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End-of-Treatment Intracerebral and Ventricular Hemorrhage Volume Predicts Outcome: A Secondary Analysis of MISTIE III

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Abstract

Background and Purpose: Trials have shown potential clinical benefit for minimally invasive clot evacuation of intracerebral hemorrhage (ICH). Prior research showing an association between ICH size and functional outcome did not fully address the spectrum of hematoma volumes seen after clot evacuation.

Methods: In this secondary analysis of the Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation III (MISTIE III) trial, we included patients randomized to the surgical arm. The primary outcome was good outcome (modified Rankin Scale score 0–3 at one year from study enrollment). The primary predictors were the end-of-treatment (EoT) ICH and IVH volumes and an EoT ICH stratification scale called the ETIV score.

Results: In 247 patients, the EoT computed tomography (CT) was performed an average of 5.38 days from onset. For patients with good versus poor outcomes, the mean EoT ICH and IVH volumes were 12.9 versus 18.0 mL ($p=0.001$) and 0.52 versus 2.3 mL ($p<0.001$), respectively. The probability of a good outcome decreased from 73% for ETIV 3 (<5 mL) to 28% for ETIV 0 (>20 mL) ($p<0.001$).

Conclusion: After surgical clot evacuation, both ICH and IVH volumes have a strong association with good neurologic outcome. The ETIV score needs independent verification, but such an approach could be used for prognostication and therapeutic planning.

Keywords

acute intracerebral hemorrhage; intraventricular hemorrhage; clot evacuation; neurologic outcome

Subject Terms

intracranial hemorrhage; prognosis cerebrovascular disease/stroke

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Introduction

Spontaneous intracerebral hemorrhage (ICH) is a common form of stroke that affects over 2 million adults every year and has a one-month mortality rate of 40% with substantial morbidity in survivors.[1–3] The Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation III (MISTIE III) trial explored whether surgical clot evacuation could improve functional outcomes. MISTIE III failed to show benefit for the primary outcome of the proportion of patients with a modified Rankin Scale (mRS) score of 0–3 at one year, but showed a signal for possible benefit in patients who achieved a reduction in their ICH volume to ≤15 mL.[4] However, prior research has not fully evaluated whether the post-surgical intervention volume of ICH and IVH is a predictor of outcome across the full spectrum of clot evacuation.

Methods

This is a secondary analysis of MISTIE III (clinicaltrials.gov identifier) using a deidentified dataset that is publicly available at https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets. MISTIE III was a phase III trial that randomized 506 patients with nontraumatic supratentorial ICH of ≥30 mL to minimally invasive catheter evacuation with thrombolysis or standard of care. We included patients randomized into the MISTIE III surgical arm. The primary outcome was an mRS score of 0–3 at 1 year from enrollment, which is termed “good outcome.” Additional outcomes included the ordinal mRS, Barthel Index (BI), EuroQol-Visual Analogue Scale (EQ-VAS) of quality of life, extended Glasgow Outcome Scale (eGOS), and a utility-weighted mRS (UW-mRS). The predictor variables were the integer values for EoT ICH and IVH. The volumetric EoT quantification was performed by the MISTIE imaging core on OsiriX software, which requires a user to manually draw a boundary for the ICH and IVH on individual CT slices and then calculates a three-dimensional volume. We also stratified patients into an EoT ICH volume (ETIV) score: ETIV 3 = <5 mL; ETIV 2 = 5–10 mL; ETIV 1 = 10–20 mL; and ETIV 0 = >20 mL. We divided EoT IVH volume into 0, 0.1–1, 1–3, and >3-mL groups, but did not create a separate score because the confidence intervals around ETIV were tighter. Additional analyses were conducted with the predictor variables of percentage change in ICH and IVH volume from prerandomization to EoT. We fit logistic and ordinal logistic regression models to our outcomes. Model 1 was unadjusted; Model 2 was adjusted *a priori* for established predictors of outcome after ICH,[3] including patient age, baseline GCS, sex, white race, current smoking, premorbid mRS, history of diabetes, history of hypertension, prerandomization systolic blood pressure, and mechanical ventilation; and Model 3 was adjusted for baseline covariates with $p<0.05$ after stepwise backwards selection. We defined statistical significance as $p<0.05$.

Results

Of the 506 patients in MISTIE III, 256 were treated surgically. Our cohort included 247 (97%), with 2 patients censored for missing outcomes and 7 for missing EoT volumes. The mean age was 61 years, 156 (63.2%) were male, and 155 (62.8%) were white. Baseline demographics for the cohort and stratified by good versus poor outcome are in

Supplementary Table I. The EoT CT scan was performed at a mean±SD of 128.9±34.7 hours from ICH ictus. For patients with good versus poor outcome, the mean±SD EoT ICH volumes were 12.9±10.1 versus 18.0±14.1 mL (p=0.001), respectively, and the mean EoT IVH volumes were 0.52±1.1 versus 2.3±4.7 mL (p<0.001), respectively. The logistic regression models showed a consistent relationship between EoT ICH and IVH volumes and outcome (Table 1). The adjusted predicted probabilities of the individual scores of the mRS show a robust relationship between EoT volumes (Figure 1) and good outcome (Supplementary Figure I). The percentage change from the baseline to EoT in ICH or IVH volume did not have an association with good outcome (Supplementary Table II). After using threshold cutoffs to place patients in ETIV score categories, we found the rate of good outcome decreased across the scores (Table 2, Supplementary Figure II). The addition of the baseline ICH or IVH volumes slightly reduced the strength of our associations, but the direction of effect persisted and remained significant (Supplementary Table III). The ETIV score and EoT IVH volume also accurately predicted the ordinal mRS, BI, eGOS, and UW-mRS (Supplementary Table IV).

Discussion

Lower EoT ICH and IVH volumes, at an average of 5 days from ictus, are consistently associated with better functional outcome after nontraumatic supratentorial ICH treated with the MISTIE III surgical intervention. We explored the predictive ability of EoT ICH volume below the MISTIE III threshold of <15 mL and showed significant predictive capacity for EoT IVH volume, both of which have not previously been explored in this cohort. The percentage change in ICH or IVH volume from prerandomization to EoT failed to predict outcome. Our analysis suggests that it is the EoT volume of ICH and IVH that has an effect on outcome, more than percentage change in volume, potentially because EoT volume is the true burden that the brain is exposed to in the weeks and months after ICH ictus.

We chose the ETIV score cutoffs for their clinically meaningful thresholds that are achievable goals during safe and efficacious surgical evacuation.[4,5] The risk factors identified for elevated EoT ICH volume after treatment, which would be a low ETIV score, include large initial ICH volume, irregular hematoma shape, surgical protocol deviation, catheter manipulation, number of alteplase doses, and surgeon experience.[6] Our study has several limitations, including that it is a secondary analysis of clinical trial data, that there are multiple comparisons, and that the methodology of hemorrhage quantification included manual measurement components. However, these are offset by unique strengths such as the rigor of outcome adjudication, standardized measurement of potential confounders, and the novel cohort of patients who underwent the MISTIE surgical intervention.

Conclusion

Both intracerebral and intraventricular hemorrhage EoT volumes had a strong association with good outcome in patients who underwent the surgical clot evacuation used in MISTIE III. Although our analysis builds upon the excellent work already performed with the MISTIE III cohort,[6] we delved further into crucial aspects of the predictive ability of final ICH and IVH volume. We also introduce the ETIV score for prognostication using post-

surgical evacuation ICH volume, which will require additional study and validation prior to clinical use. Automated processing of ICH and IVH volumes on CT will soon be viable with commercial software, allowing ICH and IVH quantified volumes to be incorporated into routine patient care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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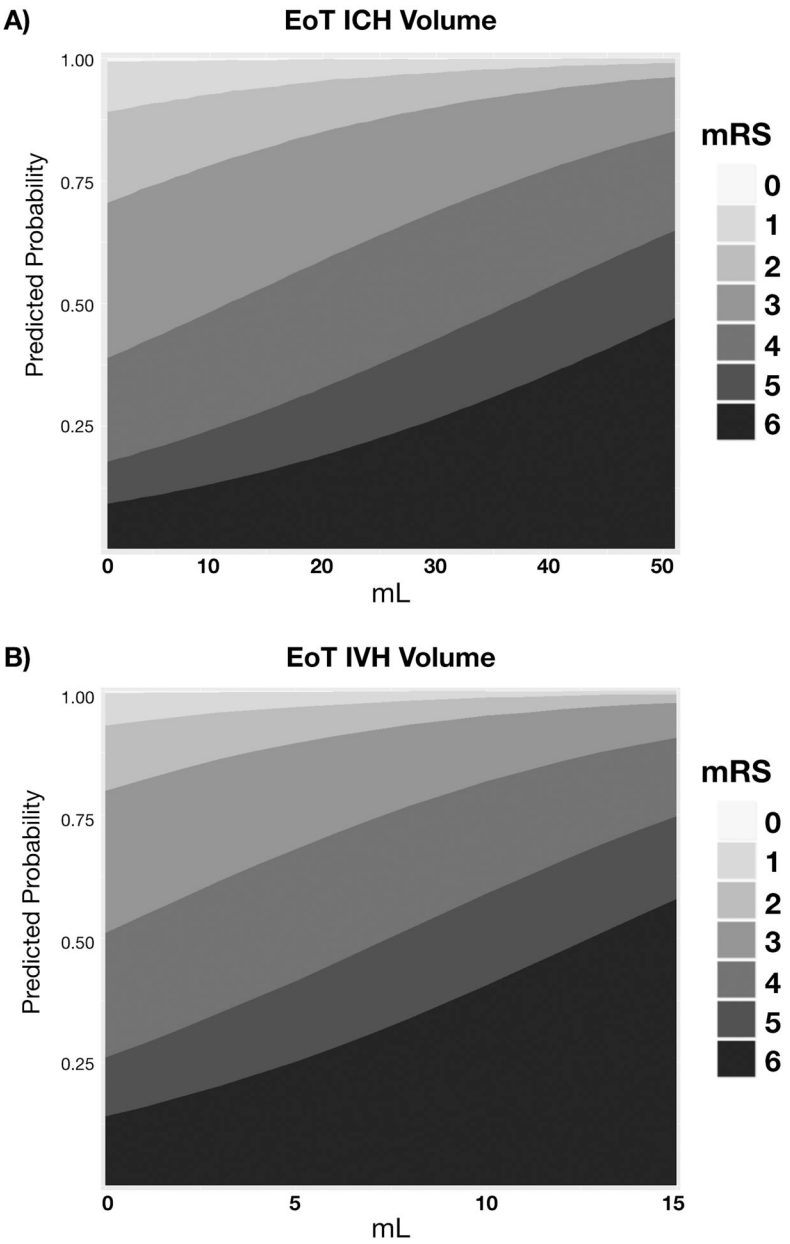

Figure 1.

Predicted probabilities of individual modified Rankin Scale (mRS) scores with the predictor variables of (A) end-of-treatment (EoT) intracerebral hemorrhage (ICH) volume 0–50 mL and (B) EoT intraventricular hemorrhage (IVH) volume 0–15 mL, adjusted for covariates from Model 2.

Table 1.

Logistic regression models fit to primary outcome for unadjusted Model 1 and adjusted Models 2/3.

	Modified Rankin Scale score 0–3		
	Odds ratio (per 1-mL volume shift)	**95% CI**	**p value**
End-of-treatment intracerebral hemorrhage volume (range 0.64–110.3 mL, mean 15.7 mL)			
Model 1 *	0.96	0.94–0.99	0.002
Model 2 †	0.96	0.93–0.99	0.003
Model 3 ‡	0.96	0.93–0.99	0.005
End-of-treatment intraventricular hemorrhage volume (range 0–37.0 mL, mean 1.5 mL)			
Model 1 *	0.65	0.52–0.81	<0.001
Model 2 †	0.64	0.50–0.83	0.001
Model 3 ‡	0.68	0.53–0.86	0.002

* Model 1 unadjusted

† Model 2 *a priori* adjusted for variables seen in Methods section

‡ Model 3 is adjusted for baseline covariates selected with backwards stepwise selection set to $p<0.05$, which included patient age, baseline National Institutes of Health Stroke Scale, deep versus lobar intracerebral hemorrhage, intracranial pressure monitor, and history of diabetes.

Table 2.

Proportion of patients by ETIV score and EoT IVH volumes meeting the primary outcome

Outcome	EoT ICH Volume (ETIV score)				p value*
	ETIV 3 (<5 mL, n=30)	ETIV 2 (5–10 mL, n=62)	ETIV 1 (10–20 mL, n=91)	ETIV 0 (>20 mL, n=64)	
Good mRS (0–3)	73.3%	50.0%	44.0%	28.1%	<0.001
Poor mRS (4–6)	26.7%	50.0%	56.0%	71.9%	
Outcome	**EoT IVH Volume**				**p value***
	0 mL (n=91)	**0.1–1 mL (n=84)**	**1–3 mL (n=39)**	**>3 mL (n=33)**	
Good mRS (0–3)	70.3%	34.5%	33.3%	15.2%	<0.001
Poor mRS (4–6)	29.7%	65.5%	66.7%	84.9%	

* p values calculated with Chi-squared test

EoT, end of treatment; IVH, intraventricular hemorrhage; ICH, intracerebral hemorrhage; ETIV, EoT ICH volume; mRS, modified Rankin Scale score