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Primary Intraventricular Hemorrhage Outcomes in the CLEAR III Trial

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Abstract

Background: Intraventricular hemorrhage (IVH) occurs due to intracerebral hemorrhage with intraventricular (IVR) extension or without apparent parenchymal involvement, known as primary IVH.

Aims: We evaluated the prognosis of primary IVH patients in the CLEAR III trial (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage).

Methods: In patients with primary IVH versus those with secondary IVH, we compared IVR alteplase response and outcomes including modified Rankin Scale (mRS), Barthel Index (BI), National Institutes of Health Stroke Scale (NIHSS), and extended Glasgow Outcome Scale (eGOS) at 30, 180 and 365 days. Outcomes were also compared in primary IVH patients who received IVR alteplase versus placebo (normal saline) and in matched primary and secondary IVH patients using inverse-probability-weighted regression adjustment.

Results: Of 500 patients enrolled in CLEAR III, 46 (9.2%) had primary IVH. Combining both treatment groups, primary IVH patients had larger IVH volumes (median: 34.2 mL versus 20.8 mL, $p<0.01$) but similar IVH removal (51.0% versus 59.0%, $p=0.24$) compared to secondary IVH patients, respectively. Confirming previous studies, primary IVH patients achieved better NIHSS, mRS, BI and eGOS scores at days 30, 180 and 365 (all $p<0.01$), although mortality was similar to

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secondary IVH patients; matching analysis yielded similar results. Primary IVH patients who received IVR alteplase (n=19) and saline (n=27) achieved similar outcomes.

Conclusions: In CLEAR III, primary IVH patients who survived achieved better long-term outcomes than surviving secondary IVH patients with similar mortality. Outcomes and safety were similar between primary IVH patients receiving alteplase and those receiving saline.

Keywords

intraventricular hemorrhage; intracerebral hemorrhage; acute stroke; alteplase; outcome

INTRODUCTION

Spontaneous intraventricular hemorrhage (IVH) can be associated with high mortality and morbidity, including decreased consciousness, hydrocephalus, and cognitive problems.[1] Best management of IVH is not fully defined, but may include care in a neurocritical care unit, maintaining adequate cerebral perfusion pressure, and insertion of an extraventricular drain (EVD).[1] In the CLEAR III (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage) trial, intraventricular (IVR) injection of alteplase was shown to be safe and to improve mortality but not functional outcomes in patients with IVH.[2]

IVH occurs as a primary clinical presentation (primary IVH) or secondary to intracerebral hemorrhage (ICH) with extension into the ventricles (secondary IVH). Primary IVH can be due to hypertension, vascular lesions such as arteriovenous malformations, and/or coagulopathies.[3] In convenience samples, better outcomes may be associated with primary IVH.[4–6].

AIMS

In a well-curated population we assessed whether primary IVH patients without structural pathology have an improved prognosis compared to secondary IVH patients in the CLEAR III trial and also performed inverse-probability-weighted regression adjustment (IPWRA) to compare these populations more rigorously by balancing key covariates. To identify whether primary IVH patients benefit from IVR thrombolysis, we also compared their response to alteplase versus normal saline (placebo).

METHODS

CLEAR III ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00784134) identifier [NCT00784134](https://clinicaltrials.gov/ct2/show/study/NCT00784134)) was a prospective, randomized, multicenter, multinational phase III clinical trial of patients with IVH obstructing the 3rd or 4th ventricles and ICH volume <30 mL on computed tomography (CT) within 24 hours of symptom onset requiring a pragmatically placed EVD. Patients with underlying vascular etiology or uncorrected coagulopathy were excluded. Subjects were randomized to receive alteplase or placebo (normal saline) via EVD until 3rd and 4th ventricles were radiographically open, 80% of IVH was removed, 12 doses of study agent had been given, or an adverse endpoint occurred. Details regarding inclusion and exclusion criteria, randomization, treatment, and outcomes were reported with the primary results.[2]

Participating sites had approval from their respective institutional review boards, and written informed consent was obtained from patients or their legally authorized representatives. The current study was approved by The Johns Hopkins University Institutional Review Board (IRB00113574).

We compared patients in the trial with primary IVH (ie, no parenchymal source of IVH on the diagnostic CT scan after vascular imaging to rule out structural causes; n=46) and secondary IVH patients and performed a matched analysis using IPWRA (see below). We also compared response to study agent (alteplase versus saline) in primary IVH patients. Because minor bleeding sites in parenchyma are not infrequently found in primary IVH patients, 4 trained image readers supervised by a neuroradiologist reviewed all protocolized CT scans from the trial for evidence of a parenchymal source of IVH. After adjudication, 16 of the initial 46 patients with primary IVH were found to have a parenchymal hemorrhage (5 caudate, 1 putamen, 10 other periventricular locations) while 3 additional patients were found to have primary IVH. A sensitivity analysis was performed comparing outcomes in the adjudicated 33 primary IVH patients with secondary IVH patients using the same methodology. All image readers were blinded to outcome data and discrepancies were resolved by the single neuroradiologist.

Variables examined included age, total doses of study agent, days in the intensive care unit, initial IVH (iIVH) and ICH volumes, determined at the last CT scan prior to randomization (termed “stability”), and end-of-treatment IVH volume (eotIVH), measured 24 hours after last dose of study agent. IVH percent clearance was then calculated as $100 \times (iIVH - eotIVH) / iIVH$. Safety outcomes included occurrence of bacterial ventriculitis at day 180, symptomatic intracranial hemorrhage within 72 hours of last study agent dose, and requirement for ventriculoperitoneal (VP) shunting. Long-term outcome measures included those prospectively evaluated in CLEAR III at days 30, 180, and 365: National Institutes of Health Stroke Scale (NIHSS); modified Rankin Scale (mRS); Barthel Index (BI); Stroke Impact Scale-16 (SIS-16; 16 items measuring self-reported physical functioning from 1-most impaired to 5-not impaired); EuroQol visual analogue scale (EQ-VAS[7]; quality of life scale with scores ranging from 0-worst imaginable health state to 100-best); Mini-Mental State Exam (MMSE); and extended Glasgow Outcome Scale (eGOS). mRS was dichotomized as good (mRS 0–3) and poor (mRS 4–6) functional outcome similar to CLEAR III’s primary efficacy outcome.

Statistical Analysis

Data are presented as median (interquartile range) unless otherwise specified. We used Wilcoxon rank-sum test or Student’s t-test to compare group differences for continuous variables; categorical variables were analyzed using Pearson’s chi square test (Fisher exact test when appropriate). Baseline characteristics and outcomes were compared in univariable analyses between all primary and secondary IVH patients, and between primary IVH patients by treatment group (alteplase versus saline). To remove confounding, primary IVH and secondary IVH patients were matched using inverse-probability-weighted regression adjustment (IPWRA), in which coefficients whose weights are estimated inverse probabilities of IVH group (primary versus secondary) are used to calculate predicted

outcomes. IPWRA is doubly robust; one model predicts IVH group status and another model predicts outcomes, and IVH group is assumed to be independent of outcomes. Outcomes assessed included dichotomized mRS at days 180 and 365 and mortality at days 30, 180, and 365. Included in both the IVH group model and outcome model were age, IVH volume, treatment group, and Glasgow Coma Scale (GCS). These variables were chosen based on their clinical relevance to the CLEAR III trial or previously recognized influences on functional outcome.[2,8] We also evaluated whether treatment effect differed in primary IVH by testing the interaction term between primary IVH and alteplase using logistic regression analyses that also included age, IVH volume, and GCS. We tested for effect modification by IVH volume*primary IVH (versus secondary IVH) and created plots of this interaction for outcome prediction. Missing data were not imputed. All statistical analyses were performed using Stata 13.0 (Stata Corp, College Station, TX). Statistical significance was determined at $p < 0.05$.

RESULTS

Of 500 patients enrolled in CLEAR III, 46 (9.2%) had primary IVH. Primary IVH patients were demographically similar, but more likely to have coronary artery disease ($p = 0.03$) and previous use of anticoagulant medications ($p = 0.02$; Table 1). They also had larger enrollment IVH volumes (median (IQR): 34.2mL (23.3–52.1) versus 20.8mL (12.5–34.2), $p < 0.01$). However, they experienced similar IVH clearance compared to secondary IVH patients (51.0% (32.3–71.4) versus 59.0% (34.8–77.1), $p = 0.24$) despite the use of bilateral EVDs being more common in primary IVH patients (41.3% versus 26.0%, $p = 0.03$). The primary IVH group had the largest IVH volumes (i.e., 134.8mL and 132.6mL). Total study agent doses, days in the intensive care unit, and complications were similar (all $p > 0.05$). Parenchymal hematoma location in secondary IVH patients was 293 (64.5%) thalamic, 71 (15.6%) caudate, 28 (6.2%) globus pallidus/putamen, 7 (1.5%) lobar, and 55 (12.1%) other/unknown periventricular locations.

Primary IVH patients achieved better outcomes for NIHSS, mRS, BI, eGOS, MMSE and SIS-16 scores at days 30, 180 and 365 (all $p < 0.01$; Figure 1). EQ-VAS score was higher in primary versus secondary IVH patients at days 30 and 180 but not at day 365. Mortality at 30, 180 and 365 days was similar.

Nineteen (41.3%) of the 46 primary IVH patients received IVR alteplase and 27 (58.7%) received saline (Table 2). Enrollment IVH volume was lower in the alteplase group (27.9mL (20.7–42.5) versus 48.0mL (23.8–67.8), $p = 0.02$). Percent IVH removal was greater in the alteplase group (71.4% (60.6–86.8) versus 41.1% (22.3–53.6), $p = 0.01$), and a greater percentage of patients in this group achieved the CLEAR III goal of $>80\%$ IVH removal[2] (36.8% versus 7.4%, $p = 0.01$).

Among primary IVH patients, there were no significant differences in intensive care unit course, complications, or outcomes between alteplase and saline groups. IVH volume at enrollment was larger in primary IVH patients with poor (mRS 4–6) versus good outcome (mRS 0–3) at days 30 (44.8mL versus 23.3mL, respectively; $p < 0.01$) and 180 (62.4mL versus 26.3mL, respectively; $p < 0.01$). Sensitivity analysis using the 33 primary IVH patients

identified by independent adjudication showed overall similar results comparing primary and secondary IVH patients and between alteplase- and saline-treated primary IVH patients (Supplemental Tables 1 and 2).

In IPWRA matched analysis, proportion of patients with mRS 0–3 was greater for primary (vs. secondary) IVH patients at days 180 and 365, but mortality was not different (Table 3). Interaction of alteplase and primary IVH was not significant for mRS 0–3 at days 180 or 365 or for mortality at all time points (all $p > 0.05$). Similarly, for primary IVH patients identified by independent adjudication, IPWRA analyses revealed a greater proportion of patients with mRS 0–3 in the primary IVH group at days 180 and 365 (with no difference in mortality), and interaction of alteplase and primary IVH was not significant (data not shown). For IVH volume $> 60\text{mL}$, mortality was 78% (7/9) in primary IVH versus 48% (10/21) in secondary IVH patients ($p = 0.08$ for the interaction IVH volume*primary IVH (versus secondary IVH); Figure 2).

DISCUSSION

IVH is a life-threatening condition. In a pooled analysis of 13 studies, risk of death was 19.5% for ICH without IVH but increased to 51.2% for ICH with IVH.[9] Primary IVH may be associated with better outcomes than IVH secondary to ICH,[4–6] but primary IVH mortality has been found to vary widely (7%–46%).[3]

We found that despite overall better outcomes in primary versus secondary IVH patients, mortality at all time points was not different.[10] In general, the literature suggests that greater IVH volume correlates with poorer outcome for secondary[6,10–16] and primary IVH,[3,17–21] though not always.[4,5,22,23] Our study provides evidence that, in the CLEAR III trial, IVH volume had a complex relationship to outcome. Primary IVH patients with mRS 4–6 versus 0–3 at days 30 and 180 began with larger initial IVH volumes. On the other hand, despite greater enrollment IVH volume for all primary IVH (versus secondary), primary IVH patients overall had better outcomes. This latter finding is consistent with previous studies showing better outcomes in survivors of primary vs secondary IVH, and that ICH volume independently affects outcome in IVH patients.[4–6,12,24]

ICH location can differentially affect outcome. Primary IVH patients later found to have parenchymal ICH on independent adjudication consisted of caudate lesions in 31.3% (5/16) and no thalamic lesions. Considering that only 15.6% of lesions in secondary IVH patients were caudate in origin, which are associated with decreased mortality and disability, and that 64.5% were thalamic in origin with higher associated morbidity[25–26] it is not surprising that secondary IVH patients had worse outcomes.

In primary IVH patients treated with alteplase versus saline, long-term outcomes were similar. There were no differences between primary and secondary IVH patients regarding alteplase-associated symptomatic bleeding; IVR fibrinolysis in primary and secondary IVH patients thus appears to be safe.

This study's major limitation is the small number of primary IVH patients, which limited power and ascertainment of IVR thrombolysis' effect. This is partially mitigated by

randomization, the large number of sites, and monitored nature of the data evaluated. Importantly, if the 9.2% estimate of primary IVH patients is generally correct, a prospective trial of 500 primary IVHs would require screening ~116,000 ICH patients.[2] Thus, studies of primary IVH are not feasible. Further, MRI was not routinely available for CLEAR III participants so it is possible that additional primary IVH patients after independent adjudication also had parenchymal ICH. This substudy was not pre-specified, and findings may not be generalizable (i.e., patients with ICH volume >30mL were excluded, many patients with small IVH volumes likely did not require an EVD and thus were not included). Although adjustment for confounders was not possible due to small sample size, inverse-probability-weighting helps to remove confounding and its assumptions (i.e., primary IVH status is independent of outcomes, each individual could be primary IVH or not, each individual's primary IVH status and outcome status are independent of others) are reasonable, except that primary IVH may be associated with positive outcomes. Finally, we could not distinguish between good outcomes attributable to ICH absence and those attributable to alteplase and clot size reduction.

In CLEAR III, patients with primary IVH achieved better outcomes than those with additional small parenchymal lesions, and outcomes in primary IVH patients who received alteplase versus placebo were similar. Parenchymal injury avoidance was associated with better outcomes across domains including activities of daily living, Mini Mental State Exam, and quality of life. Future investigation of primary (vs. secondary) IVH with advanced imaging modalities (e.g., diffusion tensor imaging, lesion mapping) may help understand why IVH patients vary greatly in their recovery, especially in cognitive domains, which have significant impact.[1] To what extent are these impairments dependent on ICH site, IVH, or external factors (e.g., genetics, co-morbidities)?

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
mRS score distribution in primary and secondary IVH patients at (A) 180 and (B) 365 days.

Figure 2.

Interaction of IVH volume and primary versus secondary IVH for (A) day 180 poor mRS and (B) day 180 mortality. IVH volume threshold below approximately 60mL appears to have lower probability of poor mRS and mortality at day 180 in primary versus secondary IVH. Above this threshold, probability of both poor mRS and mortality increases more in primary IVH versus secondary IVH.

Table 1.

Primary versus secondary IVH characteristics and outcomes

	Primary IVH (n=46)	Secondary IVH (n=454)	P value
Age (years), mean (SD)	58.6 (12.1)	58.6 (11.1)	0.98
Females, n (%)	22 (47.8)	200 (44.1)	0.62
Race/ethnicity, n (%)			0.26
White	27 (58.7)	225 (49.6)	
Black	14 (30.4)	156 (34.4)	
Hispanic	2 (4.3)	56 (12.3)	
Other	3 (6.5)	17 (3.7)	
Medical history			
Hypertension, n (%)	41 (89.1)	424 (93.4)	0.28
Hyperlipidemia, n (%)	11 (23.9)	96 (21.1)	0.66
Diabetes mellitus, n (%)	14 (30.4)	139 (30.6)	0.98
Coronary artery disease, n (%)	6 (13.0)	23 (5.1)	0.03
Smoking, n (%)	17 (37.0)	115 (25.3)	0.09
Anticoagulant use, n (%)	9 (19.6)	40 (8.8)	0.02
Antiplatelet use, n (%)	12 (26.1)	116 (25.6)	0.94
Alteplase group, n (%)	19 (41.3)	230 (50.7)	0.23
Glasgow Coma Scale at randomization	9 (7–14)	10 (7–12)	0.47
Measured volumes			
Enrollment IVH volume (mL)	34.2 (23.3–52.1)	20.8 (12.5–34.2)	<0.01
Enrollment ICH volume (mL)	0 (0–0.1)*	8.9 (3.9–15.5)	<0.01
Decrease in IVH volume at EOT (mL)	14.5 (9.3–30.0)	10.8 (5.7–18.3)	0.01
Percent IVH removed at EOT (%)	51.0 (32.3–71.4)	59.0 (34.8–77.1)	0.24
Day 30 outcomes			
mRS	4 (3–5)	5 (4–5)	<0.01
BI	75 (18–100)	5 (0–45)	<0.01
NIHSS	2 (0–10)	11 (4–20)	<0.01
eGOS	3 (3–4)	3 (3–3)	<0.01
EQ-VAS	60 (35–80)	40 (20–65)	0.03
SIS-16	69 (31–86)	29 (11–56)	<0.01
MMSE	24 (11–29)	15 (2–25)	0.01
Mortality, n (%)	6 (13.0)	52 (11.5)	0.75
Day 180 outcomes			
mRS	3 (1–6)	4 (3–5)	0.02
BI	100 (90–100)	80 (35–100)	<0.01
NIHSS	0 (0–1)	3 (1–9)	<0.01
eGOS	5 (3–7)	3 (3–4)	0.01
EQ-VAS	80 (50–90)	70 (50–80)	0.02
SIS-16	88 (78–98)	65 (40–82)	<0.01
MMSE	29 (25–30)	26 (18–29)	0.01

	Primary IVH (n=46)	Secondary IVH (n=454)	P value
Mortality, n (%)	12 (26.1)	107 (23.8)	0.73
mRS 0–3, n (%)	28 (60.9)	199 (44.7)	0.04
Day 365 outcomes			
mRS	3 (1–6)	4 (3–6)	0.01
BI	100 (95–100)	90 (45–100)	<0.01
NIHSS	0 (0–1)	2 (0–7)	<0.01
eGOS	6 (4–8)	4 (3–5)	<0.01
EQ-VAS	80 (50–93)	70 (50–88)	0.19
SIS-16	90 (73–100)	70 (48–88)	<0.01
MMSE	29 (26–30)	27 (20–29)	<0.01
Mortality, n (%)	13 (28.9)	124 (27.8)	0.88
mRS 3, n (%)	29 (64.4)	212 (47.6)	0.03
Complications and other outcomes			
Total study doses	9 (5–12)	8 (4–12)	0.50
Days in intensive care unit	15 (11–20)	15 (11–21)	0.56
Total EVDs placed per patient	1 (1–2)	1 (1–2)	0.28
Bilateral EVDs used for study agent, n (%)	19 (41.3)	118 (26.0)	0.03
Required VP shunt, n (%)	5 (10.9)	85 (18.7)	0.19
Symptomatic ICH within 72h of last study dose, n (%)	0 (0)	11 (2.4)	0.29
Bacterial ventriculitis, n (%)	2 (4.3)	21 (4.6)	0.93

Data presented as median (IQR) unless otherwise specified.

* 16 primary IVH patients found to have parenchymal ICH after adjudication.

BI, Barthel Index; eGOS, extended Glasgow Outcome Scale; EOT, end of treatment; EQ-VAS, EuroQol visual analogue scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MMSE, Mini Mental State Exam; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SIS-16, Stroke Impact Scale.

Table 2.

Primary IVH patients: alteplase versus saline

	Alteplase (n=19)	Saline (n=27)	P value
Age (years), mean (SD)	57.4 (11.5)	59.5 (12.6)	0.47
Females, n (%)	9 (47.4)	13 (48.1)	0.96
Race/ethnicity, n (%)			0.12
White	11 (58.0)	16 (59.3)	
Black	5 (26.3)	9 (33.3)	
Hispanic	0 (0)	2 (7.4)	
Other	3 (15.8)	0 (0)	
Medical history			
Hypertension, n (%)	17 (89.5)	24 (88.9)	0.95
Hyperlipidemia, n (%)	5 (26.3)	6 (22.2)	0.75
Diabetes mellitus, n (%)	7 (36.8)	7 (25.9)	0.43
Coronary artery disease, n (%)	4 (21.1)	2 (7.4)	0.18
Smoking, n (%)	6 (31.6)	11 (40.7)	0.53
Anticoagulant use, n (%)	4 (21.1)	5 (18.5)	0.83
Antiplatelet use, n (%)	5 (26.3)	7 (25.9)	0.98
Glasgow Coma Scale at randomization	10 (7–13)	9 (8–14)	0.98
Measured volumes			
Enrollment IVH volume (mL)	27.9 (20.7–42.5)	48.0 (23.8–67.8)	0.02
Decrease in IVH volume at EOT (mL)	18.7 (9.3–30.0)	12.9 (8.5–31.0)	0.70
Percent IVH removed at EOT (%)	71.4 (60.6–86.8)	41.1 (22.3–53.6)	0.01
Day 30 mortality, n (%)	1 (5.3)	5 (18.5)	0.19
Day 180 outcomes			
Mortality, n (%)	3 (15.8)	9 (33.3)	0.18
mRS 0–3, n (%)	14 (73.7)	14 (51.9)	0.14
Day 365 outcomes			
Mortality, n (%)	4 (22.2)	9 (33.3)	0.42
mRS 0–3, n (%)	14 (77.8)	15 (55.6)	0.13
Complications and other outcomes			
Total study doses	4 (3–7)	12 (9–12)	<0.01
Days in intensive care unit	14 (11–16)	15 (11–21)	0.36
Required VP shunt, n (%)	2 (10.5)	3 (11.1)	0.95
Symptomatic ICH within 72h of last study dose, n (%)	0	0	N/A
Bacterial ventriculitis, n (%)	0	2 (7.4)	0.23

Data presented as median (IQR) unless otherwise specified.

EOT, end of treatment; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; N/A, not applicable.

Table 3.

Inverse-probability-weighted regression adjustment analyses: primary versus secondary IVH

Model	Risk difference	95% CI	P value
mRS 0–3, day 180	17.2	6.0 to 28.3	<0.01
mRS 0–3, day 365	19.0	7.7 to 30.4	<0.01
Mortality, day 30	5.4	–4.0 to 14.9	0.26
Mortality, day 180	2.6	–9.1 to 14.3	0.66
Mortality, day 365	6.0	–5.4 to 17.4	0.30

Risk difference = percent of primary IVH patients - percent of secondary IVH patients.