified surgical goal. It is, therefore, not surprising that the small excess reduction in IVH volume did not translate into improved functional outcome. Moreover, those with IVH had a larger ICH volume at stability of 51.6 mL, compared with 45.8 mL in the full cohort. One other factor to consider is that five of the six patients with IVH expansion >5 mL after stability CT scan were in the surgical group as were all seven patients with a new

Table 2 Factors associated with a change in intraventricular haemorrhage volume

Model/variable	β (95% CI)	P value*
Unadjusted analysis		
MIS+alteplase	−1.20 (−2.16 to −0.25)	0.01
Multivariable analysis		
MIS+alteplase	−0.80 (−1.37 to −0.22)	0.007
Age (years)	0.02 (0.003 to 0.04)	0.09
Male sex	0.29 (−0.27 to 0.85)	0.31
Black race†	0.09 (−0.64 to 0.83)	0.80
Hispanic ethnicity	0.40 (−0.34 to 1.15)	0.29
Diabetes	0.19 (−0.39 to 0.77)	0.52
GCS at randomisation	0.14 (0.03 to 0.26)	0.02
ICH volume, stability	0.03 (0.01 to 0.05)	<0.001
IVH volume, stability	−0.53 (−0.57 to −0.48)	<0.001
Ictus to EOT time (hours)	−0.01 (−0.02 to −0.0004)	0.06
Baseline WBC	0.15 (0.11 to 0.19)	<0.001
EVD placement	0.22 (−0.55 to 0.99)	0.57

*P<0.05 was considered statistically significant.
†Black race was considered separately because black patients had higher ICH severity and poor outcomes.
EOT, end of treatment; EVD, external ventricular drainage; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; MIS, minimally invasive surgery; WBC, white blood cell.

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Table 3 Association between change in intraventricular haemorrhage volume and outcomes

	Modified Rankin Scale score, 4–6 at 12 months*		Mortality at 12 months*	
Outcome	**OR (95% CI)**	**P value†**	**OR (95% CI)**	**P value†**
Unadjusted analysis				
Entire cohort (unadjusted)	0.99 (0.95 to 1.05)	0.87	1.00 (0.93 to 1.09)	0.92
Multivariable analysis				
Entire cohort (adjusted)	1.02 (0.96 to 1.08)	0.61	0.99 (0.92 to 1.06)	0.77
Admission ICH volume (mL)				
<45	1.01 (0.92 to 1.11)	0.79	0.95 (0.87 to 1.03)	0.20
≥45	1.02 (0.93 to 1.12)	0.68	1.03 (0.93 to 1.14)	0.52
Deep ICH location	0.98 (0.88 to 1.09)	0.69	0.97 (0.89 to 1.06)	0.46
Lobar ICH location	1.04 (0.96 to 1.14)	0.42	1.05 (0.94 to 1.18)	0.38

*Model was adjusted for age, sex, black race, Glasgow Coma Scale at randomisation, admission parenchymal ICH volume, parenchymal ICH location and treatment randomisation arm.
†P<0.05 was considered statistically significant.
ICH, intracerebral haemorrhage

IVH >1 mL, but <5 mL after stability CT. There appears to be a small but not insignificant risk of IVH expansion with exposure to intrahaematomal alteplase although overall, despite these events, the overall effect was in favour of IVH volume reduction.

Our study is limited by the inclusion of patients with large supratentorial ICH, so these findings are not generalisable to smaller ICH, or to secondary ICH aetiologies (ie, traumatic brain injury). However, this post hoc exploratory analysis from a large clinical trial benefits from blinded outcome assessment and relatively well-balanced groups on important variables, such as stability ICH and IVH volumes, which minimises other potential biases. We acknowledge that multiple hypotheses have been tested in this data set, although our findings are highly congruent with a similar question investigated in the CLEAR-III trial.[9] This study also supports reproducibility of the concept of intercompartmental volume contraction through use of thrombolytic agents for haemorrhage removal.

Although a major reason for failure to detect an association between change in IVH volume and functional outcome was likely due to the high clinical severity and large ICH volume of all participants in MISTIE-III, this study also may have lacked power to detect such an association. To demonstrate a clinical benefit, future studies would need to carefully control for IVH volume changes via EVD and monitor drainage output in all patients while undergoing thrombolysis. Whether the benefit of stereotactic thrombolysis is greater in patients with smaller ICH and larger IVH volumes is also unclear, as MISTIE-III excluded patients with very large IVH. However, this concept highlights the potential ability of minimally invasive procedures using thrombolysis to safely dissolve both intraparenchymal and intraventricular clots.

We acknowledge several other limitations. First, semiautomated technology was used to calculate ICH and IVH volumes, which, in the case of deep haemorrhage abutting the ventricle, may lead to inaccuracies in volume measurements. Second, all participants had stable ICH and IVH at the time of surgery, and we cannot speculate about how this strategy may impact anticoagulated ICH.

In conclusion, minimally invasive, stereotactic surgery plus alteplase in patients with large ICH and any IVH was associated with a small but significant reduction in IVH volume. However, this change did not translate into better long-term outcomes. Further investigation into how this strategy can potentially reduce both parenchymal and intraventricular volumes may be warranted.

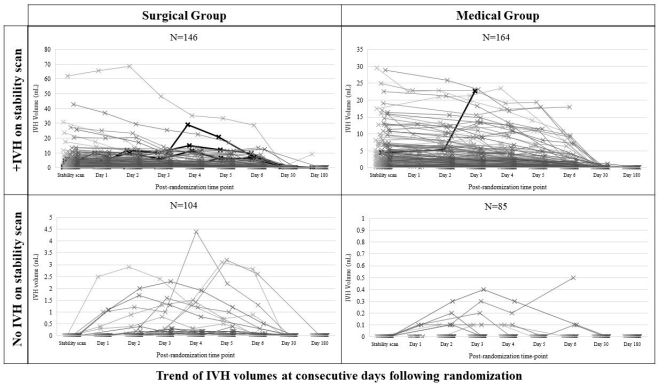

Figure 4 Line graphs showing trends in intraventricular haemorrhage (IVH) volumes among all MISTIE-III patients for 6 days after stability CT, separated into four groups, depending on initial presence of IVH on stability CT scan, and treatment group. Each line represents one patient. Grey lines are patients without postrandomisation IVH expansion, while black lines are those with an expansion. MISTIE-III, Minimally Invasive Surgery plus Alteplase for Intracerebral Hemorrhage Evacuation Phase III.

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Data availability statement Data are available upon reasonable request. Interested researchers may formally request access to the dataset by submitting a proposal.

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